E.U. GRADUATE SCHOOL OF NATURAL AND APLIED SCIENCES

EGE UNIVERSITY

DOCTORATE THESIS

CHEMOMETRIC APPROACH FOR THE OPTIMIZATION OF CONTROLLED RELEASE TABLETS WITH RESPECT TO REFERENCE PRODUCT

Evrim ORHAN MANDIRACI

Supervisor: Prof. Dr. H. İsmet GÖKÇEL

Co-Supervisor: Doç. Dr. Hasan ERTAŞ

Department of Chemistry

Presentation Date: 31.01.2018

Bornova - İZMİR
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Evrim ORHAN MANDIRACI tarafından **Doktora** tezi olarak sunulan **"Chemometric Approach for the Optimization of Controlled Release Tablets with Respect to Reference Product"** başlıklı bu çalışma E.Ü. Lisansüstü Eğitim ve Öğretim Yönetmeliği ile E.Ü. Fen Bilimleri Enstitüsü Eğitim ve Öğretim Yönergesi'nin ilgili hükümleri uyarınca tarafımızdan değerlendirilerek savunmaya değer bulunmuş ve 31.01.2018 tarihinde yapılan tez savunma sınavında aday oybirliği ile başarılı bulunmuştur.

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EGE ÜNİVERSİTESİ FEN BİLİMLERİ ENSTİTÜSÜ

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E.Ü. Lisansüstü Eğitim ve Öğretim Yönetmeliğinin ilgili hükümleri uyarınca Doktora Tezi olarak sunduğum "**Chemometric Approach for the Optimization of Controlled Release Tablets with Respect to Reference Product**" başlıklı bu tezin kendi çalışmam olduğunu, sunduğum tüm sonuç, doküman, bilgi ve belgeleri bizzat ve bu tez çalışması kapsamında elde ettiğimi, bu tez çalışmasıyla elde edilmeyen bütün bilgi ve yorumlara atıf yaptığımı ve bunları kaynaklar listesinde usulüne uygun olarak verdiğimi, tez çalışması ve yazımı sırasında patent ve telif haklarını ihlal edici bir davranışımın olmadığını, bu tezin herhangi bir bölümünü bu üniversite veya diğer bir üniversitede başka bir tez çalışması içinde sunmadığımı, bu tezin planlanmasından yazımına kadar bütün safhalarda bilimsel etik kurallarına uygun olarak davrandığımı ve aksinin ortaya çıkması durumunda her türlü yasal sonucu kabul edeceğimi beyan ederim.

31.01.2018

Evrim ORHAN MANDIRACI

ÖZET

KONTROLLÜ SALIM YAPAN TABLETLERİN REFERANS ÜRÜNE GÖRE OPTİMİZASYONUNA KEMOMETRİK YAKLAŞIM

ORHAN MANDIRACI, Evrim

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Genellikle ilaç etken maddeleri hastalara tek başına verilmez. Yan etkileri önemli ölçüde azaltmak, biyoyararlanımı arttırmak, ilaç salımını kontrol etmek ve hasta rahatını sağlamak için yardımcı maddeler kullanılarak bir formülasyon oluşturulur. Kontrollü salım (CR) sistemler, ilaç etken maddesinin en yüksek derişim düzeyinde, kontrol edilebilir bir hızla ve insan bünyesine zararlı etkisi azaltılarak, doğrudan verilmesini sağladığı için oldukça ilgi çekicidir. Bu tür tabletlerin formülasyonunun geliştirilmesi ve optimizasyonu, birçok faktörün optimize edilmesini içeren karmaşık bir prosedürdür.

Bu tezde CR tabletlerin üretilmesi amaçlanmıştır. Aktif bileşen haricindeki her bir bileşen miktarı optimize edildikten sonra, üretilen tabletler bir referans ürünle karşılaştırıldı. Bu amaçla, ilaç etken maddesi olarak, güçlü bir lipid modifiye edici ajan olan Niasin seçilerek, farklı CR tablet formülasyon denemeleri yapıldı. Referans ürün olarak seçilen Niascor 500 mg ER Tablet ile benzer bir formülasyon elde etmek için, üretim basamağında kuru granülasyon ve yaş granülasyon teknikleri uygulandı.

Üç deneysel parametre (birinci deney tasarım için HPMC E15, HPMC K 100M ve Avicel PH 102 miktarları; ikincisi için HPMC K 100M CR, Laktoz Monohidrat ve Avicel PH 102 miktarları) Fraksiyonel Faktöriyel Tasarım Metodolojisi kullanılarak optimize edildi. 16 formülasyon denemesinin tümünde (Seri no: 01N14-16N14) aktif farmasötik bileşen (Niasin) ve stearik asit miktarları sabit tutuldu.

İlk olarak, üretilen tabletlerin su içeriği, boyut (kalınlık, çap), ortalama ağırlık, sertlik ve ufalanabilirlik gibi fiziksel testleri yapıldı ve elde edilen sonuçlar referans ürünün test sonuçları ile karşılaştırıldı. Sonuç olarak, elde edilen sonuçların tümünün limit içinde olduğu saptandı. Üretilen formülasyonlardaki niasin miktarları aynı HPLC yöntemiyle saptandı ve elde edilen tüm sonuçların (mg niasin / tablet ve % nasin / tablet olarak) limitler içinde olduğu görüldü.

Daha sonra, tüm formülasyonlar için, yeni ilaç ürünleri için en önemli kalite kontrol testi olan dissolüsyon testleri, uygun dissolüsyon ortamlarında, UV spektrofotometrik yöntem ile 262 nm'de gerçekleştirildi ve her formülasyon için altışar tablette ilaç salım yüzdeleri hesaplandı. Buna ek olarak, benzerlik faktörü (f2) ve fark faktörü (f1) değerleri hesaplandı ve referans ürününkilerle karşılaştırıldı.

Sonuç olarak, bu tez kapsamında üretilen Niasin 500 mg ER Tablet-Kapsüller, farklı pH ortamlarında (0.1 N HCI, pH 4.5 asetat tamponu, pH 6.8 fosfat tamponu ve distile su) referans ürün Niascor 500 mg ER Tablet ile benzer çözünme hızı profilleri gösterdi. Benzerlik hesaplaması, 'Endüstri için Kılavuz, Uzatılmış Salım Oral Dozaj Formları' kılavuzuna göre gerçekleştirildi ve tüm karşılaştırmalar sonunda 500.0 mg Niasin, 140.0 mg HPMC K 100M CR, 35.0 mg Laktoz Monohidrat, 13.0 mg Avicel PH 102 ve 5.0 mg Stearik asit içeren 16N14 numaralı yaş granülasyon ile üretilen formülasyon bu çalışmanın nihai formülasyonu olarak seçilmiştir.

Anahtar sözcükler: Niacin, kontrollü salım, yaş granülasyon

ABSTRACT

CHEMOMETRIC APPROACH FOR THE OPTIMIZATION OF CONTROLLED RELEASE TABLETS WITH RESPECT TO REFERENCE PRODUCT

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Ph.D. in Chemistry
Supervisor: Prof. Dr. H. İsmet GÖKÇEL
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An active drug is usually not used for a patient alone. A formulation is generated to reduce the side effects, to improve bioavailability, to control active drug release and to provide patient compliance with the use of excipients. Controlled release (CR) systems are of great interest for the delivery of active drugs because they provide directly delivery of maximum concentration level of it at controlled rate with causing less harm. Developing and optimizing the formulation of such tablets is a complex procedure since it includes the optimization of many factors.

In this thesis, production of CR tablets was aimed. After optimizing each component's amount except active ingredient, the produced tablets were compared with a reference product. For this purpose, Niacin, a potent lipid modifying agent, was chosen as the drug substance where different CR tablet formulation trials were performed. In order to obtain a similar formulation to the reference product, Niascor 500 mg ER Tablet, dry granulation and wet granulation techniques were applied in the production step.

Three experimental parameters (amount of HPMC E15, HPMC K 100M and Avicel PH 102 for the first design of experiments; amount of HPMC K 100M CR, Lactose Monohydrate and Avicel PH 102 for the second one) were optimized by using the Fractional Factorial Design Methodology. In all 16 formulations trials (Batch no: 01N14 - 16N14), the active pharmaceutical ingredient (Niacin) and stearic acid amounts were constant.

Firstly, physical tests, like water content, dimensions (thickness, diameter), average weight, hardness and friability of the produced tablets, were applied and obtained results were compared with the test results of reference product. As a consequence, all results were found to be within the limits. The assay analyses of formulated products were conducted with the same HPLC method and all obtained results (as mg niacin/tablet and as % niacin/tablet) varied within acceptable limits.

Afterwards, dissolution tests, a primary quality control test for new drug products, were performed for all the formulations using a UV Spectrophotometric method at a wavelength of 262 nm in the suitable dissolution medium and the percentage drug release of six tablets for each formulation were calculated. In addition, the similarity factor (f2) and the difference factor (f1) values were calculated and compared with those of the reference product.

In conclusion, Niacin 500 mg ER Tablet-Capsule drug product, produced within the scope of this thesis, showed similar dissolution profiles in different pH media (0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and distilled water) with the corresponding reference drug product Niascor 500 mg ER Tablet. Similarity calculation was performed according to 'Guidance for Industry, Extended Release Oral Dosage Forms' and after all comparisons, unit formula of the 16N14 numbered wet granulated formulation, consists of 500.0 mg of Niacin, 140.0 mg of HPMC K 100M CR, 35.0 mg of Lactose Monohydrate, 13.0 mg of Avicel PH 102 and 5.0 mg of Stearic acid, was revealed as the final formulation for this study.

Keywords: Niacin, controlled release, wet granulation

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2018, İZMİR

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LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredient
AV	Acceptance Value
AW	Average Weight
BCS	Biopharmaceutical Classification System
CCD	Central Composite Design
COST	Changing One Single (or Separate) Factor at a Time
CMC	Carboxymethyl Cellulose
DoE	Design of Experiments
EP	European Pharmacopeia
ER	Extended Release
FDA	Food and Drug Administration
FFA	Free Fatty Acids
GI	Gastrointestinal
HDL	High-density Lipoprotein
HEC	Hydroxyethyl Cellulose
HPC	Hydroxypropyl Cellulose
HPLC	High Pressure Liquid Chromatograph
HPMC	Hydroxypropylmethyl Cellulose
IVIVC	In Vitro - In Vivo Correlation
LDL	Low-density Lipoprotein
MDI	Metered-dose Inhalers
NA	Nicotinic Acid
NM	Nicotinamide
ODT	Orally Disintegrating Tablet

LIST OF ABBREVIATIONS (continued)

Ph. Eur.	European Pharmacopeia
RSD	Relative Standard Deviation
SD	Standard Deviation
USP	United States Pharmacopeia

1. INTRODUCTION

Humans have always searched for medicines in order to struggle against diseases and improve their daily life. An active drug is never used for a patient as it stands. It is always necessary to design it under a form that facilitates the administration and increases its efficiency. The drawbacks have to be as low as possible. In other words, it is necessary to notably reduce side effects, to improve the bioavailability and to control the active drug release rate (Diarra et al., 2003).

Drugs can be delivered to patients with different routes and different dosage form (Figure 1.1 and 1.2) (Wen and Park, 2010). But the oral administration of the drugs is by far the most used (Diarra et al., 2003). It has long been the most convenient and commonly employed route of drug delivery because of its ease of administration, least aseptic constraints and flexibility in the design of the dosage form (Abdul and Poddar, 2004).

Tablets, capsules and powders are the most common types of solid dosage forms. However, disadvantages linked to the administration by conventional dosage forms result not only from the brief duration of activity of medicines and the necessity of repeated intakes but also from the lack of tissular specificity of many pharmacological agents (Diarra et al., 2003).

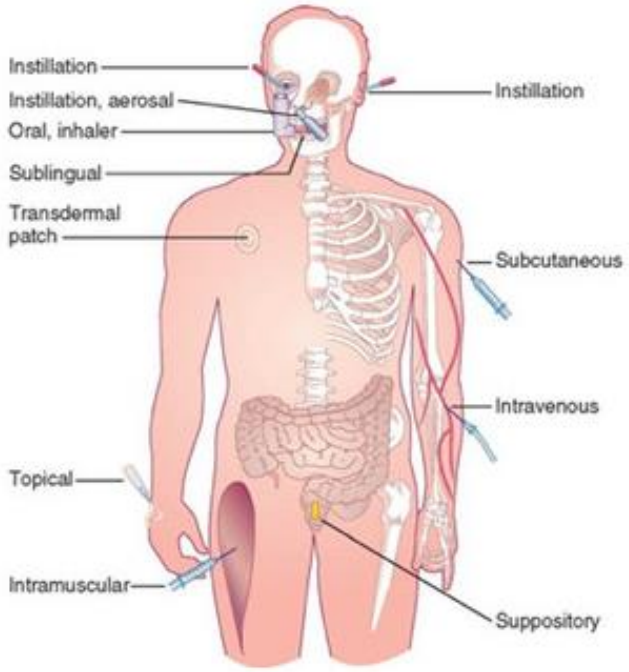


Figure 1.1 Routes of drug administration (https://quizlet.com/9891156/module-4-pharmacotherapy-and-safe-medication-administration-flash-cards/, 2015)

1.1. Pharmaceutical Dosage Forms

A dosage form is the combination of drug substance(s) and/or excipient(s) to facilitate dosing, administration, and intake of the medicine by the patient. Design, materials, manufacturing, and testing of all dosage forms target drug product quality (United States Pharmacopeia (USP) 37-NF 32, 2014). The administration routes of pharmaceutical dosage forms can be presented as in (Figure 1.2). Every group and their sub-groups will be respectively elaborated below.

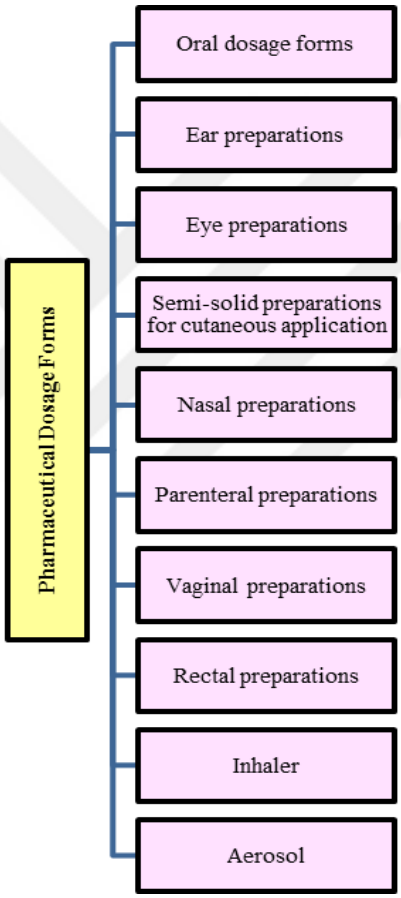


Figure 1.2 Pharmaceutical dosage forms

1.1.1. Oral dosage forms

1.1.1.1. Tablet

Capsules and tablets constitute a major portion of drug delivery systems that are currently available which differ from each other in that material in capsules is less impacted than in compressed tablets. Tablets generally disintegrate first into

granules and then into primary particles in stages. Tablet disintegration was once considered a sufficient criterion to predict in vivo absorption. This was proven inadequate, however, and dissolution is now recognized as a better criterion. Particle size is an important criterion for dissolution rate of the tablet, because, when particle size decreases, due to increased surface area, dissolution rate increases. Submission of dissolution data is a requirement of regulatory agencies for all new oral formulations. The increasingly wide acceptance of dissolution as the best available in vitro parameter to predict in vivo absorption is reflected in the proliferation of such tests in official compendia (Welling, 2007).

1.1.1.2. Effervescent tablet

Effervescent tablets can be defined as uncoated tablets or granules that generally contain acid substances (citric and tartaric acids) and carbonates or bicarbonates. They starts to release carbon dioxide once contact with water. The dosage form is dissolved or dispersed in water to initiate the effervescence prior to ingestion (USP 37-NF 32, 2014).

$$C_6H_8O_7 + 3NaHCO_3 \rightarrow 3CO_2 + 3H_2O + Na_3C_6H_5O_7$$

Citric Acid — Sodium Citrate

1.1.1.3. Orally disintegrating tablet (ODT)

Many patient groups such as the elderly, children, and mentally retarded, uncooperative, nauseated, or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Pharmaceutical technologists have designed a novel dosage form called Orally Disintegrating Tablets (ODTs) to meet for this group of patient's medical needs. ODT is a solid dosage form which disintegrates and dissolves rapidly in saliva, usually within 60 seconds or less, without water. Over the past three decades, ODTs have gained considerable attention as a preferred alternative to conventional tablets and capsules due to better patient compliance (Hirani et al., 2009).

1.1.1.4. Chewable tablet

Chewable tablets are defined in USP 37-NF 32, 2014 as tablets that attribute of a solid dosage form that is intended to be chewed or crushed before swallowing.

1.1.1.5. Buccal tablet and sublingual tablet

Sublingual and buccal medications are administered by placing them in the mouth, either sublingual (under the tongue) or buccal (between the gum and the cheek). These types of products dissolve rapidly and are absorbed through the mucous membranes of the mouth, then enter into the bloodstream. Absorption from either route is rapid, sublingual more so apparently because of greater permeability of sublingual membranes and rich blood supply. The mean pH of saliva is approximately 6 so that drug absorption, predominantly passive in nature, is favored for unchanged molecules, acids with $pK_a>3$, and bases with $pK_a<9$ (Welling, 2007).

1.1.1.6. Pastille

Pastille is a solid dosage form which disintegrates or dissolves slowly in the mouth (USP 37-NF 32, 2014).

1.1.1.7. Controlled release tablet

Controlled release term is used to describe dosage forms having drug release characteristics based on time, course, and/or location and are designed to accomplish therapeutic or convenience objectives not offered by conventional or immediate release dosage forms. Drugs for chronic conditions with short half-lives, possessing a good therapeutic index and uniform absorption pattern are ideal candidates for such dosage forms. These are either delayed release or extended release (ER) preparations. ER dosage forms allow at least a twofold reduction in dosing frequency as compared to the conventional dosage forms. In the other hand, delayed release dosage forms are designed to release all or a portion of drug at times much later than the time of administration (Figure 1.3). The delay can be time based or environment specific. Some other controlled release dosage forms include repeat action and targeted release dosage forms. Most controlled release products are good examples of ER dosage forms. These

dosage forms can be classified by their mechanism of release and/or type of formulation (Singh and Naini, 2007).

Controlled release dosage forms are intended to dispatch or release active drugs at a constant rate directly into the pharmacologically active site (Diarra et al., 2003).

Controlled release products include extended-release (sustained or slow release) products and delayed-release (enteric-coated) products (Dyas and Shah, 2007).

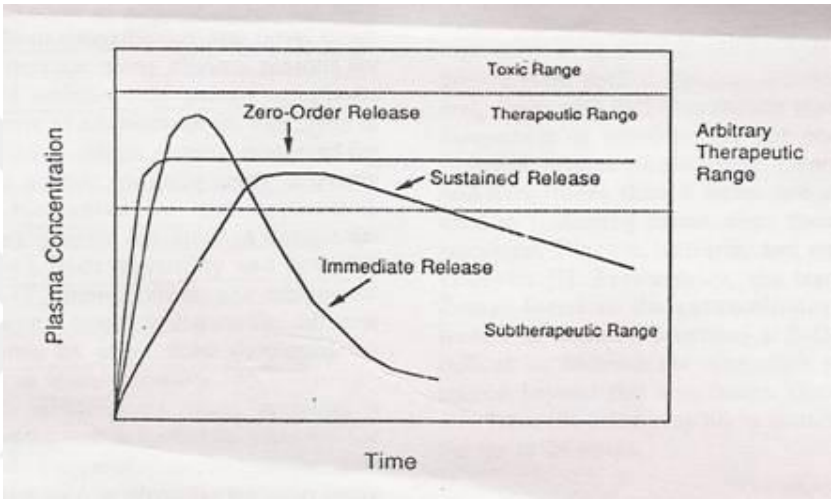


Figure 1.3 Drug level versus time profile (Jantzen and Robinson, 2002)

1.1.1.8. Multi-layered tablet

The term multi-layered tablet means tablet containing two or more subunits which may include same or two to three different drugs. These type of tablets are designed to control the dissolution and release characteristics and they are prepared with one layer of drug for immediate release while second layer designed to release drug latter, either as second dose or in an extended release manner (Jadhav et al., 2011).

Multiple-layered tablets have some obvious advantages like avoiding chemical incompatibilities of formulation components by physical separation or modifying release profiles by combining layers with different release patterns, or by combining slow-release with immediate-release layers compared to conventional tablets (Zerbe and Krumme, 2003).

1.1.1.9. Capsule

Capsule is a solid dosage form in which the drug substance is filled into a hard or soft shell or coated on the capsule shell with or without other excipients. Most capsule shells are made of gelatin (USP 37-NF 32, 2014), however, they may also be made from cellulose polymers or other suitable material. Once a capsule dissolves, the contents generally disperse quickly. One of uncommon disadvantage of this dosage forms is the capsule material, although water soluble, can block the dissolution of drug by interacting with the drug (Welling, 2007).

The shells may be composed of two pieces (a body and a cap) as in hard-shell capsules, or they may be composed of a single piece as in soft-shell capsules. This two-piece and one-piece capsule distinction, although imprecise, reflects differing levels of plasticizers in the two compositions and the fact that one-piece capsules typically are more pliable than two-piece capsules. Most capsules are designed for oral administration but also some types are delivered via rectal or vaginal route. When no deliberate effort has been made to modify the drug substance release rate, capsules are referred to as immediate-release. If the capsule consists of two telescoping cap and body pieces in a range of standard sizes it is called two-piece or hard-shell capsules. If the capsule is just one-piece it is called one-piece or soft-shell capsules and generally used to deliver a drug substance as a solution or suspension form. Liquid formulations placed into one-piece capsules may offer advantages by comparison with dry-filled capsules and tablets in achieving content uniformity of potent drug substance(s) or acceptable dissolution of drug substance(s) with poor aqueous solubility. Because the contact between the shell wall and its liquid contents is more intimate than in dry-filled capsules, undesired interactions may be more likely to occur (including gelatin cross linking and pellicle formation) (USP 37-NF 32, 2014).

The term caplet refers to a tablet dosage form in the capsule shape (USP 37-NF 32, 2014).

1.1.1.10. Pellet

Pellet term is used for dosage forms composed of small, solid particles of uniform shape sometimes called beads, although the use of the term “beads” as a dosage form is not preferred. Even though it is not a requirement, typically, pellets are nearly spherical. The administration of pellets can be done with two different

way; orally (gastrointestinal route) or by the injection route (USP 37-NF 32, 2014). Pellets can be produced in different sizes, designated according to the diameter of ten pellets measured in millimeters (Welling, 2007).

1.1.1.11. Cachets

Cachets are solid preparations include a single dose of one or more active substances in a hard shell pack. The cachet shell is made of unleavened bread usually from rice flour and consists of two prefabricated flat cylindrical sections. The cachets are immersed into the water for a few seconds before use, then, placed on the tongue and swallowed with a draught of water (European Pharmacopeia (EP) 8.4, 2015).

1.1.1.12. Syrup

Syrup is homogeneous liquid dosage form that contains high concentrations of sugars, one or more chemical substances dissolved in a solvent or mixture of mutually miscible solvents (USP 37-NF 32, 2014).

1.1.1.13. Suspension

According to USP 37-NF 32, 2014, suspension is a biphasic preparation consisting of solid particles dispersed throughout a liquid phase. This dosage forms can be formulated for specific routes of administration such as inhalation, topical, oral, ophthalmic, injectable, otic, etc. Also suspensions can be produced with two different ways. One of them is ready to use suspensions in suspension form already, the other one is powder form suspension which is used by diluting with suitable vehicle immediately prior to use.

1.1.2. Ear preparations

Ear preparations are liquid, semi-solid or solid preparations intended for instillation, spraying, insufflation, and application to the auditory meatus or as an ear wash (EP 8.4, 2015).

They usually contain one or more active substances and excipients, for example, to adjust tonicity or viscosity, to adjust or stabilize the pH, to increase the solubility of the active substances, to stabilize the preparation or to provide

adequate antimicrobial properties in a suitable vehicle. The excipients do not adversely affect the intended medicinal action of the preparation or, at the concentrations used, cause toxicity or undue local irritation (EP 8.4, 2015).

Ear preparations can be categorized as below:

– ear drops and sprays
– semi-solid ear preparations
– ear powders
– ear washes
– ear tampons (EP 8.4, 2015).

1.1.3. Eye preparations

Eye preparations are liquid, semi-solid or solid sterile dosage forms intended for administration upon the eyeball and/or to the conjunctiva, or for insertion in the conjunctival sac (EP 8.4, 2015).

Several categories of eye preparations are listed below:

– eye drops,
– eye lotions,
– powders for eye drops and powders for eye lotions,
– semi-solid eye preparations (EP 8.4, 2015).

1.1.4. Semi-solid preparations for cutaneous application

According to EP 8.0, 2014, these dosage forms are homogeneous preparations intended for local or transdermal delivery of active substances, or for their emollient or protective action.

1.1.4.1. Ointment

Ointments are semi-solid preparations generally used for external application to the skin/mucous membranes. Drug substances delivered in ointments are intended for local action or for systemic absorption. They generally

include less than 20% water and volatiles, and more than 50% hydrocarbons, waxes, or polyols as the vehicle. Ointment bases recognized for use as vehicles fall into four general classes: hydrocarbon bases, absorption bases, water-removable bases, and water-soluble bases (USP 37-NF 32, 2014).

1.1.4.2. Cream

Creams are semi-solid emulsion dosage forms often containing more than 20% water and volatiles, and/or containing less than 50% hydrocarbons, waxes, or polyols as the vehicle for the drug substance. Creams are generally intended for external application to the skin or mucous membranes. Creams have a relatively soft, spreadable consistency and can be formulated as either a water-in-oil emulsion or as an oil-in-water emulsion (USP 37-NF 32, 2014).

1.1.4.3. Gel

They are semi-solid system administered by the topical or mucosal routes in which a liquid phase is constrained within a 3-D polymeric matrix having a high degree of physical or chemical cross-linking. It's a dosage form that is a semi-solid dispersion of small particles or a solution of large molecules interpenetrated by a solution containing a gelling agent to provide stiffness (USP 37-NF 32, 2014).

1.1.5. Nasal preparations

These are liquid, semi-solid or solid preparations intended for administration to the nasal cavities to obtain a systemic or local effect which contain one or more active substances. Nasal preparations should be as far as possible non-irritating and should not block the functions of the nasal mucosa and affect its cilia. Aqueous nasal preparations are usually isotonic and may contain excipients, for example, to adjust the viscosity of the preparation, to adjust or stabilize the pH, to increase the solubility of the active substance, or to stabilize the preparation (EP 8.4, 2015).

Several categories of nasal preparations may be distinguished:

– nasal drops and liquid nasal sprays,

– nasal powders,

– semi-solid nasal preparations,

– nasal washes,

– nasal sticks (EP 8.4, 2015).

A spray is a dosage form that contains drug substance(s) in the liquid state, either as a solution or as a suspension, and is intended for administration as a mist. Sprays are distinguished from aerosols in that spray containers are not pressurized. Most of the sprays are generated by manually squeezing a flexible container or actuation of a pump that generates the mist by discharging the contents through a nozzle. As an attribute, spray describes the generation of droplets of a liquid or solution to facilitate application to the intended area (USP 37-NF 32, 2014).

Mouthwashes/gargles are used for the treatment of infection and inflammation of the oral cavity. Formulations designed for this purpose employ water as the vehicle, although a co-solvent, e.g. alcohol, may be employed to solubilise the active agent (Jones, 2008).

1.1.6. Parenteral preparations

EP 8.4, 2015 defines the parenteral preparations as sterile preparations intended for administration by injection, infusion or implantation into the human or animal body. Some of them include excipients, for example to make the preparation isotonic with respect to blood, to adjust the pH, to increase solubility, to prevent deterioration of the active substances or to provide adequate antimicrobial properties, but not to adversely affect the intended medicinal action of the preparation or, at the concentrations used, to cause toxicity or undue local irritation.

Categories of parenteral preparations:

– injections,

– infusions,

– concentrates for injections or infusions,

– powders for injections or infusions,

– gels for injections,

– implants (EP 8.4, 2015).

Injection (by injection) is a route of administration of a liquid or semi-solid deposited into a body cavity, fluid, or tissue by use of a needle. The term “for injection” indicates dry solids that, upon the addition of a suitable vehicle, yield solutions conforming in all respects to the requirements for injections (USP 37-NF 32, 2014).

1.1.7. Vaginal preparations

Vaginal preparations are dosage forms which are used to have a local effect in vagina and can be liquid, semi liquid or solid form (EP 8.0, 2014).

1.1.8. Rectal preparations

Rectal preparations are applied via rectal route in order to obtain a systemic or local effect, or for diagnostic purposes (EP 8.0, 2014).

1.1.9. Inhaler

An inhaler can be defined as a drug product combined with a medical device used for delivering medication into the body via the lungs. Potential absorption surface of a lung can reach to 70 m^2, which is a much larger surface compared to the small intestine. However, the lungs and their associated airways are designed to deny access of administered compounds to the highly absorptive peripheral lung surfaces. Even though the system is designed to deny access to particulate matter, absorption can be very efficient when compounds can reach the peripheral region of the lung. Also it has to be considered that most of the inhalation devices can deliver ~10% of the administered dose to the lower respiratory tract (Welling, 2007).

The aerosol term refers to a type of inhaler product which is packaged under pressure and consists of therapeutic agent(s) and a propellant that are released upon actuation of an appropriate valve system. With the actuation of the valve system, only one dose of the drug substance is released from the preparation upon actuation of a metered valve as a plume of fine particles or droplets. In the case of topical products and depending on the nature of the drug substance and the conditions being treated, actuation of the valve may result in a metered release of a controlled amount of the formulation or the continuous release of the formulation as long as the valve is depressed. Typical components of aerosols can be listed as one or more drug substance(s) and propellant combination, the

container, the valve, and the actuator as a packaging material. Each of the components affect the droplet size distribution or particle size distribution, uniformity of delivery of the therapeutic agent, rate of delivery, and plume velocity and geometry of the drug product. There are different routes to deliver aerosol dosage forms. The components like canister, actuator, and metering valve, as well as the formulation, are designed to target the administration site of the aerosol. Inhalation aerosols, commonly known as metered-dose inhalers (MDIs), are intended to produce fine particles or droplets for inhalation through the mouth and deposition in the pulmonary tree while, nasal aerosols (commonly known as nasal MDIs) produce fine particles or droplets for delivery through the nasal vestibule and deposition in the nasal cavity. Each actuation of the valve releases a measured mass of the drug substance with appropriate quality characteristics. Lingual aerosols are intended to produce fine particles or droplets for deposition on the surface of the tongue and topical aerosols produce fine particles or droplets for application to the skin (USP 37-NF 32, 2014).

1.2. Controlled Release Dosage Forms

According to Welling, 2007 in tablets, capsules or the other dosage forms along with active material a variety of so-called inert ingredients are present, such as hydroxyethyl cellulose (HEC), starch, hydroxypropylmethyl cellulose (HPMC), magnesium aluminum silicate, carboxymethyl cellulose (CMC), lactose, xanthan gum, kaolin, talc, calcium sulfate, polyvinyl acetate and magnesium stearate. Also variety of coating materials can be a good choice not only to improve stability, but also taste, appearance of the tablets, and to determine drug release characteristics. Even though these additives are considered to be inert, they can affect the dissolution and absorption of the drug product. For example, changing an excipient from calcium sulfate to lactose and increasing the proportion of magnesium silicate, increases the activity of oral phenytoin. As another sample, systemic availability of thiamine and riboflavin is reduced by the presence of fuller’s earth. Absorption of tetracycline from capsules is reduced by calcium phosphate due to complexation. Most of these types of interactions were reported some time ago and are unlikely to occur in the current environment of rigorous testing of new dosage forms and formulations.

Due to the difficulty in developing new drugs, more and more emphasis has been given to developing new drug delivery systems for existing drugs as well as

new chemical entities (Wen and Park, 2010). Therefore, it is interesting to develop new pharmaceutical forms as controlled release systems (Diarra et al., 2003).

For several years researchers working in drug formulation field have focused on the systems that delay the release of drugs after administration. There have been considerable advances in the area, and indeed can be found in the literature. The reasons, among others, that have led to the formulation of sustained release drug delivery systems stem from the wish to achieve the slow release of highly water-soluble compounds, direct such compounds to the target organ or cell, achieve release rates that match a given aim, decrease the number of daily administrations, and improve compliance and minimize side effects. Sustained release drugs are generally administered by orally to the patients as for immediate release formulations, because of its easy delivery, a better adjustment of the doses administered, better acceptance by patients and cost-effective manufacture, etc. Since the appearance of the first sustained release formulation commercialized worldwide in 1952, Spansules™ (Smith Kline and French), which were hard gelatine capsules filled with pellets, different strategies and technologies have been developed with a view to achieving controlled drug release (Maderuelo et al., 2011).

There are many ways to design modified release dosage forms for oral administration; from film coated pellets, tablets or capsules to more sophisticated and complicated delivery systems such as osmotically driven systems, systems controlled by ion exchange mechanism, systems using three dimensional printing technology and systems using electrostatic deposition technology. The design of modified release drug product is usually intended to optimize a therapeutic regimen by providing slow and continuous delivery of drug over the entire dosing interval whilst also providing greater patient compliance and convenience. The most common controlled delivery system has been the matrix type such as tablets and granules where the drug is uniformly dissolved or dispersed throughout the polymer, because of its effectiveness, low cost, ease of manufacturing and prolonged delivery time period (Abdul and Poddar, 2004).

Common types of oral modified release delivery include delayed-release as in enteric coated products; site-specific or timed release as in colonic delivery

systems; extended-release as in zero-order, first-order, biphasic release, etc.; programmed release as in pulsatile, delayed extended-release drug products (Qiu et al., 2009).

The science of controlled release is approximately 40 years old. Initial goals included zero-order release devices and the mathematics to accurately describe drug release from polymeric matrices (Kosto and Nauman, 2003).

1.2.1. Materials used for modifying drug release

The most common materials used in controlled release oral solid dosage forms are long chain substituted or unsubstituted hydrocarbons and polymers. Natural or synthetic long chain hydrocarbons such as fatty acids, fatty acid esters, glyceryl esters, alcohol esters, and waxes were among the earliest materials applied in modifying drug release from matrix systems. The use of waxes for prolonging the medicinal effect of herbal medicines can be traced back to the fourth century. Polymers are sourced from natural products (e.g., polysaccharides), chemically modified natural products (e.g., cellulose ethers and esters) or synthetic in nature (e.g., methacrylic ester copolymers). Today, polymers have become the dominating rate-controlling excipients in the modified-release arena, due to their multitude of functionalities and properties that are relatively easy to control from batch to batch (Qiu et al., 2009).

The materials most widely used in preparing matrix systems include hydrophilic and hydrophobic polymers, as well as long chain hydrocarbons. Commonly available hydrophilic polymers include:

- Non-ionic soluble cellulose ethers, such as hydroxypropylmethyl cellulose; e.g., Methocel K100 LV, K4 M, K15 M, K100 M; Benecel MP 843, MP 814, MP 844; Metolose® 100, 4000, 15000 and 100 000 SR), hydroxypropyl cellulose (HPC); e.g., Klucel GXF, MXF, HXF), hydroxyethyl cellulose; e.g., Natrosol 250 HHX, HX, M, G) with varying degrees of substitutions and viscosity grades
- Nonionic homopolymers of ethylene oxide, such as poly(ethylene oxide), $[H(OCH_2CH_2)_nOH]$ with a molecular weight range of 100 000 to 8 000 000 (e.g., Polyox WSR N-12K, WSR N-60K, WSR-301, WSR-coagulant, WSR-303, WSR-308)

- Water-soluble natural gums of polysaccharides of natural origin, such as xanthan gum, alginate, and locust bean gum
- Water swellable, but insoluble, high molecular weight homopolymers and copolymers of acrylic acid chemically cross-linked with polyalkenyl alcohols with varying degree of cross-linking or particle size (Carbopol® 71G NF, 971P, 974P and 934P)
- Polyvinyl acetate and povidone mixtures (Kollidon SR)
- Cross-linked high amylose starch
- Ionic methacrylate copolymers (Eudragit L30D, FS 30D) (Qiu et. al, 2009).

1.2.2. Types of modified release systems

1.2.2.1. Delayed release (e.g., using an enteric coating)

Delayed release, defined with lag phase and followed with release phase, is obtained when the entire surface of core is compression-coated. Lag time for drug release could be controlled by the application of different polymeric coats which were differentiated with triggering factors to control drug release as mainly mentioned in colonic drug delivery system (Aher et al., 2011).

1.2.2.2. Site-specific or time controlled release (e.g., for colonic delivery)

A delayed release tablet consists of a drug core which is compression-coated with different polymeric (pH independent) barriers. The lag time of drug release is controlled by the compression coating, which prevents drug release from the core until the polymer coat is completely eroded, swollen or ruptured (Aher et al., 2011).

1.2.2.3. pH controlled release

A delayed release system using enteric polymers as a coating can provide site-specific drug delivery especially for colon. This system has attracted great interest for the local treatment of a variety of bowel diseases and for improving systemic absorption of therapeutic agents susceptible to enzyme digestion in the upper gastrointestinal (GI) tract, while time controlled release cannot achieve this owing to large variations in gastric emptying time (Aher et al., 2011).

1.2.2.4. Microbial controlled release

A delayed release system may be aimed at for colon drug targeting. This system is based on the degradation of the polymeric compression-coat by specific enzymes produced by enterobacteria in the colon (Aher et al., 2011).

1.2.3. Common oral extended-release systems

Matrix, reservoir and osmotic systems are common oral extended-release systems and utilize in commercial products (Qiu et al., 2009) (Table 1.1).

1.2.3.1. Matrix systems

- Hydrophilic Matrix Systems
- Hydrophobic Matrix Systems

1.2.3.2. Reservoir (or membrane controlled) systems

- Membrane controlled
- Membrane-matrix combination

1.2.3.3. Osmotic systems

- Elementary osmotic pump
- Microporous osmotic pump
- Layered osmotic pump

Table 1.1 Oral extended release systems commonly utilized in commercial products (Qiu et al., 2009)

	Matrix	Reservoir	Osmotic
Systems	Hydrophilic matrix Erosion/ diffusion controlled Swelling/ erosion controlled Hydrophobic matrix Homogenous (dissolved drugs) Heterogeneous (dispersed drugs)	Membrane controlled Constant activity Non-constant activity Membrane-matrix Combination	Elementary osmotic pump Microporous osmotic pump Layered osmotic pump (e.g., Push-Pull®, Push-Stick®)
Common dosage forms	Monolithic tablet Multi-unit minitablets Layered tablet Compression coated tablet	Multi-unit coated beads Multi-unit coated minitablets Monolithic coated tablet	Coated monolithic tablet Coated layered tablet

1.2.4. Factors affecting on the drug release

Tablet cores (drug solubility, tablet core formulation) and compression coating (polymer type, particle size of used polymer, core-coat ratio, compression force) are the two main factors which can affect the rate of drug release. Their mechanism of action was explained below via attached samples from researchers' formulation studies.

1.2.4.1. Tablet cores

Drug solubility

The effect of drug solubility has been investigated in 2002: diclofenac sodium, theophylline anhydrous and salbutamol sulfate in cores containing

sodium starch glycolate (50% of drug) as disintegrant and ethyl cellulose (fined powder) was used as the compression-coat. Higher solubility drug containing cores in compression-coated tablets provided shorter lag time than lower solubility drug containing cores. Rapidly and completely release of diclofenac sodium and salbutamol sulfate was presented, while theophylline anhydrous exhibited fast release and curved down after 60%. The partial transformation of theophylline anhydrous to theophylline hydrate was their explanation for the retardation release behavior (Rujivipat, 2010).

Tablet core formulation

Many research showed that drug release from compression-coated tablet containing a fast release core was faster than extended release core containing coated tablet when the same coating composition was used. This has been revealed that the release behavior and the lag time were dependent on the type of excipient used in the core (Rujivipat, 2010).

1.2.4.2. Compression coating

Polymer type

The pharmaceutical polymers used (single or combination) in compression coating are cellulose derivatives (e.g. hydroxypropylmethyl cellulose acetate succinate, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose and hydroxyethyl cellulose), polysaccharides (e.g. guar gum, sodium alginate and pectin), water soluble polymer (polyethylene oxide) and wax (behenic acid) and methacrylate copolymers. The coats containing these polymers could be divided into groups such as water insoluble (ethyl cellulose), erodible (low molecular weight hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyethylene oxide), gellable or swellable (high molecular weight hydroxypropylmethyl cellulose), pH dependent soluble (hydroxypropylmethyl cellulose acetate succinate, methacrylic acid copolymer), waxy and bacterial digestible. The properties of these polymers control drug release in different manners as previously mentioned (Rujivipat, 2010).

Conte et al. (1993) showed that the release behavior from compression coated tablets was controlled and modulated by type and molecular weight of the polymer used as shell. Drug release starts when the shell is completely eroded

swollen or dissolved. A purely erodible coating is supposed to prevent drug release from the core until it is removed from by dissolution medium. The release behavior of the cores from compression-coated tablets containing erodible shell would not be modified by the erodible coating. Instead, drug release from compression-coated tablets which have a gellable coat would be delayed and altered the release performance. Smaller molecular weight of gellable coat (hydroxypropylmethyl cellulose 2208) would provide a faster release rate after lag time than higher molecular weight (Rujivipat, 2010).

Particle size of polymer used

Compression-coated tablets prepared with smaller particles sizes of ethyl cellulose provided longer lag time. The smaller particle size of ethyl cellulose used in coat provided less porosity and higher tortuous path for medium infiltration, then the longer lag time of drug release was obtained. Lag time of compression-coated tablets containing ethyl cellulose mixtures (granules and fine powder, 1:1) as coat was only slightly different from tablets containing fine powder as because fine ethyl cellulose powder was filled the inter- and intraparticulate gaps of coarse ethyl cellulose powder. The influence of particle size of coating material in form of granules was more pronounced than in form of powder. Compression-coated tablets from granulated coat provided faster drug release and shorter lag time compared to tablets from fine powder coat. Different lag time and drug release mechanism of ethyl cellulose compression-coated tablets were illustrated by incorporation of different excipients into the upper coat of compression-coated tablets with the same lower coat, ethyl cellulose coarse powder (Rujivipat, 2010).

Core-coat ratio

For the time controlled release system from compression-coated tablets, the amount of the outer shell is a key factor for controlling the lag time. Higher amount of the outer coating added would prolong the lag time of drug release. For insoluble polymer coat like ethyl cellulose, the influence of polymer amount or thickness of coat on the lag time and drug release was investigated. Insufficient polymer amount of coat would result in absent of the lag time, since the drug might be released through the incomplete form of ethyl cellulose compression-coat (Rujivipat, 2010).

Compression force

The effect of compression force applied to inner core on drug release from ethyl cellulose compression-coated tablet was studied in 2001. The influence of compression force applied to the coat on the drug release of ethyl cellulose compression-coated tablets was presented. When an insoluble coat is applied on a core with different compression forces, the lag time and drug release rate will be modified. The lag time of drug release increased and the release rate decreased when the compression force applied to the coating increased till a critical point. The results explained that by a decrease of coat porosity with higher compression forces leading to slower diffusion or lower permeability of water through the porous polymer matrix as compression coat. Also, Rujivipat (2010) agreed that higher compression force applied in compression coating leading to lesser porosity in the coat results in longer lag time.

1.2.5. Matrix systems

Most commercial hydrophilic matrices are obtained by compression; in most cases term of matrix tablet can be used. Thus, the basic operations involved in the preparation of the matrices are the same as those used to prepare conventional tablets, such as mixing and compressing the components. Granulation prior to mixing and the coating of matrix tablets are complementary operations widely used to manufacture matrix tablets. As well as the drug and the release-limiting polymer, other excipients are usually added as diluents, lubricants and anti-adherents (Maderuelo et al., 2011).

In a matrix system, the drug substance is homogeneously mixed into the rate-controlling material(s) and other excipients as a crystalline, amorphous or, in rare cases, molecular dispersion. Drug release occurs either by drug diffusion and /or erosion of the matrix system. Based on the characteristics of the rate-controlling material, the matrix system can be divided into two categories as hydrophilic and hydrophobic systems depending on the rate-controlling agent's behavior, as shown in Figure 1.4-1.6 (Qiu et al., 2009).

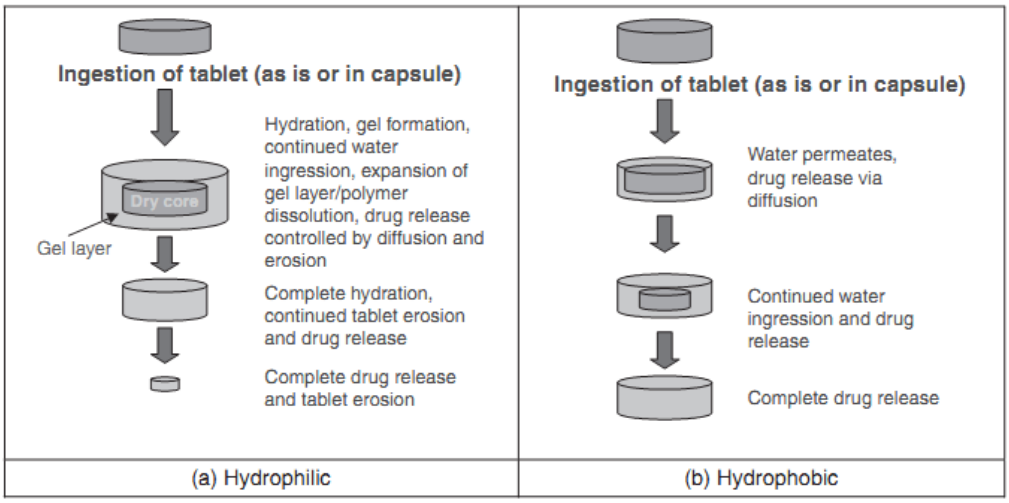


Figure 1.4 Hydrophilic and hydrophobic matrix systems and corresponding drug release process (Qiu et al., 2009)

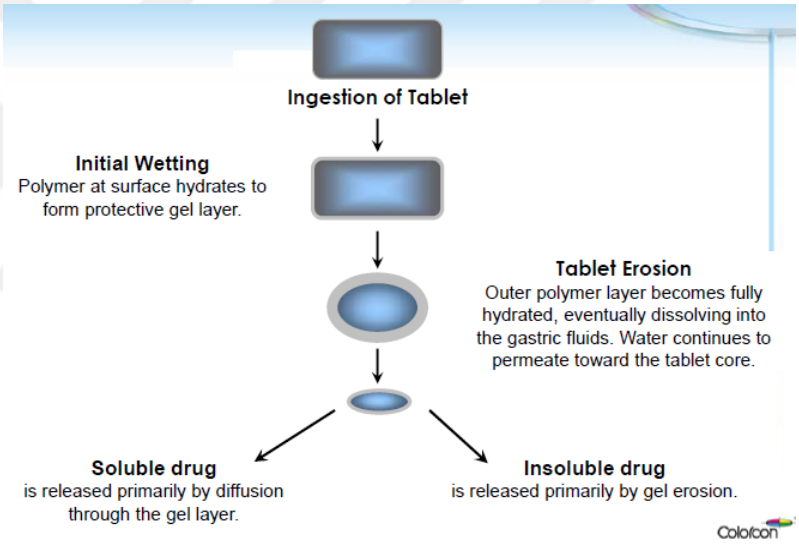


Figure 1.5 Hydrophilic Matrices (Colorcon, 2014)

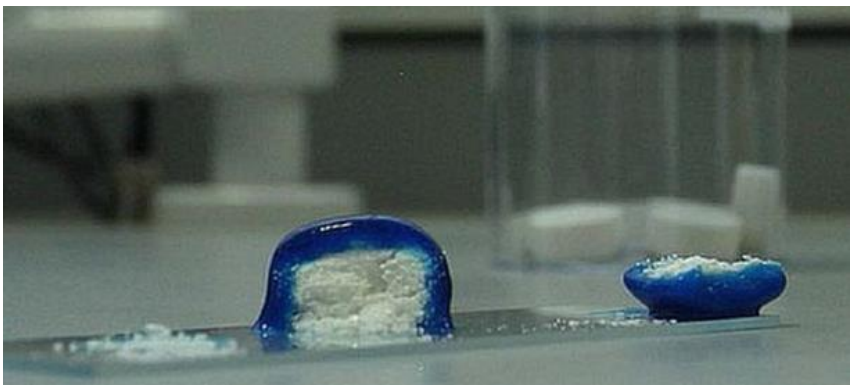


Figure 1.6 Matrix gel layer formation (Colorcon, 2014)

Nowadays, hydrophilic matrices have been made using a large number of polymers, natural or synthetic, alone or in mixtures, as release-retardant excipients (Table 1.2). One of the most widely used groups of polymers is derivatives of cellulose, which with the exception of cellulose esters and ethyl cellulose, are composed of monomers with a certain degree of hydrophilia. They have a regular structure along their chain, in which it is possible to establish a high number of bonds per hydrogen bridge and conform a structure in which the entry of water will be hindered (Maderuelo et al., 2011).

Table 1.2 Common natural polymers and derivatives used in oral controlled release formulations (Wen and Park, 2010)

Polymer	**Comments**
HPC	Used in matrix sustained release formulations
HPMC	Widely used in matrix sustained release formulations
Ethyl cellulose	Insoluble in water. Widely used in matrix sustained release applications. Also used in matrix tablets for diffusion-controlled controlled release formulation, that is, lipophilic matrix
Methyl cellulose	Not as efficient as HPMC and HPC in slowing down drug release rate
Carboxymethyl cellulose, Na	Sometimes used in matrix tablets together with HPMC
Alginate, Na	Beside thickening, gel-forming, and stabilizing properties, it can also easily gel in the presence of a divalent cation such as Ca^{2+}
λ-Carrageenan	-
Chitosan	pH-dependent hydrogelation of chitosan matrixes
Heparin	-
Xanthan gum	-
Starch (thermally modified)	-

Hydroxypropylmethyl cellulose cellulose ethers are water-soluble polymers derived from cellulose, the most abundant polymer in nature. These products have been used as key ingredients in pharmaceutical and other applications for over 50 years. HPMC as the controlled release agent in hydrophilic matrix systems offers a wide range of properties, consistently high quality, and broad regulatory approval (The Dow Chemical Company, 2014). Chemical structures of HPMC and particle morphology of HPMC CR were shown in Figure 1.7 and 1.8, respectively.

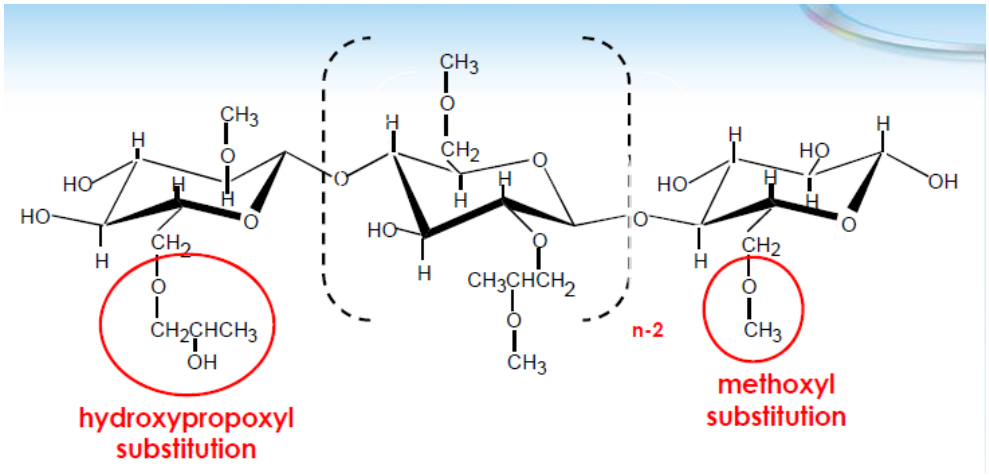


Figure 1.7 Chemical structure of HPMC (Colorcon, 2014)

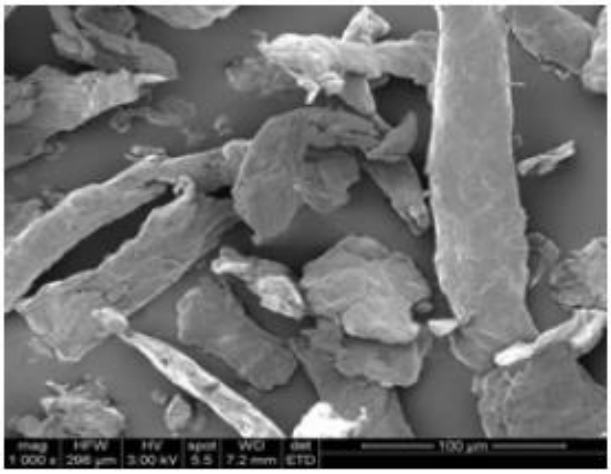


Figure 1.8 Particle morphology of HPMC CR (Colorcon, 2014)

In general it is seen that regardless of the physicochemical characteristics of the polymer and of the compound in question the drug release rate decreases with the increase in the percentage of polymer in the matrix. The greatest percentage of polymer corresponds to a lower porosity of the matrix, which achieves slower drug release rates (Maderuelo et al., 2011).

1.2.6. Advantages of modified release systems

Advantages of oral extended-release systems, listed by Wen and Park (2010), are maintenance of optimum drug concentration and increased duration of therapeutic effect, improved efficiency of treatment with less amount of drug, minimized side effects, less frequent administration, increased patient convenience and compliance (Figure 1.9 and 1.10).

Controlled release tablet formulations are preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase the safety margin for high-potency drugs (Gouthami et al., 2013).

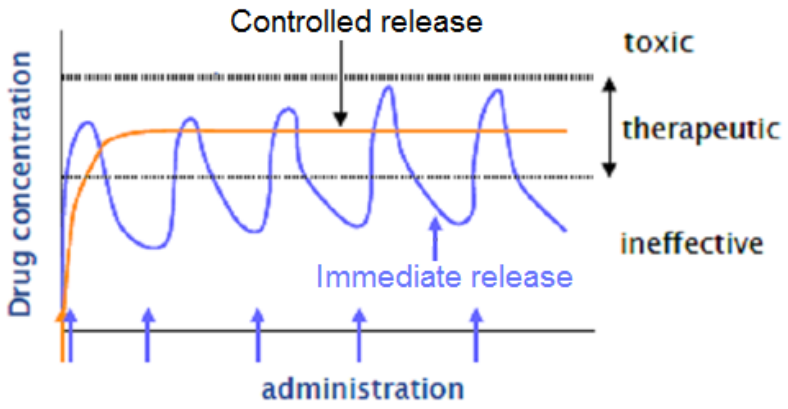


Figure 1.9 Active concentrations in blood for different release forms (Colorcon, 2007)

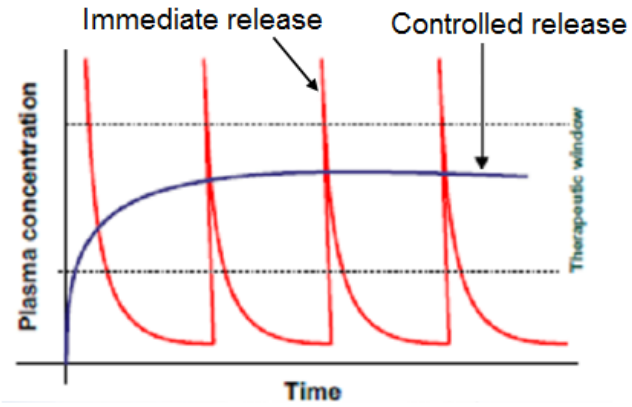


Figure 1.10 Comparison of side and toxic effects for controlled release and immediate release forms (Colorcon, 2007)

1.2.7. Disadvantages of oral extended-release systems

Disadvantages of an oral extended-release system can be listed as, higher amounts of drug in one dosage compared to a single dose of conventional dosage forms, possibility to reaching the toxic level of the drug concentration, the potential of dose dumping, once the drug release begins, it is difficult to stop the release even if it is necessary, higher costs of producing the controlled release formulation (Wen and Park, 2010).

1.2.8. Drug release mechanisms

Flexibility of drug release profile, the rate and extent of release are dependent on the technology used.

1.2.8.1. Zero order release systems

The amount of drug eliminated for each time interval is constant, regardless of the amount in the body. In other words the amount of drug in the body does not change with the amount or concentration of the drug in the body (Figure 1.11 and 1.12).

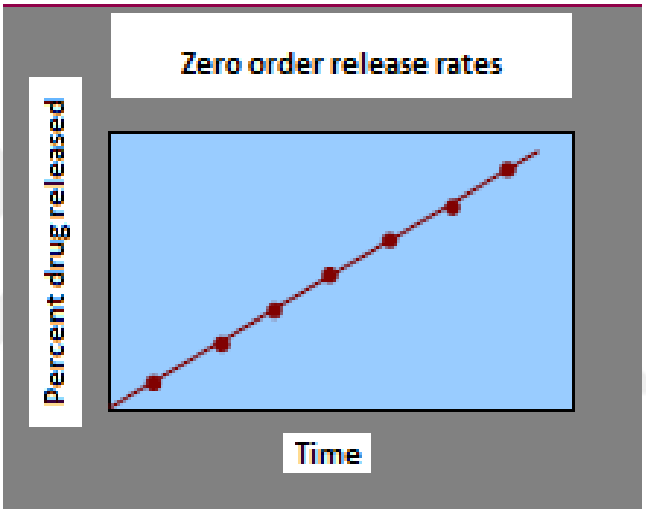


Figure 1.11 Zero order drug release (Colorcon, 2007)

$Q_t = Q_0 + K_0 t$

where, Q_t: Amount of drug dissolved in time t
Q_0: Initial amount of drug in the solution
K_0: Zero order release constant

1.2.8.2. First order release systems

Most drugs are eliminated by a first order process in which eliminated drug amount in a set amount of time is directly proportional to the amount of drug in the body. The amount of drug eliminated over a certain time period increases as the amount of drug in the body increases; likewise, the amount of drug eliminated

per unit of time decreases as the amount of drug in the body decreases. But the fractions of a drug remain constant. This concept is different from zero order elimination, in which the amount of drug eliminated for each time interval is constant, regardless of the amount of drug in the body (Figure 1.12 and 13).

Figure 1.12 First order drug release (Colorcon, 2007)

$InQ_t = In\ Q_0 + K_1 t$

where, Q_t: Amount of drug dissolved in time t

Q_0: Initial amount of drug in the solution

K_1: First order release constant

Many compounds are not suitable for modified release delivery, due to a variety of reasons, such as undesirable drug properties, dose, and lack of pharmacological rationale or technical feasibility. Generally, failures in the innovator companies can be partly attributed to the simple fact that the molecule of interest is not feasible for modified release delivery. It may also be related to a lack of expertise in rational design and development of a robust modified release product. For generic companies, unsuccessful attempts are mostly related to inadequate knowledge and skill in developing modified release products and/or overcoming patent hurdles, because feasibility of the active has already been proven by the innovator's product (Qiu et al., 2009).

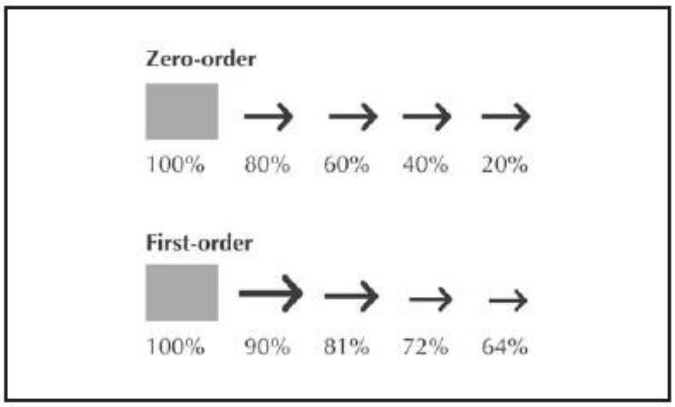


Figure 1.13 Zero versus first order elimination. The size of the arrow represents the amount of drug eliminated over a unit of time. Percentages are the fraction of the initial drug amount remaining in the body

1.3. Niacin (Nicotinic Acid)

The Biopharmaceutical Classification System (BCS) is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from immediate release solid oral dosage forms: dissolution, solubility, and intestinal permeability. According to the BCS, drug substances are classified as Figure 1.14 (Food and Drug Administration (FDA), 2015).

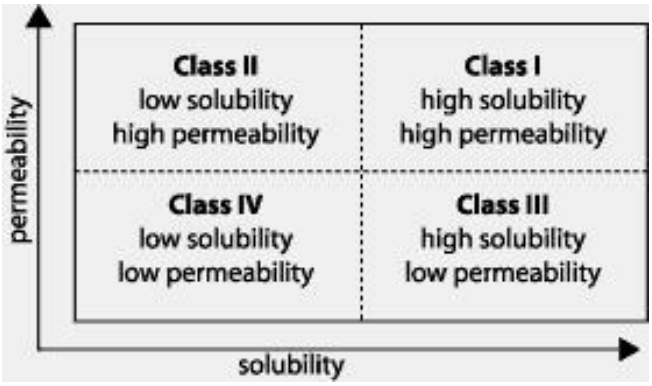


Figure 1.14 Biopharmaceutical classification system

The solubility class boundary is based on the highest strength of an immediate release product that is the subject of a biowaiver request. A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media over the pH range of 1.0-6.8. The volume estimate

of 250 mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water (FDA, 2015).

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed) of a drug substance in humans, and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, other systems capable of predicting the extent of drug absorption in humans can be used (e.g., in situ animal, in vitro epithelial cell culture methods). A drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 85 percent or more of an administered dose based on a mass balance determination (along with evidence showing stability of the drug in the gastrointestinal tract) or in comparison to an intravenous reference dose (FDA, 2015).

Niacin is a Biopharmaceutical Classification System I drug based on its high solubility in water and good permeability. Its melting point is 236.6°C and pK_a 2.2 (Chuong et al., 2010).

Niacin is also known as nicotinic acid. It is chemically, 3-pyridine carboxylic acid (Figure 1.15), and has been used for many years in the treatment of hyperlipidemia and hypercholesterolemia (US2010/0144800A1, 2010). Niacin is a form of vitamin B_3, one of the water-soluble B-complex vitamins (Davidson, 2008).

Figure 1.15 Molecular formula for niacin

1.3.1. History of niacin

Nicotinic acid, or niacin, has been discovered in the 20th century, but its most important roles may lie ahead. Designated in the mid-1930s as a B-complex vitamin, the deficiency of which causes pellagra, it was found in 1955 to reduce plasma cholesterol in humans and atherosclerosis in the rabbit. It was subsequently shown to have major dose-dependent effects on a broad spectrum of plasma lipoproteins-effects that are predictably favorable in terms of atherosclerosis risk. An evolving understanding of the metabolic mechanisms of niacin's effects, and of its side effects, has put scientists in a position to engineer its gastrointestinal release profile and to combine it with adjunctive treatments to minimize its side effects. Specifically, identification of the so-called "niacin receptor," a G_i-coupled membrane protein on the adipocyte and the cutaneous Langerhans cell, holds promise for the development of more effective and tolerable pharmaceuticals. Because lipid therapies focused on raising high-density lipoprotein (HDL) cholesterol and lowering low-density lipoprotein (LDL) cholesterol are comparably beneficial and are additive in their impact on vascular disease, niacin's most predictable future is its use in combination with LDL cholesterol-lowering agents such as the statins. As the current most effective HDL cholesterol-raising agent, niacin in various combinations appears to hold great promise for improved prevention of cardiovascular diseas (Brown et al., 2009). The effects of niacin on plasma lipoprotein classes was summarized in Table 1.3.

Table 1.3 Summary of the effects of niacin on plasma lipoprotein classes (Carlson, 2005).

LIPOPROTEIN	EFFECT
Chylomicrons	↓
VLDL	↓
β-VLDL	↓
IDL	↓
LDL	↓
sdLDL	↓
HDL	↑
HDL_2	↑
LP(a)	↓

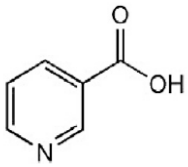
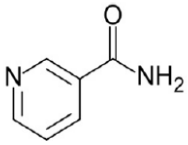
1.3.2. Early discoveries

Nicotinic acid from liver extract was found, to prevent and cure pellagra. The active vitamin ingredient was nicotinamide, an amide metabolite of nicotinic acid, now a member, B_3, of the B-complex vitamin group. In 1955, researches showed that niacin, but not nicotinamide, lowered cholesterol in humans and that it reduced lipid accumulation in aortas of cholesterol-fed rabbits. Parsons et al. found that niacin 3 to 6 g daily lowered total cholesterol by 16%, but reduced the β/α cholesterol ratio (~LDL/HDL) from 5.0 to 2.8 (44%) in humans, first suggesting niacin's increase of HDL cholesterol (Brown et al., 2009).

1.3.3. Clinical use of niacin

"Niacin" is typically termed as nicotinic acid (NA), even though it can be also defined as "nicotinamide (nicotinic acid amide), nicotinic acid (pyridine-3-carboxylic acid), and derivatives that exhibit the biological activity of nicotinamide". Whether other compounds that are converted to NA or that contain NA, nicotinamide (NM), or their releasable moieties should be referred to as "niacin" depends on the biological effects that are attributed to the compound, the interpretation of the evidence for the rates of uptake and metabolism, and/or the release of the chemical components (apparent bioavailability) that produce biological effects similar to the primary forms of niacin (Table 1.4). According to MacKay et al. (2012) the cholesterol lowering effects of niacin was the first reported by Altschul et al. in 1955. Since then, numerous clinical trials have demonstrated that niacin reduces the risk of coronary artery disease and is the most potent lipid regulating agent for increasing levels of HDL-C (MacKay et al., 2012).

Table 1.4 Supplemental Niacin Forms (MacKay et al., 2012)

Form of niacin	Biological effects	Indications/effectiveness	Flushing effect
Nicotinic acid 	At physiological amounts, the effects of nicotinic acid and nicotinamide are indistinguishable (see nicotinamide) Supraphysiological doses of nicotinic acid decrease total cholesterol, LDL cholesterol, and triglycerides and increase HDL cholesterol	Physiological amounts prevent vitamin B3 deficiency Supraphysiological doses of nicotinic acid are indicated for dyslipidemia, atherosclerosis, and cardiovascular disease	Yes Prostaglandin D2-mediated vasodilatation of small cutaneous blood vessels that result in cutaneous flush
Nicotinamide 	Precursor to nicotinamide adenine dinucleotide phosphate (NADP), which is required for ATP synthesis, oxidation-reduction reactions, and ADP-ribose transfer reactions	Prevents vitamin B3 deficiency No effect on lipid levels in individuals with dyslipidemia	None

Niacin is available in various formulations, including prescription and dietary supplement forms (Alsheikh-Ali et al., 2008).

Of the currently available pharmacologic agents, niacin, used either as monotherapy or in combination with other agents, is the most effective in raising HDL cholesterol levels (Alsheikh-Ali et al., 2008).

Several hypotheses have been studied regarding the basic mechanism of action for the effect of niacin on blood lipids. They include inter alia a relation to the vasodilation, a vitamin effect, a decreased hepatic cholesterol synthesis, an increased cholesterol oxidation, etc. However, the most plausible explanation seems to be inhibition of lipolysis in adipose tissue, resulting in a decreased mobilization of free fatty acids (FFA) (Carlson, 2004).

Niacin has long been known to provide beneficial cholesterol lowering effects for treatment of disorders such as hyperlipidemia. Immediate release niacin formulations typically require multiple daily doses to be effective. Modified release niacin formulations are desirable because they can achieve better control of hyperlipidemia for a longer period of time compared to immediate release formulation. Immediate release formulations often required multiple dosing in a single day. Therefore, modified release niacin formulations are more convenient and result in better patient compliance (US2009/0130208A1, 2009).

Niacin-ER is the most widely used prescription niacin, with release characteristics that are intermediate between immediate- and sustained- release niacin. Immediate- and sustained-release niacin preparations are available without prescription as dietary supplements, whereas niacin-ER is FDA approved for treating dyslipidemia and available only by prescription. Although the safety of niacin-ER has been examined in several clinical trials, the risk for adverse events associated with other niacin formulations is not well defined (Alsheikh-Ali et al., 2008).

Niacin-ER is an intermediate release formulation that balances metabolism along two pathways, a conjugative and an amidation or non-conjugative pathway, responsible for flushing and hepatotoxicity, respectively (Worz and Bottorff, 2003). Flushing may be classified as a nuisance effect which can result in an intense itching or burning sensation of the skin (MacKay et al., 2012).

The patients may be started to the therapy with an extended-release/immediate-release preparation of niacin such as free nicotinic acid. Niacin therapy should be avoided in individuals with liver abnormalities, peptic ulcer disease, and gout. The adage “start low and go slow” is the most robust way to approach free nicotinic acid therapy. Hepatic function and serum lipids data should be evaluated as niacin is titrated. Flushing is a well-known side effect of niacin with both the free nicotinic acid and the extended-release forms, but even so according to MacKay et al., (2012); it is possible to control this symptom by taking niacin with food, avoiding alcohol, and, for those individuals on aspirin therapy, consuming aspirin one-half hour before ingesting niacin. Also patient can ingest the free nicotinic acid form in divided doses with different meals, making it possible to achieve therapeutic goals (MacKay et al., 2012).

U.S. Patent No. 5,268,181, assigned to Upsher-Smith Laboratories Inc., discloses a therapeutic method to treat hyperlipidemia by administering to a human patient a single daily dose of a prolonged release dosage form of niacin, so that nocturnal cholesterol synthesis is effectively suppressed. Also, disclosed is a sustained or controlled release tablet comprising, a water soluble medicament, a hydroxypropyl methyl cellulose having sustaining action, a pharmaceutical binding agent, and a hydrophobic component (US2010/0144800A1, 2010).

WO2007/120385, assigned to Kos Pharmaceuticals, disclosed an extended release matrix formulation capable of being directly compressed into tablets

comprising niacin, a release retarding agent, and other excipients. Hydroxypropyl methyl cellulose having a methoxyl degree of substitution of about 0.20 to about 0.22 is disclosed as the preferable polymer (US2010/0144800A1, 2010).

Niacin, or nicotinic acid, is a potent lipid-modifying agent with broad-spectrum effects. Niacin reduces low-density lipoprotein cholesterol, triglyceride, and lipoprotein (a) levels, while increasing high-density lipoprotein cholesterol. Niacin was the first lipid-lowering agent to significantly reduce cardiovascular events in the Coronary Drug Project, which randomized 3,908 men and demonstrated that 6 years of niacin therapy reduced the risk for nonfatal myocardial infarction and resulted in an 11% reduction in all-cause mortality compared with placebo (Davidson, 2008).

Inositol hexanicotinate minimizes/avoids the flushing effect of niacin. Thus, it's combinations with Niacin-ER have been investigated for their potentially beneficial effects on serum lipids. Research on these compounds in relation to serum lipids has been performed under the assumption that by avoiding the flushing effect the known effects of niacin might be achieved. For Niacin-ER, the potential impacts on serum lipid concentrations are directly related to the release of niacin from the matrix in which it is presented. Ingesting of niacin from Niacin-ER formulations is allied to the specific delivery matrix which is significantly slower than that of niacin, but rapid enough to achieve desired plasma niacin concentrations (Menon, 2007).

According to MacKay et al. (2012), usage of Niacin-ER instead of niacin can reduce the flushing reaction, but Niacin-ER preparations carry a greater risk of liver toxicity, as indicated by the reported cases of hepatotoxicity after unsupervised switching from crystalline niacin to Niacin-ER forms. Furthermore, the Niacin-ER forms may also provide greater pharmacological benefit at any given dose. There may be wide differences in the pharmacokinetics of different Niacin-ER formulations, but the prescription products and some of the Niacin-ER dietary supplements have known and predictable characteristics. In general, the Niacin-ER forms produce lower peak serum concentrations, but these are sustained for longer periods. The data for a direct quantitative comparison of the Niacin-ER and niacin forms are not robust, but compared with the crystalline niacin form, the risk of hepatotoxicity seems approximately twice as high with the Niacin-ER forms. If this is taken into account to help ensure the beneficial effects

and avoid the more serious types of toxicity, the Niacin-ER forms have significant advantage in lowering the tendency to cause flushing effects, which should lead to better acceptance and compliance by the patient (MacKay et al., 2012).

1.3.4. Bioavailability of niacin

The U.S. Food and Drug Administration defines “bioavailability” as “the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action”. Because, in practice, it is uncommon to determine the concentration of the drug at the site of action. Therefore, to describe the bioavailability as “the rate and extent that the active drug is absorbed from a dosage form and becomes available in the systemic circulation” is more common. According to Dalton and Yates (2007), bioavailability term is used for the absorption of all drug products, for example a solution, suspension, tablet, capsule, powder, or elixir from the gastrointestinal tract following oral administration of a dosage form.

Intakes of niacin via intestinal route are more rapid and nearly stoichiometric. Once it is absorbed in the intestine, almost 15–30% of the plasma niacin is bound to protein. The overall dose-response relationships of niacin are well known. Nutritional functions related to NM-containing coenzymes occur at lower levels of intake (15–18 mg/day), while the undesirable vasodilative flushing effect may occur when intakes exceed 50 mg/day. The beneficial effects on serum lipid profiles occur at much higher levels of intake (500–3,000 mg/day). These widely studied impacts on serum lipids are accompanied by low but significant risks of liver and intestinal pathologies (MacKay et al., 2012).

1.3.5. Beneficial effects of niacin

This chemical form fully supports the NM-dependent coenzyme activities. Furthermore, a higher dose of niacin is an effective antihyperlipidemic agent. Niacin not only lowers LDL and very LDL cholesterol and triglycerides, but also raises HDL cholesterol. It is one of the few lipid-altering agents that have been shown to decrease mortality due to heart attacks. High-dose niacin (above 50 mg) is marketed in the United States as a dietary supplement (which may not make drug claims) and also as a prescription drug (which may make approved therapeutic claims). The beneficial lipid lowering effects of both niacin and Niacin-ER are well established, with data showing reduction of total triglyceride

levels by 20-50%, reduction of LDL-C levels by 10-25%, increases of HDL-C levels by 10-30% and reduction of lipoprotein a levels by 10-30%, which includes preferential reduction of the more atherogenic, small, dense LDL-C. Both niacin and Niacin-ER are effective in treating a range of lipid disorders, but neither has become a first line therapy because of the uncomfortable flushing side effect and the potential risk of liver and gastrointestinal side effects (MacKay et al., 2012).

1.3.6. Adverse effects of niacin

Depending on the amount of intake, nicotinic acid has the potential to produce several different side effects. Intakes of 1 g or more per day has the risk of adverse effects while providing pharmacological benefits and requires medical monitoring and supervision. High intakes of niacin produce a vasodilative effect that can result in an intense itching or burning sensation of the skin called “niacin flush” which appears about 30 minutes after intake of Niacin, and 2–4 hours after intake of Niacin-ER form. It is initiated via prostaglandin D_2-mediated vasodilatation of small subcutaneous blood vessels. The vasodilatation is associated with an unpleasant sensation of intense warmth and itching that commonly starts in the face and neck and can proceed down through the body. Some individuals may experience a rash, hypotension, and/or dizziness. . Skin-flushing reactions usually persist over only a few doses until the body develops a natural tolerance. To avoid this flushing the daily dose is administered over several hours in three parts, as the dose is administered liver function tests and tests for uric acid, fasting blood glucose, and lipid levels should be conducted. Each portion may be increased gradually until the desired total dose is achieved. When used as an antihyperlipidemic agent, adverse reactions may require decreased dosage or discontinuation in favor of other agents (MacKay et al., 2012).

1.3.7. Flushing effect of niacin

The recommended dietary intakes of 15–18 mg/day carry no known risk of adverse effects, but the vasodilative flushing effect can be quite pronounced at intakes as low as 50 mg/day and may occur infrequently at intakes as low as 30 mg/day, depending on the circumstances of the intake. Important modifiers of flushing risk include empty or full stomach; dissolved versus crystalline form of niacin; and bolus administration versus intake spread over several hours. The

flushing effect can be managed effectively in most patients, provided they are given proper instructions and the dose is slowly titrated upward to reach therapeutic levels (MacKay et al., 2012).

1.3.8. Gastrointestinal toxicity and hepatotoxicity of niacin

These adverse effects, which can be severe, definitely provide cause for concern about the safety of daily intakes of 1 g niacin or higher, the level at which toxicity usually occurs. Hepatotoxicity is detected most often as increases in serum levels of selected liver enzymes, but the severity of hepatotoxicity can range from elevated liver enzymes to acute liver failure. Although the likelihood of liver toxicity is significant, it is nevertheless low enough that niacin at intakes of up to 2-4 g/day may be used safely and effectively as an antihyperlipidemia drug under medical monitoring and supervision. Although available on the market as a dietary supplement in tablets of 500 mg and 750 mg, niacin should not be used at gram dosages without medical supervision. There is a strong correlation between the minimal adverse effects identified through clinical trials and those suggested by the published anecdotal case reports. Many severe reactions to niacin, especially liver toxicity, have involved ill-advised or uninformed switching from niacin preparations to Niacin-ER formulations without adjusting the dose (MacKay et al., 2012).

Most reported adverse reactions to niacin have occurred with intakes of 2-6 g/day. There are only two anecdotal cases reported in which intake levels below 1 g/day produced an adverse effect: in one, Niacin-ER was administered at 500 mg/day, and in the other, niacin was given at 750 mg/day. The clinical trial of McKenney et al. (1994) investigated two groups of adult subjects, one given niacin and the other Niacin-ER, each containing subgroups that covered a range of doses. These two treatment groups were observed for 6 weeks at dosage levels of 500, 1.000, 1.500, 2.000, and 3.000 mg/day. The data showed no adverse reactions at 500 mg/day for either form of niacin but did show statistically significant effects beginning at 1,000 mg/day (gastrointestinal effects for niacin, and mild liver toxicity for Niacin-ER). The gastrointestinal side effects ranged in severity from nausea to, in the extreme, recurrence of peptic ulcer that had been asymptomatic for 7 years. Quantities of niacin above 1 g should not be self-administered as a dietary supplement but may be safely used under the care and

monitoring of a healthcare provider. Such an application, it should be noted, constitutes a pharmaceutical use, not a dietary supplement use (MacKay et al., 2012).

1.4. Niacin Controlled Release Tablet Formulation

Disadvantages linked to the administration by conventional dosage forms result not only from the brief duration of activity of medicines and the necessity of repeated intakes but also from the lack of tissular specificity of many pharmacological agents. Therefore, it became a necessity to develop new pharmaceutical forms as controlled release systems to overcome these effects. These systems are intended to dispatch or release active drugs at a constant rate directly into the pharmacologically active site. Thus it makes the patient compliance easier (Diarra et al., 2009).

Drug formulations are designed to provide an attractive, stable, and convenient method to use products. Conventional dosage forms may be broadly characterized in order of decreasing dissolution rate as solutions, solid solutions, suspensions, capsules and tablets, coated capsules and tablets, and controlled release formulations (Welling, 2007).

Granulation is frequently preferred technique to improve excipient properties (flowability, compactibility, bulk density, granule strength, dissolution rates, etc.) in solid dosage forms. This process generally includes binder atomization, fluidization, adsorbing and spreading on powder surfaces, particle agglomeration, and so on. In addition, binder adsorbed onto the particle surface can also provide solid bridges between particles. The process and final properties of the granules can be affected by different factors because of the complex granulation procedure. However, the adsorption of the binder solution on solid surfaces, especially at the point of contact between particles or granules, is the key to the granulation process. A suitable amount of binder adsorbed onto the granular surface at the points of contact, as well as their physical properties such as viscosity and flowability, are very important for granule growth (Wen, 2007).

Because of developing and optimizing a formulation of ER tablet is a complex procedure, simultaneous determination of several factors needs to be done. The traditional approach entails studying the influence of the corresponding factors by Changing One Single (or Separate) factor at a Time (COST), whilst keeping the others constant (Barmpalexis et al., 2009).

However, many factors can affect the release profile of the drug like the chemical–physical properties of the drug and excipients, the composition and the amount of the each component's in the formulations, as well as the manufacturing process parameters. Therefore, to obtain desired release profile many complex, expensive and time-consuming pre-formulation studies are often performed. Moreover, although an incremental improvement can be achieved through successive approximation experiments by means of a classic mono-varied approach, it is not possible to establish when and whether the optimal formulation has been actually obtained, nor to identify and quantify possible interaction effects among the variables (Furlanetto et al., 2006).

Systematic experimental design, such as design of experiments (DoE) combined with a regression technique (statistical DoE) has proved to be an efficient alternative approach (Barmpalexis et al., 2011). These experimental design methodologies are powerful, efficient and systematic tools in the design of pharmaceutical dosage forms, allowing a rational study of the influence of formulation and/or processing parameters on the selected responses with a shortening of the experiment time and an improvement in the research and development work. The main objective of the experimental design strategies is to plan experiments in order to obtain the maximum information regarding the considered experimental domain with the lowest number of experiments. Moreover, the multi-varied strategy of experimental design enables the simultaneous evaluation of the influence of the different variables involved in any process, being therefore particularly useful when, as in the case of pre-formulation studies, multiple factors have to be evaluated contemporaneously. In particular, optimization by means of statistical experimental design methodologies has been successfully applied in the development of different kinds of modified release dosage forms, allowing a quick and efficient quantification and prediction of the effects of formulation changes on the considered crucial responses (Furlanetto et al., 2006).

1.5. Experimental Design

Experience shows there is rarely a one-to-one relationship between the number of experiments performed and the information obtained, since the quality of the experiments, in terms of the variations among them, affects their

information content as well as their quality (Eriksson et al., 2008). Conventional methods for developing controlled release drug delivery systems (such as trial and error) require an increased amount of experiments in order to identify an acceptable solution (not always global optimum) (Barmpalexis et al., 2011).

Experimental design is a careful balancing of several features including “power”, generalizability, various forms of “validity”, practicality and cost (Seltman, 2014). It is a systematic technique for designing an experimental process, in which the measurements of responses are evaluated and analyzed using a statistical approach. There are many approaches that can be used to construct such experiments, one of which is the two- level full factorial design (Muhammad et al., 2014). Experimenters utilize fractional factorial designs to study the most important factors or process/design parameters that influence critical quality characteristics (Antony, 2014).

Factorial designs are based on systematic multivariate optimization schemes instead of univariate procedures. In a statistical experimental design the variables, i.e., the factors, are thus varied at the same time, making it possible to distinguish between effects, e.g., responses, caused by a single variable or by interacting variables. Replicating center-points can be added to provide protection against curvature (quadratic effects) caused by interactions in the model and to obtain an independent estimate of the error. It is possible to reduce the number of experiments by focusing on the main effects and to run only a fraction of the complete factorial experiment, a so-called fractional factorial design (Persson et al., 1997).

The relationship in between chemometrics and different disciplines is illustrated in Figure 1.16. On the left are the enabling sciences, mainly quite mathematical and not laboratory based (Brereton, 2003).

Statistical approaches are based on mathematical theory, so statistics falls between mathematics and chemometrics. Computing is important as much of chemometrics relies on software. However, chemometrics is not really computer science. Engineers, especially chemical and process engineers, have an important need for chemometric methods in many areas of the work, and have a quite different perspective from the mainstream chemist (Brereton, 2003).

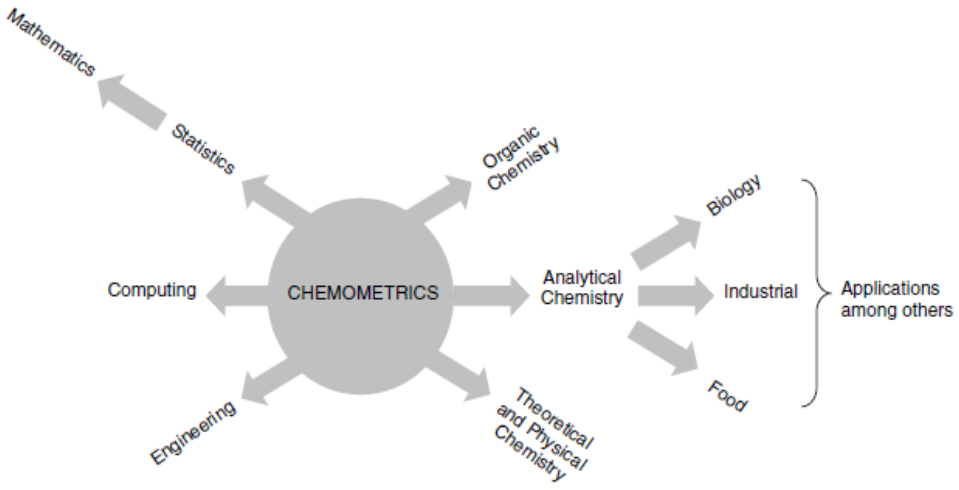


Figure 1.16 How chemometrics relates to other disciplines (Brereton, 2003)

Researchers from different workspace, mostly application scientists on environmental, clinical, food, industrial, biological, physical, organic chemistry etc.), will be interested in chemometrics, as illustrated in Figure 1.17. Many of these will not have a very strong mathematical background, and their main interest is to define the need for data analysis, to design experiments and to interpret results (Brereton, 2003).

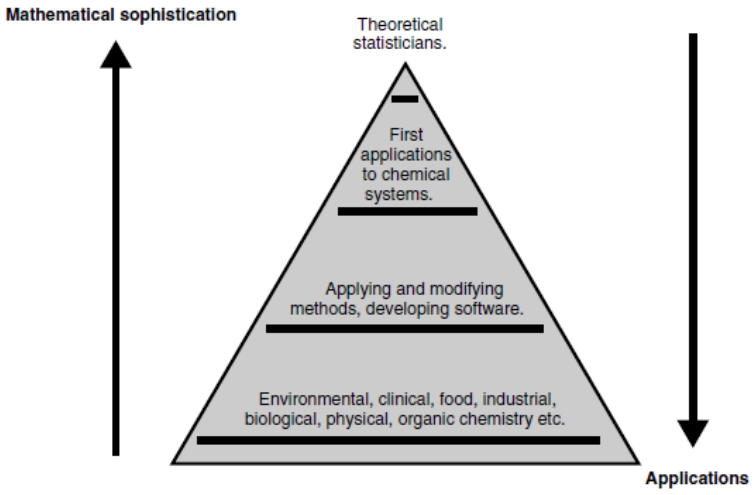


Figure 1.17 People interested in chemometrics (Brereton, 2003)

1.5.1. Types of experimental design

Factorial designs are some of the simplest, often used for screening or when there are a large number of possible factors. Even though they have limitations, still it is the easiest to understand (Brereton, 2003).

Factorial designs are regularly used with two-to-four factors, but with five or more factors the number of experiments required tends to be too demanding. Hence, when many factors are screened, fractional factorial designs constitute a more appealing alternative (Jones, 2008).

Types of experimental design were listed in below.

- Factorial Designs
    - Full Factorial Designs
    - Fractional Factorial Designs
    - Plackett–Burman and Taguchi Designs
    - Partial Factorials at Several Levels: Calibration Designs
- Central Composite or Response Surface Designs
- Mixture Designs

Full factorial designs at two levels are mainly used for screening, that is, to determine the influence of a number of effects on a response, and to eliminate those that are not significant, the next stage being to undertake a more detailed study. Sometimes, where detailed predictions are not required, the information from factorial designs is adequate, at least in situations where the aim is fairly qualitative (e.g. to improve the yield of a reaction rather than obtain a highly accurate rate dependence that is then interpreted in fundamental molecular terms) (Brereton, 2003).

A set of experiments can be proposed to study these two factors, each at two levels, using a two level, two factor experimental design. The number of experiments is given by $N = l^k$, where l is the number of levels, and k the number of factors. When $l = 2$ and $k = 2$ so in this case $N = 4$. For three factors, the number of experiments will equal 8, and so on, provided that the design is performed at two levels only (Brereton, 2003). The following stages are used to construct the design and interpret the results:

- The first step is to choose a high and low level for each factor.
- The next step is to use a standard design. The value of each factor is usually coded as “-” (low) or “+” (high).
- Next, perform the experiments and obtain the response.

- The next step is to analyze the data, by setting up a design matrix.
- Calculate the coefficients. It is not necessary to employ specialist statistical software for this.
- Finally, interpret the coefficients (Brereton, 2003).

The large number of experiments need to be performed can be listed as a weakness of full factorial designs. For example, for a 10 factor design at two levels, 1024 experiments are must be performed, which may be impracticable. These extra experiments do not always result in useful or interesting extra information and so are wasteful of time and resources.

When a three factor, two level design is considered, eight experiments should be performed which are listed in Table 1.5 (the conditions being coded as usual). Figure 1.18 is a symbolic representation of the experiments, often presented on the corners of a cube, whose axes correspond to each factor. The design matrix for all the possible coefficients can be set up as is also illustrated in Table 1.5 and consists of eight possible columns, equal to the number of experiments. How can the number of experiments safely and systematically be reduced? Two level fractional factorial designs are used to reduce the number of experiments by 1/2, 1/4, 1/8 and so on.

Table 1.5 Full factorial designs for three factors together with the design matrix

Experiment No.	Factor 1	Factor 2	Factor 3	Design matrix							
				x_0	x_1	x_2	x_3	x_1x_2	x_1x_3	x_2x_3	$x_1x_2x_3$
1	+	+	+	+	+	+	+	+	+	+	+
2	+	+	−	+	+	+	−	+	−	−	−
3	+	−	+	+	+	−	+	−	+	−	−
4	+	−	−	+	+	−	−	−	−	+	+
5	−	+	+	+	−	+	+	−	−	+	−
6	−	+	−	+	−	+	−	−	+	−	+
7	−	−	+	+	−	−	+	+	−	−	+
8	−	−	−	+	−	−	−	+	+	+	−

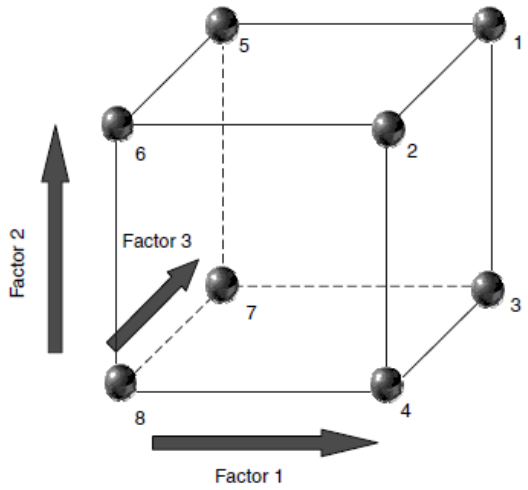


Figure 1.18 Representation of a three factor, two level design

A possible fractional factorial design that enables all factors to be studied was illustrated in Table 1.6. There are a number of important properties:

- Every column in the experimental matrix is different;
- In each column, there are an equal number of "–" and "+" levels;
- For each experiment at level "+" for factor 1, there are equal number of experiments for factors 2 and 3 which are at levels "+" and "–", and the columns are orthogonal as shown in Table 1.6 (Brereton, 2003).

The properties of this design can be understood better by visualization (Figure 1.19): half the experiments have been removed. For the remainder, each face of the cube now corresponds to two rather than four experiments, and every alternate corner corresponds to an experiment. As the number of experiments is reduced, the amount of information is correspondingly reduced.

Table 1.6 Fractional factorial designs for three factor together with the design matrix

Experiment No.	Factor 1	Factor 2	Factor 3	Matrix of effects							
				x_0	x_1	x_2	x_3	x_1x_2	x_1x_3	x_2x_3	$x_1x_2x_3$
1	+	+	+	+	+	+	+	+	+	+	+
2	+	−	−	+	+	−	−	−	−	+	+
3	−	−	+	+	−	−	+	+	−	−	+
4	−	+	−	+	−	+	−	−	+	−	+

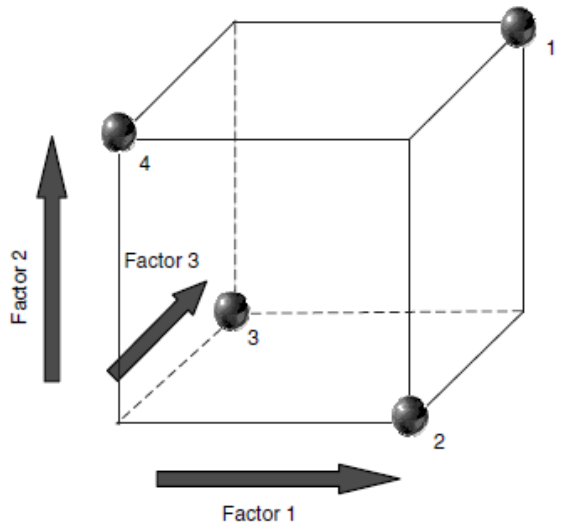


Figure 1.19 Fractional factorial design

There are obvious advantages in two level fractional factorial designs, but these do have some drawbacks: there are no quadratic terms, as the experiments are performed only at two levels; there are no replicates; the number of experiments must be a power of two (Brereton, 2003).

1.6. Importance of Dissolution In Vitro - In Vivo Correlation (IVIVC)

Dissolution testing of drug product became a key development and quality control technique for the pharmaceutical industry recently. Determination of in vitro drug release performance of the drug has always attempted to predict the in vivo performance (Jorgensen and Bhagwat, 1998).

The dissolution test plays an important role both in the development process of a new formulation and as a means of production control. The dissolution tests have been successfully implemented on conventional dosage forms, and generalized monographs described in pharmacopeias are usually sufficient to test any such new formulation. However, when it becomes to controlled release or sustained release dosage forms this is not the case (Khan, 1996).

The term ‘assumed in vivo/in vitro correlation’ has been coined to describe the initial model in which dissolution data is used to develop prototype formulations. In the first stage of formulation evaluation, Dissolution performance testing can supply much valuable information about the risks at the beginning of formulation evaluation such as dose dumping, food effects and the interactions

between the drug substances and excipients in the formulation. Generic products present special formulation challenges. According to Jorgensen and Bhagwat (1998), comparing dissolution test profiles of the innovator product under various conditions to those of test formulations, always keeping in mind the differences between ER systems can be useful while developing a bioequivalent product. (). In vitro - in vivo correlations data are often used during pharmaceutical development for development time saving and optimizing the formulation (Cardot et al., 2007).

Formal guidelines to evaluate sustained or controlled release products do not exist. The current trend is to evaluate each and every sustained or controlled release dosage form on individual basis. The formulation scientists and regulatory authorities face an enormous challenge of generalizing the test conditions for dissolution testing because most individual drug candidates for sustained or controlled release dosage forms and their delivery design possess diverse physicochemical and pharmacokinetic properties requiring specific considerations (Khan, 1996).

An ideal situation, an extended release oral dosage form should be tested in vitro throughout the entire physiological pH (1-7.8) of the GI tract in order to simulate the in vivo conditions (Khan, 1996).

1.7 Aim of the Thesis

In this pharmaceutical development study, the optimum ratio of all ingredients in a compressed tablet aimed to determine via a chemometrical approach.

In the first step, a drug substance was chosen on the basis of literature survey. Then, controlled release tablet formulation trials were performed with this drug substance and ingredients via dry granulation or wet granulation techniques to obtain a similar formulation to the reference product, Niascor 500 mg ER Tablet.

The production of controlled release tablet was taken great attention since the rate of dissolution of active substance within the body may cause some acute toxicity or even death. Therefore, with this project, the desired concentration levels for each component and active substance within the tablets were optimized in such a way that the release rate of active compound can be controlled and its maximum concentration level within the body would not to cause any harmful consequences.

Due to the this fact that production of the dry or wet granulated and compressed tablets with optimum concentration levels for each component and active ingredients were targeted during this project to avoid some non-compliance for patients.

2. EXPERIMENTAL

2.1. Materials

2.1.1. Chemicals and reagents

All reagents were of analytical grade and high quality ultra pure water was used for preparing all solutions. Water for chromatography was purified (18 $M\Omega cm^{-1}$) with a Milli-Q system (Millipore, Bedford, MA, USA).

Acetonitrile for liquid chromatography (ACN) (Batch no: I739530, Merck), methanol for liquid chromatography (MeOH) (Batch no: 1404129004, JT Baker), phosphoric acid (H_3PO_4) (Batch no: K39704073 906, Merck), glacial acetic acid (CH_3COOH) (Batch no: K45695463, Merck), hydrochloric acid (HCl) (Batch no: K45732617, Merck) were used.

Analytical reagent grade potassium dihydrogen phosphate ((KH_2PO_4) (Batch no: AM0444173) and sodium hydroxide pellets (NaOH) (Batch no: B0964298) were from Merck.

Analytical reagent grade hexane-1-sulphonic acid sodium salt (Batch no: 12J100003) was from VWR Prolabo, sodium acetate (Batch no: V16767031M) was from Carlo Erba.

2.1.2. Reference product, active pharmaceutical ingredient (API) and excipients

Nicotinic acid (Niacin) (Batch no: 5937 and 5938) was purchased from DSM Nutritional Products Ltd. (Holland) (Appendix 1) and two different batches of Niascor 500 mg ER Tablet (Lot no: 1803201 and 1803202) from Koçak Farma İlaç ve Kimya Sanayi A.Ş. (Turkey) as commercial reference.

Hydroxypropyl methylcellulose K100 LV (HPMC K100 LV) (Methocel K100 LV, Batch no: DT199337, Dow Chemical Company), hydroxypropyl methylcellulose E15 (HPMC E15) (Methocel E15, Batch no: 2011/1, Dow Chemical Company), hydroxypropyl methylcellulose K 100M CR (HPMC K 100M CR, 9.5-11.5 % hydroxypropyl content, 22-24 % methoxyl content, controlled release grade) (Methocel K 100M CR, Batch no: DT377767, Dow Chemical Company) (Figure 2.1 and Appendix 2), hydroxypropyl methylcellulose

E4M (HPMC E4M) (Methocel E4M, Batch no: 1J31012N12, Dow Chemical Company), lactose monohydrate (Batch no: 679096, DFE Pharma) (Appendix 3), microcrystalline cellulose PH 102 (Avicel PH 102, Batch no: 71248C, FMC Biopolymer) (Appendix 4), magnesium stearate (Batch no: 2015/2, Nikita), carboxymethyl cellulose sodium (Batch no: RY13L148/C35, Ashland), stearic acid (Batch no:0008241191, BASF) (Appendix 5) were used. No: 00 colorless Capsugel hard gelatin capsules (Batch no: 33800621) were used for filling tablets (Appendix 6).

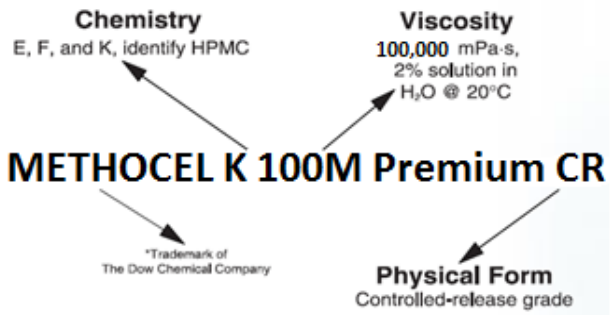


Figure 2.1 Example of nomenclature for HPMC

2.2. Equipments

2.2.1. Equipments for production stage

Mettler Toledo AX205 balance and Mettler Toledo SG 32001 balance, IKA RCT standard magnetic mixer were used to mix and weight processes.

Biocomponents inversina turbula shaker was used for dry granulation shaking processes (Figure 2.2).

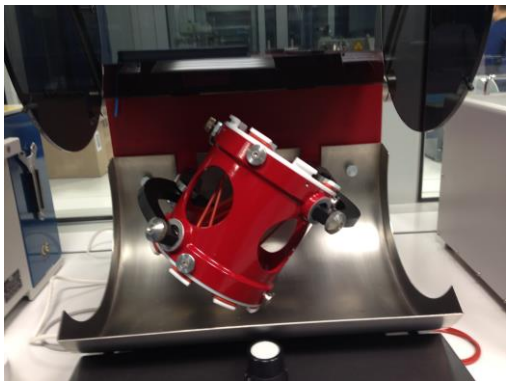


Figure 2.2 Turbula shaker

GEA Ultima Gral10 collette high shear granulator equipped with a peristaltic pump (Figure 2.3), Binder ED240 oven (Figure 2.4), Erweka AR401 cubic mixer (Figure 2.5) and Frewitt TC-Lab dry milling division (Figure 2.6) were used for granulation, drying, mixing and sieving steps respectively during wet granulation processes.

Figure 2.3 High shear granulator

Figure 2.4 Granule drying process

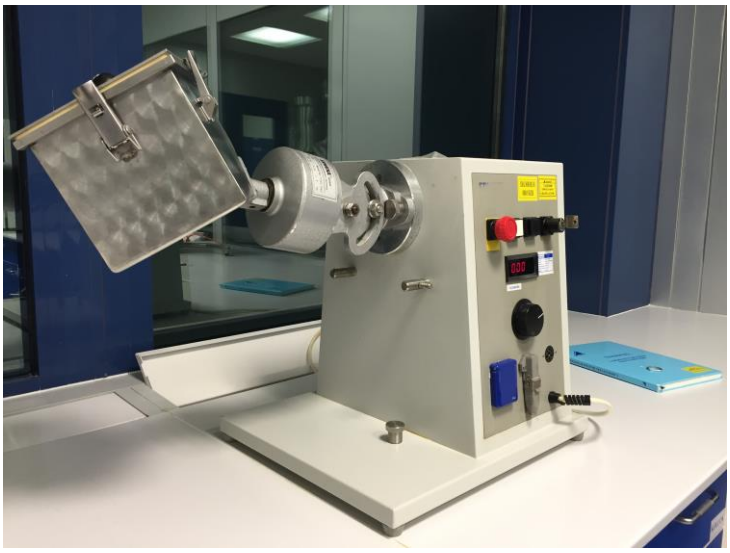


Figure 2.5 Cubic mixer

Figure 2.6 Dry milling division

Tablets of 500 mg weight were prepared by the direct compression and wet granulation methods. The homogenous mixture obtained by final mixing is pressed as each tablet has the determined specifications. The tablets were compressed on 19.0×7.5 mm biconvex punch set using Korch XPI Tablet Press Machine (Figure 2.7 and 2.8).

Figure 2.7 Tablet press machine

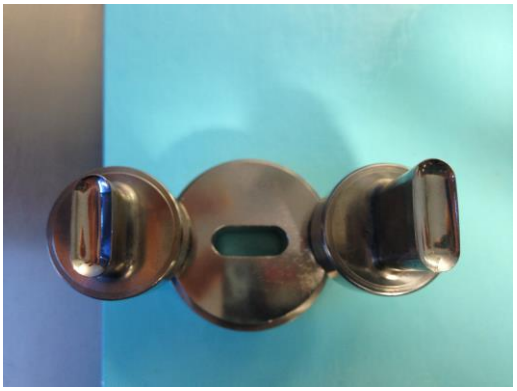


Figure 2.8 Punch set

2.2.2. Equipments for analysis

All batches were evaluated for physical parameters, dissolution rate, assay and uniformity of content. Each batch (at n=6) was subjected to 12 hours dissolution profile in 0.1N HCl, phosphate buffer medium (pH 6.8), acetate buffer

medium (pH 4.5) and distilled water using USP Type I apparatus at 100 rpm. Samples were withdrawn at 1, 2, 4, 5, 6, 8, 10 and 12 hours interval and analyzed for percentage of dissolved drug using UV spectrophotometric method.

Dissolution tests were performed on a Distek Evolution 6100 Dissolution System equipped with an Agilent 8453 UV Spectrophotometer (Figure 2.9).

Figure 2.9 Dissolution-UV spectrophotometer system

Chromatographic Assay and uniformity of dosage unit analyses were performed on an Agilent 1200 Series High Pressure Liquid Chromatograph (HPLC) (Agilent, USA) equipped with a G1311A quarternary Pump, a G1322A degasser, a G1315D photodiode array detector and a G1329A Autosampler as shown Figure 2.10. A 250×4.6 mm i.d. Luna 5 µm C18 (2) (Phenomenex, USA) column was used with Hexane-1-Sulphonic Acid Sodium Salt: Methanol: Acetonitril: Glacial Acetic Acid based eluent. The column temperature and tray temperature were set at 25^{o}C and all samples were filtered through 0.45 µm Macherey Nagel Chromafil PET-45/25 filters. MPower 2 chromatography software allowed controlling data collection and the operation of all components in the system.

Tablet hardness and friability test were conducted using Ewreka TBH 450iC TD hardness testing device and Ewreka TAR120 friability testing device, respectively (Figure 2.11 and 2.12).

Figure 2.10 HPLC system

Figure 2.11 Hardness testing device

Figure 2.12 Friability testing device

2.3. Description of Manufacturing Process and Process Controls

Formulation of reference product (Niascor 500 mg ER Tablet) was given in Table 2.1 (The prospectus of Niascor 500 mg ER Tablet).

Table 2.1 Formulation of Niascor 500 mg E.R. tablet as reference product

Niascor 500 mg ER Tablet	
Function	**Amount** (mg/tablet)
Drug substance *Niacin*	500
Extended release agent	*
Diluent	*
Disintegrant	*
Lubricant	*
Total tablet weight	707 mg

* The amounts and types of excipients weren't given in the prospectus of Niascor 500 mg ER Tablet.

In oral products, HPMC is primarily used as a tablet binder, in film-coating, and as a matrix for use in extended release tablet formulations. High viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80% w/w in tablets and capsules. We used high viscosity HPMC as extended release agent for our formulations with different concentrations.

Lactose is widely used as a filler and diluent in tablets and capsules. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics.

Microcrystalline cellulose is also widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. Microcrystalline cellulose PH 102 was used as a diluent with a concentration of 1.5-4.5 % in our generic tablet formulations. This type of microcrystalline cellulose is preferred, due to its possession of poor flow characteristics and enhancing compressibility characteristics of granules.

Stearic acid was used as the lubricant in the formulation. It prevented the sticking problem of the powder to punches, making an easy tablet compression. Since tablet dissolution rate and crushing strength decreased at the time of blending increased, blending time should be controlled.

Two different manufacturing methods were evaluated, direct compression and wet granulation. The amount of Nicotinic acid (Niacin), in the formulation, flow-ability characteristics and resistance to direct compression of active substance were investigated. According to these investigations, because of easy process of formulation direct compression method was chosen firstly.

The design of experiment (DoE) levels were indicated in Table 2.2 for dry granulation method and 2.16 for wet granulation method.

2.3.1. Method of manufacture for dry granulation

The raw materials; HPMC K100 M, HPMC E15, lactose monohydrate and microcrystalline cellulose PH 102 are transferred to the granulator after weighing, and they are mixed in the same granulator. Nicotinic acid is added into this

mixture, after mixing for about 20 minutes the granules are sieved through 1 μm sieve and then stearic acid is added to this mixture and mixed for more five minutes. The homogenous mixture obtained by final mixing is pressed as each tablet has the determined specifications. Figure 2.13 shows the process flow diagram of dry granulation method.

Before formulation trials via dry granulation fractional factorial design parameters were decided (Table 2.2). The decided formulations for extended release tablet, called 01N14, 02N14, 03N14, and 04N14, were shown in Table 2.3. In the first formulation (01N14), Factor 1 (HPMC K100M amount) and Factor 2 (HPMC E15 amount) were kept in high level while Factor 3 (Avicel PH 102 amount) was in low level. In the second one (02N14), Factor 1 and Factor 3 were kept in high level while Factor 2 was in low level. In the third trial (03N14), Factor 2 and Factor 3 were kept in high level while HPMC K100M amount (Factor 1) was in low level. The last formulation was designed with low level of all factors. In addition, the unit formula compositions and planned batch size of Niacin 500 mg ER Tablets, which shows the size of planned production depending on relationships between quantity of active pharmaceutical ingredient and excipients, via dry granulation were shown in Table 2.4-7.

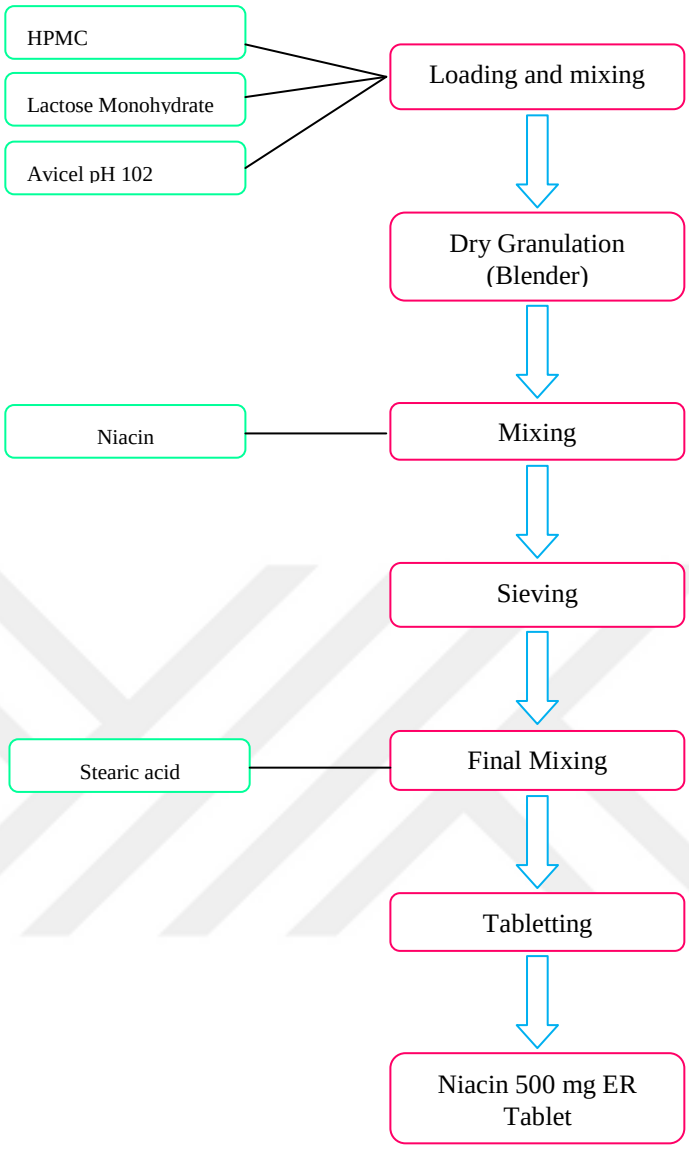


Figure 2.13 Process flow diagram of dry granulation method

Table 2.2 Fractional factorial design for tablet formulation via dry granulation

Experiment No	**Factor 1** (HPMC K100M)	**Factor 2** (HPMC E15)	**Factor 3** (Avicel PH 102)
1 (01N14)	+	+	-
2 (02N14)	+	-	+
3 (03N14)	-	+	+
4 (04N14)	-	-	-

Table 2.3 Unit formulas for fractional factorial design of tablet formulation via dry granulation

	01N14	**02N14**	**03N14**	**04N14**
	1. Formulation	**2. Formulation**	**3. Formulation**	**4. Formulation**
	Amount (mg/tablet)	**Amount (mg/tablet)**	**Amount (mg/tablet)**	**Amount (mg/tablet)**
Niacin	500.0	500.0	500.0	500.0
HPMC K100M	130.0	130.0	120.0	120.0
HPMC E15	25.0	15.0	25.0	15.0
Lactose Monohydrate	31.5	31.5	31.5	31.5
Avicel PH 102	20.0	30.0	30.0	20.0
Stearic acid	8.67	8.67	8.67	8.67
Tablet weight	715	715	715	695
Hardness	100 Newton	100 Newton	100 Newton	100 Newton

Table 2.4 Unit formula of Niacin 500 mg ER Tablet-capsule (01N14)

	1. Formulation (01N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100 M	130.0	6500.0	6.50
HPMC E15	25.0	1250.0	1.25
Lactose Monohydrate	31.5	1575.0	1.575
Avicel PH 102	20.0	1000.0	1.00
Stearic acid	8.667	433.35	0.433
Tablet weight	715	715	715
Hardness	100 Newton	100 Newton	100 Newton

Table 2.5 Unit formula of Niacin 500 mg ER Tablet-capsule (02N14)

	2. Formulation (02N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100 M	130.0	6500.0	6.50
HPMC E15	15.0	750.0	0.75
Lactose Monohydrate	31.5	1575.0	1.575
Avicel PH 102	30.0	1500.0	1.50
Stearic acid	8.667	433.35	0.433
Tablet weight	715	715	715
Hardness	100 Newton	100 Newton	100 Newton

Table 2.6 Unit formula of Niacin 500 mg ER Tablet-capsule (03N14)

	3. Formulation (03N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100 M	120.0	6000.0	6.00
HPMC E15	25.0	1250.0	1.25
Lactose Monohydrate	31.5	1575.0	1.575
Avicel PH 102	30.0	1500.0	1.50
Stearic acid	8.667	433.35	0.433
Tablet weight	715	715	715
Hardness	100 Newton	100 Newton	100 Newton

Table 2.7 Unit formula of Niacin 500 mg ER Tablet-capsule (04N14)

	4. Formulation (04N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100 M	120.0	6000.0	6.00
HPMC E15	15.0	750.0	0.75
Lactose Monohydrate	31.5	1575.0	1.575
Avicel PH 102	20.0	1000.0	1.00
Stearic acid	8.667	433.35	0.433
Tablet weight	695	695	695
Hardness	100 Newton	100 Newton	100 Newton

These four formulation trials showed faster dissolution rate compared to reference product, so it is decided to change the type and increase the amount of HPMC (Table 2.8).

Table 2.8 Unit formula of Niacin 500 mg ER Tablet-capsule (05N14)

	5. Formulation (05N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100 M CR	150.0	7500.0	7.50
Lactose Monohydrate	33.0	1650.0	1.65
Avicel PH 102	18.0	900.0	0.90
Stearic acid	9.0	450.0	0.45
Tablet weight	710	710	710
Hardness	100 Newton	100 Newton	100 Newton

Because of changing HPMC type and amount didn't decrease the dissolution rate different processes for dry granulation formulations were investigated with the same formulation. Granular compaction is defined as an increase of the bulk density of a granular medium submitted to mechanical perturbation. Compaction

can be conducted under two processes; either a large tablet (slug) is produced in a heavy duty tabletting press or the powder is squeezed between two counter-rotating rollers to produce a continuous sheet or ribbon of materials (roller compactor). In this formulation after production step of granules, slugging process was used (Table 2.9).

Table 2.9 Unit formula of Niacin 500 mg ER Tablet-capsule (06N14) via slugging process

	6. Formulation (06N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100 M CR	150.0	7500.0	7.50
Lactose Monohydrate	33.0	1650.0	1.65
Avicel PH 102	18.0	900.0	0.90
Stearic acid	9.0	450.0	0.45
Tablet weight	710	710	710
Hardness	100 Newton	100 Newton	100 Newton

2.3.2. Method of manufacture for wet granulation

The raw materials; Nicotinic acid (Niacin), lactose monohydrate and microcrystalline cellulose PH 102 (Avicel PH 102) are transferred to the granulator after weighing, and they are mixed in the same granulator. The mixture is granulated by addition of purified water to the granulator. After sieving by a 1 μm sieve, the granule is transferred to plate for drying at 50^{o}C in drying oven. HPMC K100 M CR is added to granule and mixed for 10-15 minutes. Stearic acid is added to this mixture and mixed for five minutes. Figure 2.14 shows the process flow diagram of wet granulation method.

The homogenous mixture obtained by final mixing is pressed as each tablet has the determined specifications.

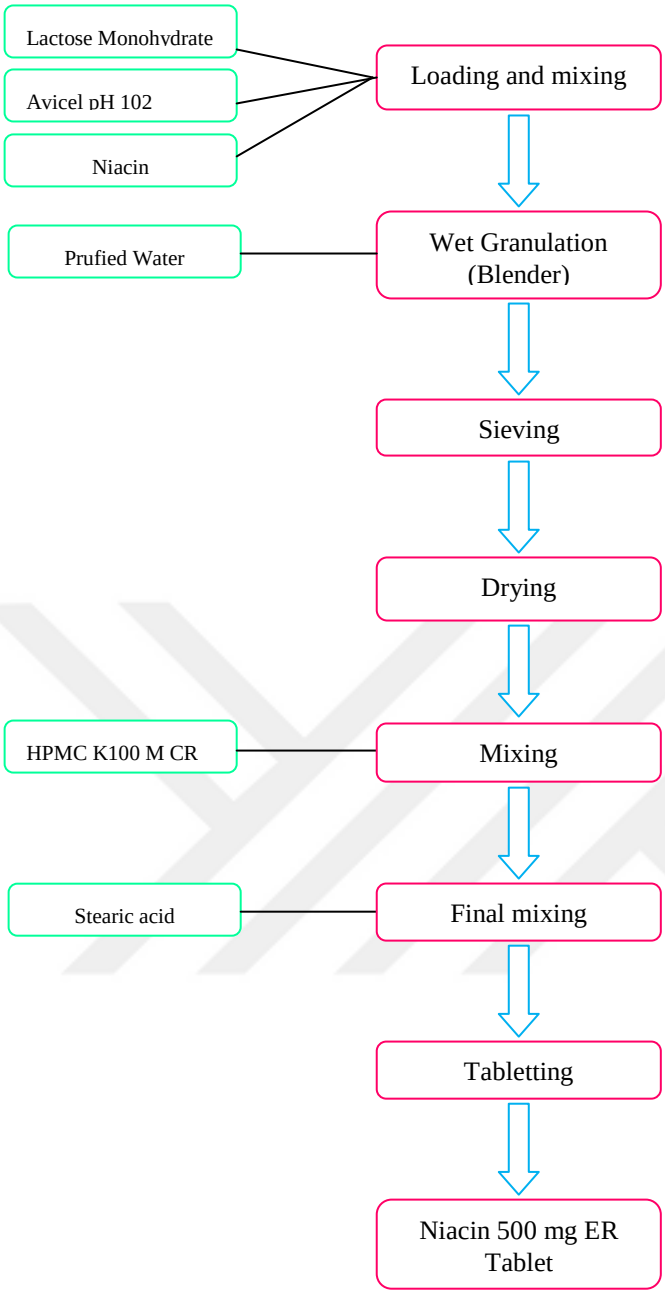


Figure 2.14 Process flow diagram of wet granulation method

Unit formula compositions of Niacin 500 mg ER Tablets production via wet granulation were shown in Table 2.10-2.15.

Table 2.10 Unit formula of Niacin 500 mg ER Tablet-capsule (07N14)

	7. Formulation (07N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100 M CR	135.0	6750.0	6.75
HPMC K100 LV	5.0	250	0.25
Lactose Monohydrate	31.3	1565.0	1.565
Avicel PH 102	27.0	1350	1.35
Stearic acid	8.7	435	0.435
Distilled water	~110	~550	~0.55
Tablet weight	707	707	707
Hardness	100 Newton	100 Newton	100 Newton

Table 2.11 Unit formula of Niacin 500 mg ER Tablet-capsule (08N14)

	8. Formulation (08N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100 M CR	150.0	7500.0	7.50
HPMC K100 LV	5.0	250.0	0.25
Lactose Monohydrate	25.0	1250.0	1.25
Avicel PH 102	20.0	1000.0	1.00
Stearic acid	5.0	250.0	0.25
Tablet weight	705	705	705
Distilled water	~48	~2400	~2.4
Hardness	100 Newton	100 Newton	100 Newton

Table 2.12 Unit formula of Niacin 500 mg ER Tablet-capsule (09N14)

	9. Formulation (09N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
Carboxymethyl Cellulose Sodium	45.0	2250.0	2.25
HPMC K100 LV (7HF)	10.0	500.0	0.50
HPMC K100 M CR	150.0	7500.0	7.50
Magnesium Stearate	3.0	150.0	0.15
Tablet weight	708	708	708
Distilled water	~140	~7000	~7
Hardness	100 Newton	100 Newton	100 Newton

Table 2.13 Unit formula of Niacin 500 mg ER Tablet-capsule (10N14)

	10. Formulation (10N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100 M CR	140.0	7000.0	7.00
HPMC E4M	100.0	5000.0	5.00
Lactose Monohydrate	25.0	1250.0	1.25
Avicel PH 102	20.0	1000.0	1.00
Stearic acid	5.0	250.0	0.25
Tablet weight	790	790	790
Distilled water	~48	~2400	~2.4
Hardness	100 Newton	100 Newton	100 Newton

Table 2.14 Unit formula of Niacin 500 mg ER Tablet-capsule (11N14)

	11. Formulation (11N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100M CR	250.0	12500.0	12.50
Lactose Monohydrate	25.0	1250.0	1.25
Avicel PH 102	20.0	1000.0	1.00
Stearic acid	5.0	250.0	0.25
Tablet weight	800	800	800
Distilled water	~140	~7000	~7
Hardness	100 Newton	100 Newton	100 Newton

Table 2.15 Unit formula of Niacin 500 mg ER Tablet-capsule (12N14)

	12. Formulation (12N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100M CR	250.0	12500.0	12.50
Lactose Monohydrate	25.0	1250.0	1.25
Avicel PH 102	20.0	1000.0	1.00
Stearic acid	5.0	250.0	0.25
Tablet weight	800	800	800
Distilled water	~140	~7000	~7
Hardness	100 Newton	100 Newton	100 Newton

After formulation trials via wet granulation and dry granulation the results showed that wet granulation technique was more suitable for our extended release tablet formulation. So it is decided to perform fractional factorial design using this technique (Table 2.16 and 2.121).

Table 2.16 Fractional factorial design for tablet formulation via wet granulation

Experiment No	**Factor 1** (HPMC K100M CR)	**Factor 2** (Lactose Monohydrate)	**Factor 3** (Avicel PH 102)
1 (13N14)	+	-	+
2 (14N14)	-	+	+
3 (15N14)	-	-	-
4 (16N14)	+	+	-

Table 2.17 Unit formulas for fractional factorial design of tablet formulation via wet granulation

	13N14	**14N14**	**15N14**	**16N14**
	1. Formulation	**2. Formulation**	**3. Formulation**	**4. Formulation**
	Amount (mg/tablet)	**Amount (mg/tablet)**	**Amount (mg/tablet)**	**Amount (mg/tablet)**
Niacin	500.0	500.0	500.0	500.0
HPMC K100M CR	140.0	100.0	100.0	140.0
Lactose Monohydrate	25.0	35.0	25.0	35.0
Avicel PH 102	15.0	15.0	13.0	13.0
Stearic acid	5.0	5.0	5.0	5.0
Tablet weight	685	655	643	693
Distilled water	~200	~200	~200	~200
Hardness	100 Newton	100 Newton	100 Newton	100 Newton

Table 2.18 Unit formula of Niacin 500 mg ER Tablet-capsule (13N14)

	13. Formulation (13N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100M CR	140.0	7000.0	7.00
Lactose Monohydrate	25.0	1250.0	1.25
Avicel PH 102	15.0	750.0	0.75
Stearic acid	5.0	250.0	0.25
Tablet weight	685	685	685
Distilled water	~200	~10000	~10
Hardness	100 Newton	100 Newton	100 Newton

Table 2.19 Unit formula of Niacin 500 mg ER Tablet-capsule (14N14)

	14. Formulation (14N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100M CR	100.0	5000.0	5.00
Lactose Monohydrate	35.0	1750.0	1.75
Avicel PH 102	15.0	750.0	0.75
Stearic acid	5.0	250.0	0.25
Tablet weight	655.0	655.0	655.0
Distilled water	~200	~10000	~10
Hardness	100 Newton	100 Newton	100 Newton

Table 2.20 Unit formula of Niacin 500 mg ER Tablet-capsule (15N14)

	15. Formulation (15N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100M CR	100.0	5000.0	5.00
Lactose Monohydrate	25.0	1250.0	1.25
Avicel PH 102	13.0	650.0	0.65
Stearic acid	5.0	250.0	0.25
Tablet weight	643	643	643
Distilled water	~200	~10000	~10
Hardness	100 Newton	100 Newton	100 Newton

Table 2.21 Unit formula of Niacin 500 mg ER Tablet-capsule (16N14)

	16. Formulation (16N14)	**Batch Size**	**Batch Size**
	Amount (mg/tablet)	**mg**	**g**
Niacin	500.0	25000.0	25.00
HPMC K100M CR	140.0	7000.0	7.00
Lactose Monohydrate	35.0	1750.0	1.75
Avicel PH 102	13.0	650.0	0.65
Stearic acid	5.0	250.0	0.25
Tablet weight	693	693	693
Distilled water	~200	~10000	~10
Hardness	100 Newton	100 Newton	100 Newton

2.3.3. Tabletting process

Niacin 500 mg ER Tablets were pressed with Korch tabletting machine. The flowability of the granules was good enough for tabletting. To prove the performance qualification study of the tablet press machine, the pressing operation was performed in minimum and maximum rate and the operation interval were validated.

2.4. Tests for Niacin ER Tablet-Capsule

After each formulation, tablets were evaluated according to test below and the result should be within the limits (Table 2.22).

1. Appearance
2. Average weight
3. Hardness
4. Friability
5. Loss on Drying
6. Assay
7. Uniformity of Dosage Units
8. Dissolution

Table 2.22 Specifications of Niacin ER Tablet-Capsule

TESTS	SPECIFICATIONS
Appearance	White colored, biconvex, oblong tablets in No: 00 colorless hard gelatin capsules
Average weight (AW)	Tablet weight (mg) ± 5 %
Hardness	Min. 80N
Friability	Maximum 1.0%
Loss on Drying	Maximum 1.5%
Assay	500 mg ± 5 % / Tablet (450 – 550 mg / Tablet)
Uniformity of Dosage Units (Uniformity of content)	85% - 115%
Dissolution Profile	10 % - 30% (at the end of 1 hour) 45 % - 70% (at the end of 5 hours) 80 % - 110% (at the end of 10 hours)

2.4.1. Appearance

Test result: White colored, biconvex, oblong tablets in No: 00 colorless hard gelatin capsules

Test procedure: 20 tablet-capsules are inspected on a white surface by visual determination.

2.4.2. Average weight (AW)

Limit: Tablet weight (mg) ± 5.0 % (707 mg ± 5.0 % for reference product)

10 doses were individually weighed and the average weight was calculated.

2.4.3. Hardness (Ph. Eur. 2.9.8)

Limit: Minimum 80 N

According to EP 2.9.8 this test is intended to determine, under defined conditions, the resistance to crushing of tablets, measured by the force needed to disrupt them by crushing.

There are two jaws in the hardness apparatus which placed horizontally and facing each other. One of these jaws is fixed while the other one is movable. Tablet is placed between these two jaws that crush the tablet. The machine measures the force applied to the tablet and detects when it fractures. Force applied to the tablets at the breaking point is the hardness value of tablets.

10 tablets were placed between the jaws and applied forces were measured for breaking of the tablets.

2.4.4. Friability (Ph. Eur. 2.9.7)

Limit: Maximum 1.0%

According to Ph. Eur. 2.9.7, for tablets weighing up to 0.65 g each, a sample of twenty tablets is taken; for tablets weighing more than 0.65 g each, ten tablets are taken. The tablets are placed on a sieve and removed any loose dust with the aid of air pressure or a soft brush. The tablet samples are accurately weighed, and placed in the drum. The drum is rotated 100 times (at 25 rpm for 4 minutes), and the tablets are removed. Any loose dust is removed from the tablets as before, and accurately reweighed. The friability is expressed as the loss of mass and it is calculated as a percentage of the initial mass.

10 tablets were weighted, placed in the drum and rotated 100 times. Any loose dust was removed from the tablets, and accurately reweighed. Then friability per cent was calculated;

$$\text{Friability (\%):} \quad \left[\frac{\text{Initial weight (mg)} - \text{Final weight (mg)}}{\text{Initial weight (mg)}}\right] \text{x}\, 100$$

2.4.5. Loss on drying

Limits: Maximum 1.5 %

Test procedure: Karl Fischer Titration

The water content of ~200 mg sample was determined by Karl Fischer titration.

2.4.6. Dimensions of tablet

Limits: Width : 6.95 ± 0.1 mm
Length : 17.45 ± 0.1 mm
Thickness : 5.95 ± 0.2 mm

Test procedure: For width measurements, a tablet was placed between pincers of a compass and width was recorded. For length measurements, a tablet was placed between pincers of a compass and length was recorded. For thickness measurements, a tablet was placed between pincers of a compass and thickness was recorded. Obtained values should be consistent with the specifications.

2.4.7. Assay determination

Limits: 500 mg (450 – 550 mg) Niacin/tablet
(90 % – 110 %)

Chromatographic conditions for niacin determination of the tablets were summarized in Table 2.23.

Table 2.23 Chromatographic conditions for assay determination

Chromatographic Method	**:**	Isocratic
Equipment	**:**	HPLC
Detector	**:**	UV, 262 nm
Injection volume	**:**	25 µL
Flow rate	**:**	1 mL/min
Column	**:**	Luna 5 µm C18 (2) 250 x 4.6 mm
Column temperature	**:**	25°C
Tray temperature	**:**	25°C
Run time	**:**	6 min.
Mobile phase solution	**:**	0.005 M Hexane-1-Sulphonic Acid Sodium Salt : Methanol : Acetonitril : Glacial Acetic Acid (78 : 14 : 7 : 1, v/v/v/v)

Preparation of diluent: Ultra pure water was used as diluent.

Preparation of mobile phase solution: A mixture of 0.005 M hexane-1-sulphonic acid sodium salt: methanol: acetonitrile: glacial acetic acid (78:14:7:1, v/v/v/v) was prepared and stirred for 10 minutes with a magnetic stirrer. Prepared solution was filtered through 0.2 µm membrane filter and degassed.

Preparation of stock standard solution: Approximately 50.0 mg of Niacin working standard was weighted into a 100 mL volumetric flask. ~50 mL of diluent was added. This solution was sonicated to dissolve for 30 minutes at 80°C, allowed to cool to room temperature, completed to volume with diluent and stirred. (C_{Niacin} = 0.50 mg/mL)

Preparation of standard solution: 1.0 mL of Niacin stock standard solution was transferred into a 10 mL volumetric flask with pipette, completed to volume with diluent and stirred. The solution was filtered through 0.45 µm Chromafil PET-45/25 filter into a HPLC sample vial. (C_{Niacin} = 0.05 mg/mL)

One more standard solution was prepared at same concentration. This solution was used as control standard.

Preparation of test solution: Accurately weighed 10 tablets were pulverized and equivalent to one tablet (707.0 mg) was transferred into 500 mL of volumetric flask. ~400 mL diluent was added. This solution was sonicated to dissolve for 30 minutes at 80°C and allowed to cool to room temperature, completed to volume with diluents and mixed. 5 mL of this solution was transferred into 100 mL of volumetric flask and completed to volume with diluent and mixed. Prepared sample solution was filtered through 0.45 µm Chromafil PET-45/25 filter into a HPLC sample vial. (C_{Niacin} = 0.05 mg/mL)

One more test solution was prepared in the same manner.

Procedure

1. 6 replicate injections from standard solution were performed. RSD of area due to 6 replicate injections of standard solution should not be more than 2.0 % (RSD ≤ % 2.0)
2. Duplicate injections were performed from control standard.

3. Single injection was performed from each of test solutions.

4. The percentages of control standard solution were calculated as test solutions. Results should be between 98.0 – 102.0 %.

System suitability: The percent relative standard deviation (RSD %) of each replicates should be less than 2.0 %.

Calculation:

The concentrations of standard solutions were calculated using the following formula:

C_{std} : $W_{std} \times P / DV$

C_{std} : Concentration of standard solution (mg/mL)

W_{std} : Weight of Niacin in standard solution (mg)

P : Percent potency value of Niacin working standard

DV : Total dilution volume (mL)

Calculation of the amount of drug substance in one tablet;

$$\text{Niacin in mg per tablet} = \left[\frac{A_T}{A_{Std}}\right] x \left[\frac{C_{Std}}{(W_T/500) x\ 5/100}\right] x\ W_{Avr}$$

A_T : Peak area of Niacin in the chromatogram obtained with test solution

A_{Std} : Average peak area of Niacin n in the chromatogram obtained with standard solution

C_{Std} : Concentration of standard solution (mg/mL)

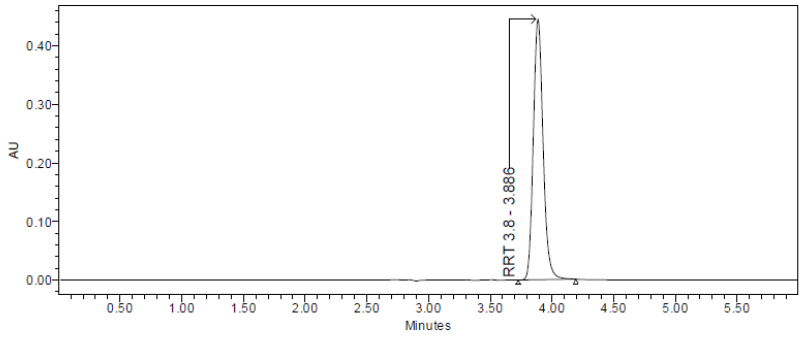
W_T : Tablet powder amount used in test preparation (mg)

W_{Avr} : Average weight of tablets (mg)

Figure 2.15 shows the chromatogram of an assay sample analyzed according to above procedure.

SAMPLE INFORMATION

Sample Name	MT_1		
Sample Set Name	DENEME_MT		
Sample Type	Unknown	Date Acquired	11/23/2012 5:28:08 PM EET
Vial	3	Acq. Method Set	MT
Injection #	1	Date Processed	11/26/2012 8:53:12 AM EET
Injection Volume	25.0 ul	Processing Meth.	MT_3
Proc. Chnl. Descr.	DAD VL AU Ch 1 Sample 262,	Channel Name	DAD VL AU Ch1
Dilution	3549160.00	Sample Weight	353.82
Processed By	evrimorhan/RD_USER	# of Results stored	1
Acquired By	evrimorhan	Int type	BB
Acquisition server	Pcag010	System Name	AG_HP_10
Sampling Rate	2.50 per sec	Processing Node	Pcag010
Equation	Y = 5.13e+007 X	R2	1.000000
Result #	1		



	Peak Name	RT	Area	Height (µV)	% Area	Amount
1	RRT 3.8	3.89	2449884	444947	100.0	478.659

Figure 2.15 Chromatogram of assay analysis

2.4.8. Uniformity of dosage units (Ph. Eur. 2.9.40)

Limit: Complies with European Pharmacopeia (Ph. Eur.) 2.9.40 (Table 2.24)

Test procedure: Isocratic, reversed phase HPLC method was used in the Uniformity of dosage units test for "tablet step" of Niacin 500 mg ER Tablets as showed Table 2.23).

Diluent, mobile phase solution, stock standard solution and standard solution were prepared as mentioned 2.47. Assay determination section.

Test solution preparation: 10 tablets were individually weighted and each of them transferred to 500 mL volumetric flasks, separately. ~400 mL diluent was added. The solution was sonicated to dissolve for 30 minutes at 80°C, allowed the solution to cool to room temperature, completed to volume with diluents and mixed. 5 mL of this solution was transferred into a 100 mL volumetric flask and completed to volume with diluent and mixed. The solution was filtered through 0.45 µm Chromafil PET-45/25 filter into a HPLC sample vial. (C_{Niacin} = 0.05 mg/mL)

The same HPLC injection procedures, system suitability requirements were used as told assay determination.

Calculation:

The same calculation formula for standard solutions concentrations was used as told assay determination.

Calculation of the amount of drug substance in one tablet;

$$\text{Niacin (\%)} = \left[\frac{A_T}{A_{Std}}\right] x \left[\frac{C_{Std}}{N/V_{Test}}\right] x \frac{100}{L}$$

A_T : Peak area of Niacin in the chromatogram obtained with test solution

A_{Std} : Average peak area of Niacin n in the chromatogram obtained with standard solution

C_{Std} : Concentration of standard solution (mg/mL)

V_{Test} : Volume of test solution (mL)

N : Number of tablets transferred into a volumetric flask

L : Label amount (mg)

The acceptance value was calculated using the formula:

$$\text{Acceptance value (AV)} = |M - \overline{X}| + ks$$

in which the terms were as defined in Table 2.24.

According to USP <905> the steps below were followed in the calculation of AV:

1. Value of T has to be known in order to determine the value of M
   T = Target drug substance percentage at time of manufacture; in the absence of excess dose T= 100, if there is excess dose of 5 % then, T= 105.
2. $\overline{X}$, mean of individual contents (x_1, x_2,..., x_n) is determined, expressed as a percentage of the label claim.

3. The value of M is determined using Table 2.24 which matches to value of $\overline{X}$ and value of T.
4. The acceptability constant "k" is determined, according to sample size (number of dosage units in a sample) using Table 2.24.
5. "s" is sample standard deviation (SD) of (x_1, x_2,...x_n).
6. AV is calculated, using the determined values of M, $\overline{X}$, k and s.
7. If AV ≤ 15 (L1); the requirements for dosage uniformity are met.
8. If AV > 15 (L1), the next 20 dosage units are tested and the acceptance value is calculated again as described above using the test results of 30 dosage units.

- AV ≤ L1 and
- $(1-L2*0.01)M \leq x_i \leq (1+L2*0.01)M$

unless otherwise specified, if L1=15 and L2=25; the requirements for dosage uniformity are met.

Table 2.24 Calculation of Acceptance Value (AV) (Ph.Eur. 2.9.40)

Variable	Definition	Conditions	Value
$\overline{X}$	Mean of individual contents (x_1, x_2,..., x_n), expressed as a percentage of the label claim		
x_1, x_2,...x_n	Individual contents of the dosage units tested, expressed as a percentage of the label claim		
n	Sample size (number of dosage units in a sample)		
k	Acceptability constant	If n=10	2.4
		If n=30	2.0
s	Standard deviation		$\left[\frac{\sum_{i=1}^{n}(x_i - \overline{X})^2}{n-1}\right]^{1/2}$
RSD	Relative standard deviation		$\frac{100s}{\overline{X}}$
M (case 1) If T≤ 101.5	Reference value	If 98.5% ≤ $\overline{X}$ ≤ 101.5%	M = $\overline{X}$ (AV = ks)
		If $\overline{X}$ < 98.5%	M = 98.5 % (AV = 98.5 - $\overline{X}$ +ks)
		If $\overline{X}$ >101.5%	M =101.5 % (AV = $\overline{X}$ -101.5+ks)
M (case 2) If T>101.5	Reference value	If 98.5% ≤ $\overline{X}$ ≤ T	M = $\overline{X}$ (AV = ks)
		If $\overline{X}$ <98.5%	M = 98.5 % (AV = 98.5 - $\overline{X}$ +ks)
		If $\overline{X}$ > T	M = T % (AV= $\overline{X}$ -T +ks)
Acceptance value (AV)			General formula: $\lvert M - \overline{X} \rvert$ + ks (Calculations are specified above for Case 1 & Case 2)
L1	Maximum allowed acceptance value		(unless otherwise specified) L1= 15.0
L2	Maximum allowed range for deviation of each dosage unit tested from the calculated value of M	(1-L2*0.01)M≤ X ≤ (1+L2*0.01)M based on L2 value of 25.0 (L2 =25); (0.75M)≤ X ≤ (1.25M)	(unless otherwise specified) L2=25.0
T	Target drug substance percentage at time of manufacture; in the absence of excess dose T= 100, if there is excess dose e.g. 5 % then, T= 105.		

2.4.9. Dissolution profile

Limit: Min. 10 % - 30% (at the end of 1 hour)
Min. 45 % - 70% (at the end of 5 hours)
Min. 80 % - 110% (at the end of 10 hours)

Test procedure: UV Spectrophotometry method was used in dissolution profile test for Niacin 500 mg ER Tablet-Capsules. Spectrophotometric conditions and dissolution test parameters were shown in Table 2.25 and 2.26.

Table 2.25 Spectrophotometry conditions

Equipment	UV
Wavelength	262 nm
Calibration curve type	Linear

Table 2.26 Multi-point dissolution profile test conditions

Equipment	Distek Evolution 6100 Dissolution instrument and UV Spectrophotometer 8300
Apparatus	Paddle with sinker
Rotation speed	100 rpm
Temperature	37 °C ± 0.5 °C
Dissolution Mediums	900 mL, 0.1 N HCl
	900 mL, pH:4.5 acetate buffer
	900 mL, pH:6.8 phosphate buffer
	900 mL, distilled water
Time	12 hours

Preparation of dissolution mediums:

Preparation of 0.1 N Hydrochloric acid solution (0.1 N HCl, pH 1.2): 100 mL of 2 N Hydrochloric acid solution was transferred into a 2000 mL volumetric flask and completed to volume with distilled water.

Preparation of acetate buffer solution (pH 4.5): 29.93 g sodium acetate trihydrate and 15.0 mL acetic acid were weighted into a 10 L volumetric flask, dissolved with about 9 L distilled water. If necessary, pH of the solution was adjusted to 4.50 ± 0.05 with acetic acid or sodium hydroxide solution (NaOH) and completed the volume to 10 L with distilled water.

Preparation of phosphate buffer solution (pH 6.8): 68.0 g potassium dihydrogen phosphate (KH_2PO_4) and 8.96 g sodium hydroxide were weighted into 10 L volumetric flask, dissolved with about 9 L distilled water. If necessary, pH of the solution was adjusted to 6.80 ± 0.05 with phosphoric acid (H_3PO_4) or sodium hydroxide (NaOH) and completed the volume to 10 L with distilled water.

Preparation of standard solution: Approximately 27.8 mg of Niacin working standard was weighted into a 50 mL volumetric flask. Sufficient amount of dissolution medium (0.1 N HCl) was added. The solution was sonicated to dissolve for 30 minutes at 80^{o}C, allowed to cool to room temperature, completed to volume with dissolution medium and stirred. This solution was transferred to a beaker, withdrawn by an auto sampling probe with a 45 µm filter and analyzed. (C_{Niacin} = 0.56 mg/mL)

Preparation of test solution: 6 tablets were individually weighted and each of these tablets were transferred into 6 separate vessels of the dissolution testing apparatus filled with 900 mL of dissolution medium warmed to 37 ºC ± 0.5 ºC. Sample solutions were withdrawn from each of the vessels at the end of 1, 2, 4, 5 and every 2 hours thereafter, until at least 80 % of the drug was dissolved by an auto sampling probe with a 45 µm filter and analyzed via an online programming of UV spectrophotometry equipment.

f_2 values were calculated using the results of dissolution profile of reference product obtained at the same time points with that of Niascor 500 mg ER Tablets.

Procedure:

1. 6 replicate absorbance values were observed from standard solution. (RSD ≤ % 2.0)
2. Duplicate absorbance values were observed from control standard solution.

3. Single absorbance values were observed from each of test solutions.

4. The percentages of control standard were calculated as test solutions. Results should be between 98.0 – 102.0 %.

System suitability parameter: The percent relative standard deviation (RSD %) of Niacin absorbance obtained from 6 replicate spectrum of standard solution should be less than 2.0 %.

Calculations:

The concentration of standard solution was calculated by the following formula:

$C_{std} = W_{std} \times P / DV$

C_{std} : Concentration of standard solution (mg/mL)
W_{std} : Weight of Niacin in standard solution (mg)
P : Percent potency value of Niacin working standard
DV : Total dilution volume (mL)

The amount of Niacin dissolved in tablets, in percentage, was calculated by the following formula:

$$\text{Niacin dissolved \% per tablet} = \left[\frac{A_T}{A_{Std}}\right] x \left[\frac{C_{Std}}{(W_T/900)}\right] x\, W_{Avr.} x \frac{100}{L}$$

A_T : Average Niacin absorbance obtained from chromatogram of test solution
A_{Std} : Average Niacin absorbance obtained from the spectrum of standard solution
C_{Std} : Calculated concentration of standard solution (mg/ml)
W_T : Weight of tablet weighed (mg)
W_{Avr} : Average tablet weight (mg)
L : Label claim (mg Niacin)

Calculation of f_2: $50 \times \log \left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} [\overline{R}(t) - \overline{T}(t)]^2}{n}}} \right]$

f_2 : Similarity factor for dissolution profile

n : Number of time points

R(t) : Cumulative percentage dissolved at each of the selected n time points of the reference product

T(t) : Cumulative percentage dissolved at each of the selected n time points of the test product

Evaluation: If f_2 value is between 50 and 100, the test and the reference profiles are identical.

3. RESULTS AND DISCUSSION

3.1. Results of Physical Tests

Throughout manufacturing process, certain procedures should be monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production. In-process controls during tablet production include physical tests as determination of water content, tablet dimensions (thickness, diameter), average weight (uniformity of mass), hardness and friability. For Niascor 500 mg ER Tablet all the physical tests were performed by employing USP, EP official or in-house methods and compared to the test results of reference product.

For the fourth formulation trial (04N14) even the uniformity of the granule had been achieved that the tablets couldn't be pressed with the tablet press machine because of the poor flowability and getting hardness issues. Because of that, physical tests and dissolution rate tests couldn't be achieved for this trial.

3.1.1. Results of water content tests

Water content may have a significant impact on a wide range of chemical, physical, and microbial properties of the drug product. Water content in pharmaceutical dosage forms may come from many sources including bulk drug, excipients, manufacturing processes, and environmental conditions, and is a result of a variety of causes. Water content may have significant effects on drug product stability, tablet compaction, wet granulation, powder flow properties, and microbial growth. Because of that water content in drug product should be controlled strictly by specification, but may vary within acceptable limits depending on the production process.

Determinations of water amount of tablet samples were performed by Karl Fischer titration method. The obtained data for reference listed drug product (Niascor 500 mg ER Tablet, Batch no: 130201 and 130202) were presented in Table 3.1.

Table 3.1 Water content of Niascor 500 mg ER Tablet (Batch no: 1803201 and 1803202)

	Water content (%)	
	1803201	**1803201**
TEST_1	1.28	1.33
TEST_2	1.41	1.44
AVERAGE	**1.35**	**1.39**

Water amount of Niacin 500 mg ER Tablet-Capsule samples were analyzed by employing the identical method. Results were tabulated below for 15 different formulation trials (Table 3.2).

For two batches of reference product (Batch no: 1803201 and 1803202) and performed all 15 formulation trials of Niacin 500 mg ER Tablet-Capsule (Batch no: 01N14 - 16N14), the displayed water amount results were found to be within the limits (Max. 1.5 %).

Table 3.2 Water content of Niacin 500 mg ER Tablet-Capsule (Batch no: 01N14 - 16N14)

Water content (%)															
	01N14	**02N14**	**03N14**	**05N14**	**06N14**	**07N14**	**08N14**	**09N14**	**10N14**	**11N14**	**12N14**	**13N14**	**14N14**	**15N14**	**16N14**
TEST_1	1.23	1.43	1.23	1.31	1.26	1.45	1.44	1.40	1.45	1.40	1.42	1.44	1.40	1.42	1.35
TEST_2	1.35	1.36	1.10	1.43	1.45	1.39	1.48	1.35	1.49	1.35	1.45	1.42	1.43	1.39	1.41
AVERAGE	**1.29**	**1.40**	**1.17**	**1.37**	**1.36**	**1.42**	**1.46**	**1.38**	**1.47**	**1.38**	**1.44**	**1.43**	**1.42**	**1.41**	**1.38**

3.1.2. Results of dimension tests of the tablets

Dimensions of the tablets are the in-process quality control parameters as water content and guarantee the effectiveness of production process. Thickness is the only variables, width and length of the tablets are pre-determined according to punch automatically. Thickness is related to hardness parameter which is an important physical parameter for tablets affect the dissolution rate. Thickness of the pressed tablets should, therefore, be controlled during the process frequently and when there is a deviation from acceptable limits, the process parameters should be re-adjusted.

The reference product is white colored, biconvex, oblong tablets. Dimensional characteristics of reference product were measured using compass. The recorded results of tablet width, length and thickness were given in Table 3.3.

Table 3.3 Dimensions of Niascor 500 mg ER Tablet (Batch no: 1803201 and 1803202)

Dimensions of Niascor 500 mg ER Tablet						
	1803201			**1803202**		
	Width (mm)	**Length (mm)**	**Thickness (mm)**	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	7.03	17.54	5.92	6.90	17.51	6.13
TEST_2	7.01	17.55	5.96	7.01	17.55	6.11
TEST_3	7.02	17.53	5.91	6.90	17.50	6.00
TEST_4	7.03	17.52	5.99	7.03	17.49	6.14
TEST_5	7.01	17.54	5.93	7.01	17.54	5.85
TEST_6	7.02	17.50	5.94	7.02	17.52	6.10
TEST_7	7.03	17.50	5.87	7.03	17.48	5.77
TEST_8	7.00	17.48	5.89	6.97	17.53	5.80
TEST_9	7.01	17.54	5.93	6.99	17.50	5.93
TEST_10	7.03	17.53	5.96	6.87	17.49	5.99
AVERAGE	**7.02**	**17.52**	**5.93**	**6.97**	**17.51**	**5.98**
SD	**0.01**	**0.02**	**0.04**	**0.06**	**0.02**	**0.14**
RSD	**0.16**	**0.13**	**0.59**	**0.87**	**0.13**	**2.34**

Niacin 500 mg ER Tablet-Capsule is white colored, biconvex, oblong tablets in No: 00 colorless hard gelatin capsules. All data (except for 04N14) were generated using the test parameters mentioned before and results were shown in Table 3.4-3.18.

Table 3.4 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 01N14)

01N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	7.04	17.53	6.14
TEST_2	7.03	17.54	6.13
TEST_3	7.03	17.49	6.08
TEST_4	7.01	17.51	6.12
TEST_5	7.04	17.47	6.09
TEST_6	7.02	17.50	6.10
TEST_7	7.01	17.46	6.10
TEST_8	7.04	17.54	6.01
TEST_9	7.03	17.54	6.14
TEST_10	7.00	17.54	6.13
AVERAGE	**7.03**	**17.51**	**6.10**
SD	**0.01**	**0.03**	**0.04**
RSD	**0.20**	**0.18**	**0.64**

Table 3.5 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 02N14)

02N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	7.00	17.55	6.10
TEST_2	7.03	17.53	6.15
TEST_3	7.05	17.50	6.10
TEST_4	7.04	17.46	6.12
TEST_5	7.04	17.53	6.07
TEST_6	7.03	17.54	6.13
TEST_7	7.00	17.54	6.14
TEST_8	7.01	17.54	6.08
TEST_9	6.99	17.51	6.10
TEST_10	7.04	17.50	6.15
AVERAGE	**7.02**	**17.52**	**6.11**
SD	**0.02**	**0.03**	**0.03**
RSD	**0.30**	**0.16**	**0.46**

Table 3.6 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 03N14)

03N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	7.02	17.47	6.09
TEST_2	7.04	17.54	6.13
TEST_3	7.04	17.53	6.10
TEST_4	7.04	17.53	6.10
TEST_5	7.01	17.54	6.05
TEST_6	7.03	17.49	6.14
TEST_7	7.03	17.50	6.14
TEST_8	7.04	17.54	6.09
TEST_9	7.03	17.54	6.12
TEST_10	7.01	17.54	6.13
AVERAGE	**7.03**	**17.52**	**6.11**
SD	**0.01**	**0.03**	**0.03**
RSD	**0.17**	**0.15**	**0.47**

Table 3.7 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 05N14)

05N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	7.00	17.50	6.10
TEST_2	7.02	17.50	6.13
TEST_3	7.02	17.54	6.14
TEST_4	7.04	17.50	6.14
TEST_5	7.01	17.53	6.14
TEST_6	7.04	17.53	6.10
TEST_7	7.04	17.54	6.14
TEST_8	7.04	17.54	6.12
TEST_9	7.03	17.53	6.14
TEST_10	7.02	17.53	6.11
AVERAGE	**7.03**	**17.52**	**6.13**
SD	**0.01**	**0.02**	**0.02**
RSD	**0.20**	**0.10**	**0.28**

Table 3.8 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 06N14)

06N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	7.03	17.54	6.13
TEST_2	7.03	17.50	6.14
TEST_3	7.01	17.49	6.14
TEST_4	6.99	17.50	6.13
TEST_5	7.03	17.46	6.14
TEST_6	7.05	17.53	6.14
TEST_7	7.05	17.53	6.12
TEST_8	7.04	17.54	6.12
TEST_9	7.05	17.54	6.11
TEST_10	7.05	17.53	6.10
AVERAGE	**7.03**	**17.52**	**6.13**
SD	**0.02**	**0.03**	**0.01**
RSD	**0.28**	**0.16**	**0.23**

Table 3.9 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 07N14)

07N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	6.99	17.50	6.10
TEST_2	6.98	17.54	6.11
TEST_3	7.01	17.51	6.10
TEST_4	7.03	17.47	6.07
TEST_5	7.05	17.47	6.10
TEST_6	7.01	17.50	6.13
TEST_7	7.02	17.50	6.05
TEST_8	6.99	17.51	6.08
TEST_9	7.00	17.50	6.11
TEST_10	7.00	17.50	6.09
AVERAGE	**7.01**	**17.50**	**6.09**
SD	**0.02**	**0.02**	**0.02**
RSD	**0.30**	**0.11**	**0.37**

Table 3.10 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 08N14)

08N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	6.90	17.52	6.09
TEST_2	7.02	17.53	6.12
TEST_3	7.01	17.45	6.10
TEST_4	6.87	17.48	6.11
TEST_5	7.02	17.39	6.03
TEST_6	7.05	17.42	6.09
TEST_7	7.00	17.45	6.10
TEST_8	6.89	17.52	6.12
TEST_9	6.92	17.50	6.03
TEST_10	6.95	17.39	6.10
AVERAGE	**6.96**	**17.47**	**6.09**
SD	**0.06**	**0.05**	**0.03**
RSD	**0.93**	**0.30**	**0.54**

Table 3.11 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 09N14)

09N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	6.98	17.52	5.95
TEST_2	6.99	17.43	5.97
TEST_3	7.01	17.45	6.02
TEST_4	7.03	17.39	6.01
TEST_5	6.89	17.52	5.99
TEST_6	7.03	17.50	5.79
TEST_7	7.02	17.51	6.12
TEST_8	7.01	17.54	6.10
TEST_9	7.00	17.40	6.11
TEST_10	6.97	17.42	6.10
AVERAGE	**6.99**	**17.47**	**6.02**
SD	**0.04**	**0.06**	**0.10**
RSD	**0.59**	**0.32**	**1.68**

Table 3.12 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 10N14)

10N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	7.01	17.50	6.12
TEST_2	7.02	17.52	6.13
TEST_3	7.02	17.51	6.15
TEST_4	7.04	17.46	6.10
TEST_5	6.92	17.35	6.03
TEST_6	6.99	17.37	6.09
TEST_7	7.00	17.36	6.15
TEST_8	7.02	17.42	6.15
TEST_9	7.03	17.45	5.99
TEST_10	6.99	17.48	6.10
AVERAGE	**7.00**	**17.44**	**6.10**
SD	**0.03**	**0.06**	**0.05**
RSD	**0.48**	**0.37**	**0.88**

Table 3.13 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 11N14)

11N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	6.98	17.48	6.12
TEST_2	6.99	17.39	6.13
TEST_3	6.98	17.46	6.15
TEST_4	7.02	17.38	6.13
TEST_5	7.03	17.52	6.11
TEST_6	7.04	17.54	6.12
TEST_7	6.93	17.49	5.94
TEST_8	6.89	17.39	5.99
TEST_9	7.03	17.36	6.11
TEST_10	7.03	17.54	6.13
AVERAGE	**6.99**	**17.46**	**6.09**
SD	**0.05**	**0.07**	**0.07**
RSD	**0.71**	**0.40**	**1.14**

Table 3.14 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 12N14)

12N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	6.90	17.53	6.10
TEST_2	6.95	17.50	6.12
TEST_3	7.02	17.51	6.05
TEST_4	6.99	17.50	6.13
TEST_5	7.03	17.43	6.07
TEST_6	7.03	17.50	5.99
TEST_7	7.00	17.39	6.02
TEST_8	7.00	17.52	6.13
TEST_9	6.96	17.46	6.12
TEST_10	6.89	17.42	6.10
AVERAGE	**6.98**	**17.48**	**6.08**
SD	**0.05**	**0.05**	**0.05**
RSD	**0.73**	**0.27**	**0.81**

Table 3.15 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 13N14)

13N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	7.00	17.45	5.95
TEST_2	7.00	17.46	5.97
TEST_3	7.03	17.45	5.99
TEST_4	6.99	17.50	5.87
TEST_5	7.03	17.52	5.92
TEST_6	6.87	17.51	5.94
TEST_7	6.98	17.51	5.80
TEST_8	7.02	17.39	5.92
TEST_9	7.01	17.42	5.90
TEST_10	7.03	17.47	6.00
AVERAGE	**7.00**	**17.47**	**5.93**
SD	**0.05**	**0.04**	**0.06**
RSD	**0.68**	**0.24**	**1.01**

Table 3.16 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 14N14)

14N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	7.02	17.37	5.97
TEST_2	7.01	17.43	5.89
TEST_3	7.00	17.40	5.86
TEST_4	7.00	17.50	5.90
TEST_5	6.99	17.51	5.92
TEST_6	6.87	17.51	5.89
TEST_7	6.95	17.48	5.83
TEST_8	6.94	17.50	5.86
TEST_9	6.90	17.43	5.92
TEST_10	7.02	17.45	5.79
AVERAGE	**6.97**	**17.46**	**5.88**
SD	**0.05**	**0.05**	**0.05**
RSD	**0.76**	**0.28**	**0.86**

Table 3.17 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 15N14)

15N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	6.89	17.38	5.80
TEST_2	7.03	17.39	5.95
TEST_3	7.03	17.41	5.92
TEST_4	7.00	17.39	5.87
TEST_5	7.01	17.43	5.93
TEST_6	6.97	17.42	6.02
TEST_7	6.93	17.36	5.90
TEST_8	6.95	17.39	5.87
TEST_9	6.99	17.41	5.91
TEST_10	7.03	17.40	5.97
AVERAGE	**6.98**	**17.40**	**5.91**
SD	**0.05**	**0.02**	**0.06**
RSD	**0.68**	**0.12**	**1.02**

Table 3.18 Dimensions of Niacin 500 mg ER Tablet-Capsule (Batch no: 16N14)

16N14	**Width (mm)**	**Length (mm)**	**Thickness (mm)**
TEST_1	7.03	17.43	6.09
TEST_2	7.02	17.51	6.10
TEST_3	6.99	17.52	5.99
TEST_4	6.95	17.53	5.89
TEST_5	6.89	17.50	6.12
TEST_6	7.03	17.49	6.07
TEST_7	6.99	17.49	6.05
TEST_8	6.88	17.39	6.02
TEST_9	6.94	17.41	6.09
TEST_10	7.02	17.46	6.10
AVERAGE	**6.97**	**17.47**	**6.05**
SD	**0.06**	**0.05**	**0.07**
RSD	**0.81**	**0.28**	**1.15**

Values in length, width and thickness results for both original reference product and formulated products were within the limits.

The variations for Niacin 500 mg ER Tablet ((Prepared in our laboratory-Batch No: 01N14 - 16N14 (except for 04N14)) in respect to replicated 10 measurements of width, length and thickness depend on the tablet press step of the process and are all at reasonable level.

3.1.3. Results of average weight (AW) tests of the tablets

To ensure the consistency of dosage units, each tablet should have active substance content within a narrow range around the label claim. Therefore, sensitive and correct measurement of weight of the tablets becomes an important issue. Each individual tablet should have an optimum weight and this parameter is controlled during the tablet press step of the production.

Average weight measurements of tablets were performed using 10 tablets. Tablets were weighted individually; average mass and the percent deviation of tablets were calculated.

According to guidance's (USP-NF) weight tolerance for uncoated tablet which has an average weight more than 324 is maximum 5 % of target tablet weight. So that for our formulations we set down the average weight limit as "tablet weight (mg) ± 5.0 %". Tablet weight depends on the formulation, so the specification of average weight changes in each formulation as described below:

Limit of tablet average weight measurement test was tablet weight (mg) ± 5.0 % (707 mg ± 5.0 %) for the reference product. The results of measurements were listed below (Table 3.19).

Table 3.19 Average weight (AW) of Niascor 500 mg ER Tablet (Batch no: 1803201 and 1803202)

AW (mg)		
	1803201	**1803202**
TEST_1	712	712
TEST_2	711	720
TEST_3	706	696
TEST_4	710	722
TEST_5	711	693
TEST_6	708	688
TEST_7	709	712
TEST_8	714	710
TEST_9	714	710
TEST_10	703	707
AVERAGE	**710**	**707**
SD	**3.3**	**11.3**
RSD	**0.5**	**1.6**

Limit of tablet average weight measurement test was tablet weight (mg) ± 5.0 % for the formulated drug products. As the target weight of the tablets were changed according to formulation trials limit of this test was determined special to that formulation. Average weight limit of 01N14 was set as 715 mg ± 5.0 % (680 mg-750 mg), average weight limit of 02N14 was set as 715 mg ± 5.0 % (680 mg-750 mg), average weight limit of 03N14 was set as 715 mg ± 5.0 % (680 mg-750 mg), average weight limit of 05N14 was set as 710 mg ± 5.0 % (675 mg-745 mg), average weight limit of 06N14 was set as 710 mg ± 5.0 % (675 mg-745 mg),

average weight limit of 07N14 was set as 707 mg ± 5.0 % (672 mg-742 mg), average weight limit of 08N14 was set as 705 mg ± 5.0 % (670 mg-740 mg), average weight limit of 09N14 was set as 708 mg ± 5.0 % (673 mg-743 mg), average weight limit of 10N14 was set as 790 mg ± 5.0 % (751 mg-829 mg), average weight limit of 11N14 was set as 800 mg ± 5.0 % (760 mg-840 mg), average weight limit of 12N14 was set as 800 mg ± 5.0 % (760 mg-840 mg), average weight limit of 13N14 was set as 685 mg ± 5.0 % (651 mg-719 mg), average weight limit of 14N14 was set as 655 mg ± 5.0 % (623 mg-687 mg), average weight limit of 15N14 was set as 643 mg ± 5.0 % (611 mg-675 mg) and average weight limit of 16N14 was set as 693 mg ± 5.0 % (659 mg-727 mg). Measurement results were listed below (except for 04N14), tablet average weights showed a slight change but all results remained well within specifications (Table 3.20).

Table 3.20 Average weight (AW) of Niascor 500 mg ER Tablet (Batch no: 01N14 - 16N14)

AW (mg)															
	01N14	**02N14**	**03N14**	**05N14**	**06N14**	**07N14**	**08N14**	**09N14**	**10N14**	**11N14**	**12N14**	**13N14**	**14N14**	**15N14**	**16N14**
TEST_1	710	734	716	710	706	705	704	709	780	802	805	680	650	645	695
TEST_2	700	720	715	711	701	702	705	710	789	805	807	687	652	646	694
TEST_3	691	683	706	708	702	706	709	712	795	810	810	680	650	645	694
TEST_4	733	703	715	709	703	703	712	720	800	799	802	685	654	645	693
TEST_5	690	730	716	707	701	705	700	708	802	803	799	680	654	644	693
TEST_6	744	745	707	709	705	706	702	705	796	795	785	690	655	643	695
TEST_7	700	712	707	712	704	707	695	713	790	799	806	695	660	653	694
TEST_8	712	718	712	702	707	710	699	719	792	803	810	702	655	640	693
TEST_9	709	706	705	705	712	702	702	709	786	805	815	675	656	635	690
TEST_10	707	709	713	704	700	701	703	708	780	810	803	682	661	640	690
AVERAGE	**710**	**716**	**711**	**708**	**704**	**705**	**703**	**711**	**791**	**803**	**804**	**686**	**655**	**644**	**693**
SD	**17.3**	**17.8**	**4.4**	**3.3**	**3.6**	**2.7**	**4.9**	**4.9**	**7.6**	**4.7**	**8.1**	**8.2**	**3.7**	**4.7**	**1.8**
RSD	**2.4**	**2.5**	**0.6**	**0.5**	**0.5**	**0.4**	**0.7**	**0.7**	**1.0**	**0.6**	**1.0**	**1.2**	**0.6**	**0.7**	**0.3**

3.1.4. Results of hardness tests of the tablets

Tablets need a certain amount of hardness and resistance to friability to withstand mechanical shocks of handling in manufacture, packaging and shipping. Hardness is one of the most important parameters for tablets. It can affect the disintegration of the tablet. If the tablet is too hard it may not disintegrate in the required period of time, if it is too soft it'll not withstand the handling during coating or packaging. Compression force in tablet press machine can affect the hardness. Hardness of the pressed tablets should, therefore, be controlled during the process frequently and when there is a deviation in hardness values the process parameters should be re-adjusted.

For hardness measurements tablets were placed between two jaws of the hardness testing machine that crush the tablets. The machine measured the force applied to the tablets and detected when they fractured. Forces applied to the tablets at the breaking point were considered to detect the hardness value of tablets. The obtained values should be minimum 100 Newton. Hardness test results of reference products were shown in Table 3.21.

Table 3.21 Hardness of Niascor 500 mg ER Tablet (Batch no: 1803201 and 1803202)

HARDNESS (N)		
	1803201	**1803202**
TEST_1	96	95
TEST_2	107	97
TEST_3	104	105
TEST_4	97	100
TEST_5	99	103
TEST_6	101	96
TEST_7	103	107
TEST_8	104	107
TEST_9	99	115
TEST_10	102	106
AVERAGE	**101**	**103**
SD	**3.5**	**6.2**
RSD	**3.4**	**6.0**

Hardness values of formulated tablets (except for 04N14) were measured with the same manner. The hardness values of both formulations were listed below (Table 3.22).

The obtained hardness data showed that all the tablets were pressed properly and within the specification.

Table 3.22 Hardness of Niacin 500 mg ER Tablet-Capsule (Batch no: 01N14 - 16N14)

HARDNESS (N)															
	01N14	**02N14**	**03N14**	**05N14**	**06N14**	**07N14**	**08N14**	**09N14**	**10N14**	**11N14**	**12N14**	**13N14**	**14N14**	**15N14**	**16N14**
TEST_1	120	110	135	130	125	135	130	135	140	142	143	127	125	120	130
TEST_2	135	120	132	135	140	140	132	140	142	145	145	125	120	125	135
TEST_3	117	120	128	121	120	139	135	135	139	150	145	126	123	124	132
TEST_4	110	130	129	120	110	131	129	136	145	138	150	130	120	120	132
TEST_5	120	135	135	125	126	121	136	130	141	148	135	125	129	123	135
TEST_6	121	120	121	137	124	143	135	141	140	148	137	126	128	121	130
TEST_7	125	120	120	130	121	126	137	138	142	145	140	125	130	120	131
TEST_8	119	125	121	126	119	125	130	130	141	140	141	129	125	120	130
TEST_9	100	120	134	125	136	120	125	135	139	138	140	130	126	118	130
TEST_10	115	137	110	119	135	121	124	135	138	139	136	130	127	120	129
AVERAGE	**118**	**124**	**127**	**127**	**126**	**130**	**131**	**136**	**141**	**143**	**141**	**127**	**125**	**121**	**131**
SD	**9.2**	**8.2**	**8.3**	**6.1**	**9.1**	**8.7**	**4.5**	**3.6**	**2.0**	**4.5**	**4.7**	**2.2**	**3.5**	**2.2**	**2.1**
RSD	**7.7**	**6.6**	**6.5**	**4.8**	**7.2**	**6.7**	**3.4**	**2.7**	**1.4**	**3.1**	**3.3**	**1.7**	**2.8**	**1.8**	**1.6**

3.1.5. Results of friability tests of the tablets

Friability testing is used to test the durability of tablets during transit of them between devices, sites and transportation to pharmacy warehouses. Measurement of tablet friability supplements other physical strength measurements, such as tablet breaking force.

At the beginning of the test tablets were weighted and abraded in the friability tester with a rotation speed of 50 rpm. The loss in sample mass was determined by weighing the sample that was carefully de-dusted using a soft brush, before and after each experiment, and the friability was then calculated. Each experiment was repeated two times and the mean value was determined (Schiano et.al, 2016)

All tablet friability test were conducted using Ewreka TAR120 friability testing device and result of these tests were varied within acceptable limits and listed below for both reference products and our formulation trials (except for 04N14) in Table 3.23 and 3.24.

Table 3.23 Friability test result of Niascor 500 mg ER Tablet (Batch no: 1803201 and 1803202)

Friability (%)		
	1803201	**1803202**
TEST_1	0.8	0.9
TEST_2	0.9	0.9
AVERAGE	**0.9**	**0.9**

Table 3.24 Friability test result of Niacin 500 mg ER Tablet-Capsule (Batch no: 01N14 - 16N14)

Friability (%)															
	01N14	**02N14**	**03N14**	**05N14**	**06N14**	**07N14**	**08N14**	**09N14**	**10N14**	**11N14**	**12N14**	**13N14**	**14N14**	**15N14**	**16N14**
TEST_1	0.9	0.7	0.9	0.4	0.7	0.9	0.5	0.9	0.8	0.9	0.8	0.9	0.3	0.5	0.7
TEST_2	0.7	0.8	0.6	0.4	0.8	0.9	0.7	0.5	0.7	0.6	0.8	0.9	0.5	0.7	0.8
AVERAGE	**0.8**	**0.8**	**0.8**	**0.4**	**0.8**	**0.9**	**0.6**	**0.7**	**0.8**	**0.8**	**0.8**	**0.9**	**0.4**	**0.6**	**0.8**

3.2. Results of Assay Tests

Assay is an analytical procedure for quantitatively measuring the presence or amount of an analyte and plays an important part in assuring the quality of drug product.

HPLC assay analyses were determined for two batches of Niascor 500 mg ER Tablet mentioned above. The analysis was carried out using the methodologies detailed in experimental part. Results were tabulated in Table 3.25.

Table 3.25 Assay results of Niascor 500 mg ER Tablet (Batch no: 1803201 and 1803202)

Assay results of Niascor 500 mg ER Tablet				
	1803201		**1803202**	
	Niacin (mg)	**Niacin (%)**	**Niacin (mg)**	**Niacin (%)**
TEST_1	478.7	95.7	484.3	96.9
TEST_2	487.6	97.5	495.2	99.0
AVERAGE	**483.1**	**96.6**	**489.7**	**98.0**
SD	**6.3**	**1.3**	**7.7**	**1.5**
RSD	**1.3**	**1.3**	**1.6**	**1.6**

Assay analyses of formulated products were conducted with the same HPLC method and their results were shown for all trials in Table 3.26 as mg niacin/tablet and in Table 3.27 as % niacin/tablet (except for 04N14). The results have some variations but all varied within acceptable limits.

Table 3.26 Assay results of Niacin 500 mg ER Tablet-Capsule (mg) (Batch no: 01N14 - 16N14)

Niacin (mg)															
	01N14	**02N14**	**03N14**	**05N14**	**06N14**	**07N14**	**08N14**	**09N14**	**10N14**	**11N14**	**12N14**	**13N14**	**14N14**	**15N14**	**16N14**
TEST_1	530.5	527.0	519.5	536.2	526.3	498.2	502.9	502.3	506.9	506.3	505.3	490.9	507.6	508.6	500.3
TEST_2	525.8	521.6	529.5	522.9	520.6	500.3	501.6	500.2	507.5	504.7	502.4	492.5	506.3	510.2	501.4
AVERAGE	**528.2**	**524.3**	**524.5**	**529.6**	**523.5**	**499.3**	**502.3**	**501.3**	**507.2**	**505.5**	**503.9**	**491.7**	**507.0**	**509.4**	**500.9**
SD	**3.3**	**3.8**	**7.1**	**9.4**	**4.0**	**1.5**	**0.9**	**1.5**	**0.4**	**1.1**	**2.1**	**1.1**	**0.9**	**1.1**	**0.8**
RSD	**0.6**	**0.7**	**1.4**	**1.8**	**0.8**	**0.3**	**0.2**	**0.3**	**0.1**	**0.2**	**0.4**	**0.2**	**0.2**	**0.2**	**0.2**

Table 3.27 Assay results of Niacin 500 mg ER Tablet-Capsule (%) (Batch no: 01N14 - 16N14)

Niacin (%)															
	01N14	**02N14**	**03N14**	**05N14**	**06N14**	**07N14**	**08N14**	**09N14**	**10N14**	**11N14**	**12N14**	**13N14**	**14N14**	**15N14**	**16N14**
TEST_1	106.1	105.4	103.9	107.2	105.3	99.6	100.6	100.5	101.4	101.3	101.1	98.2	101.5	101.7	100.1
TEST_2	105.2	104.3	105.9	104.6	104.1	100.1	100.3	100.0	101.5	100.9	100.5	98.5	101.3	102.0	100.3
AVERAGE	**105.6**	**104.9**	**104.9**	**105.9**	**104.7**	**99.9**	**100.5**	**100.3**	**101.4**	**101.1**	**100.8**	**98.3**	**101.4**	**101.9**	**100.2**
SD	**0.7**	**0.8**	**1.4**	**1.9**	**0.8**	**0.3**	**0.2**	**0.3**	**0.1**	**0.2**	**0.4**	**0.2**	**0.2**	**0.2**	**0.2**
RSD	**0.6**	**0.7**	**1.4**	**1.8**	**0.8**	**0.3**	**0.2**	**0.3**	**0.1**	**0.2**	**0.4**	**0.2**	**0.2**	**0.2**	**0.2**

3.3. Results of Uniformity of Dosage Units

To ensure the consistency of dosage units, each unit in a batch should have active substance content within a narrow range around the label claim. The term 'uniformity of dosage unit' is defined as the degree of uniformity in the amount of the active substance among dosage units. The uniformity of dosage units can be evaluated either by measuring the content uniformity or the weight of the tested units (EP 8.0, 2014).

In order to find out the content uniformity of the tablets 10 tablets were individually weighted, dissolved and analyzed by HPLC via the same method of assay analysis. Acceptance criteria (AC) values were calculated according to Ph.Eur. 2.9.40 and AC values should be ≤ 15.

Reference product uniformity of dosage units test results were shown in Table 3.28. AC values were calculated as 14.8 and 11.0 for 1803201 and 1803202 batches, respectively.

Table 3.28 Content uniformity results of Niascor 500 mg ER Tablet (Batch no: 1803201 and 1803202)

Niacin (%)		
	1803201	**1803202**
TEST_1	95.6	98.5
TEST_2	95.6	99.7
TEST_3	88.6	102.5
TEST_4	95.5	101.7
TEST_5	88.7	87.6
TEST_6	88.4	102.5
TEST_7	95.5	101.0
TEST_8	88.7	97.6
TEST_9	89.9	98.5
TEST_10	95.5	103.5
AVERAGE	**92.2**	**99.3**
SD	**3.5**	**4.6**
RSD	**3.8**	**4.6**
AC	**14.8**	**11.0**

For all formulated products results regarding uniformity of dosage units' test were performed by employing same method as presented below and the results were shown in Table 3.29 (except for 04N14). All AC values were calculated according to Ph.Eur.2.9.40 and found below 15. These results suggested showed us that variations in tablet to tablet were found to be below the limit and tablets were deemed to be uniform.

Table 3.29 Content uniformity results of Niacin 500 mg ER Tablet-Capsule (Batch no: 01N14 - 16N14)

Niacin (%)															
	01N14	**02N14**	**03N14**	**05N14**	**06N14**	**07N14**	**08N14**	**09N14**	**10N14**	**11N14**	**12N14**	**13N14**	**14N14**	**15N14**	**16N14**
TEST_1	105.5	103.5	103.5	100.3	101.2	99.4	102.3	102.5	103.5	98.5	102.5	98.5	99.9	102.4	100.0
TEST_2	106.7	102.7	103.7	101.5	102.3	101.5	101.9	99.5	104.5	98.7	104.0	100.1	102.6	100.5	101.3
TEST_3	102.1	100.5	101.6	106.4	105.6	103.5	102.5	98.7	99.6	102.6	99.9	100.2	103.5	99.6	103.5
TEST_4	107.8	107.5	105.7	107.5	103.9	100.5	99.6	103.5	98.7	103.9	99.6	98.3	98.6	102.5	99.6
TEST_5	109.5	103.5	106.7	104.3	104.6	102.1	98.5	101.9	99.0	100.8	98.3	98.7	98.2	103.5	99.3
TEST_6	101.8	100.8	104.6	102.0	104.8	99.8	103.5	101.0	101.5	100.3	105.3	99.9	99.6	103.5	100.9
TEST_7	102.5	106.8	103.1	108.5	106.8	98.5	105.7	103.5	100.9	99.6	101.3	98.0	102.3	99.8	100.7
TEST_8	105.4	105.4	102.7	109.3	107.0	105.6	102.3	104.7	100.6	102.5	99.9	100.1	101.7	102.5	99.6
TEST_9	100.5	104.7	102.9	110.0	103.6	102.7	99.5	99.6	100.3	103.2	103.5	98.2	99.4	103.7	100.0
TEST_10	107.6	106.7	108.5	106.5	103.7	106.8	98.0	100.4	102.0	100.1	102.5	99.9	102.5	99.9	100.0
AVERAGE	**104.9**	**104.2**	**104.3**	**105.6**	**104.4**	**102.0**	**101.4**	**101.5**	**101.1**	**101.0**	**101.7**	**99.2**	**100.8**	**101.8**	**100.5**
SD	**3.0**	**2.5**	**2.10**	**3.4**	**1.8**	**2.7**	**2.4**	**2.0**	**1.9**	**1.9**	**2.3**	**0.9**	**1.9**	**1.7**	**1.2**
RSD	**2.9**	**2.4**	**2.01**	**3.3**	**1.8**	**2.6**	**2.4**	**2.0**	**1.9**	**1.9**	**2.2**	**0.9**	**1.9**	**1.6**	**1.2**
AC	**10.7**	**8.6**	**7.8**	**12.4**	**7.2**	**7.0**	**5.8**	**4.9**	**4.5**	**4.6**	**5.6**	**2.2**	**4.6**	**4.3**	**3.0**

3.4. Results of Dissolution Tests

Dissolution test is a primary quality control test to determine whether a drug product can release its active substance in a timely manner and it is an important tool in the development of new drug products. This test is used; as a formulation design aid (since formulation can profoundly affect dissolution behavior), as a quality control measure for batch release / to check performance during the shelf life, to verify that the quality of a product is not adversely affected when there is a change in excipients or manufacturing method and to obtain approval for a multisource drug product (for generic drug products). An ideal situation, controlled release tablets should be tested in vitro throughout the entire physiological pH (1 - 7.8) of the GI tract in order to simulate the in vivo conditions. UV Spectrophotometry method was used in dissolution test for tablet step of Niascor 500 mg ER Tablets and Niacin 500 mg ER Tablet-Capsules. Multi-point dissolution profile test was performed in these studies.

The in-vitro dissolution profiles test results of the reference product and Niacin 500 mg ER Tablet-Capsule were evaluated in four different media (0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and distilled water (pH: 7.0)) using a UV Spectrophotometric method at a wavelength of 262 nm with apparatus 1 at a rate of 100 rpm in 900 mL of test medium. The test assembly was chosen according to reference drug product method, temperature was set to 37 ± 0.5°C and samples were withdrawn at 1, 2, 4, 5, 6, 8, 10 and 12 hours interval and analyzed for percentage of dissolved drug.

Limits for dissolution rate tests were set according to reference product as 10 % - 30 % at the end of 1 hour, 45 % - 70 % at the end of 5 hours and 80 % - 110 % at the end of 10 hours.

The dissolution test results of reference product were tabulated in Table 3.30 and 3.31 for 0.1 N HCl medium. Table 3.32 shows the dissolution test results of Niacin 500 mg ER Tablet-Capsule (Batch no: 01N14) for the same conditions. The comparative graph for this test was illustrated shown in Figure 3.1. First columns of the tables show sampling time and next columns indicate the % dissolved drug amount for each of six tablets at these sampling times,

respectively. Then average dissolved drug amounts of six tablets and standard deviations of these values were listed. Maximum and minimum amounts were indicated at the end of the tables.

f2 is similarity factor and stresses on the comparison of closeness of two comparative formulations, f1 is difference factor and focuses on the difference in percent dissolved between reference and test at various time intervals. These factors directly compare the difference between % drug dissolved per unit time for a test and a reference product. The similarity factor should be between 0 and 100. It is 100 when two comparative groups of reference and test are identical and approaches 0 as the dissimilarity increases. Generally similarity factor in the range of 50-100 is acceptable according to FDA.

The f1 and f2 calculations were performed for dissolution studies, test results of the second batch of reference product were considered for these calculations and f1 was found to be 37, while f2 was found to be 21 for 01N14 series. Table 3.33 illustrates the comparative test results.

Table 3.30 Dissolution profile of Niascor 500 mg ER Tablet (pH 1.2) (Batch no: 1803201)

Product name	Niascor 500 mg ER Tablet - 1803201
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	26.2	25.1	23.1	24.8	18.9	26.1	24	2.8	11.5	2.2	21.8	26.2
120	40.6	39.5	38.0	39.6	36.3	40.7	39	1.7	4.3	1.4	37.8	40.5
240	61.6	60.3	59.1	60.0	57.2	60.6	60	1.5	2.5	1.2	58.6	61.0
300	66.7	63.0	64.8	66.0	60.0	67.0	65	2.7	4.1	2.1	62.4	66.7
360	76.7	75.9	74.8	75.6	73.0	75.5	75	1.3	1.7	1.0	74.2	76.3
480	87.9	86.9	85.6	86.7	83.9	86.6	86	1.4	1.6	1.1	85.2	87.4
600	95.7	95.0	94.2	94.9	93.0	94.2	95	0.9	1.0	0.7	93.8	95.2
720	100.3	100.0	99.7	100.5	99.5	99.6	100	0.4	0.4	0.3	99.6	100.3

Table 3.31 Dissolution profile of Niascor 500 mg ER Tablet (pH 1.2) (Batch no: 1803202)

Product name	Niascor 500 mg ER Tablet - 1803202
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	26.2	25.6	26.3	24.3	25.8	24.0	25	1.0	3.9	0.8	24.6	26.2
120	41.3	42.7	39.2	38.9	40.3	39.7	40	1.4	3.6	1.1	39.2	41.5
180	51.3	53.5	52.7	50.6	51.0	49.8	51	1.4	2.7	1.1	50.4	52.6
240	63.4	60.5	61.4	57.6	63.5	58.0	61	2.6	4.2	2.0	58.7	62.8
300	66.9	69.5	68.2	68.7	71.5	66.9	69	1.7	2.5	1.4	67.2	70.0
360	77.0	78.6	75.9	73.2	75.9	76.0	76	1.8	2.3	1.4	74.7	77.5
420	83.0	80.7	81.5	85.3	84.6	78.7	82	2.5	3.0	2.0	80.3	84.3
480	85.9	88.5	87.5	90.2	85.2	86.5	87	1.8	2.1	1.5	85.8	88.8
540	92.3	90.8	93.5	90.7	89.6	92.8	92	1.5	1.6	1.2	90.4	92.8
600	97.8	97.0	94.3	92.1	96.3	97.5	96	2.2	2.3	1.8	94.1	97.6
720	103.5	100.3	98.7	99.8	102.5	99.0	101	1.9	1.9	1.6	99.1	102.2

Table 3.32 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 01N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 01N14
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	54.8	48.8	50.2	52.5	44.5	47.1	50	3.7	7.5	3.0	46.7	52.6
120	77.7	72.6	74.9	76.7	67.3	71.5	73	3.8	5.2	3.1	70.4	76.5
180	91.7	88.5	90.5	91.4	82.2	86.7	89	3.6	4.1	2.9	85.6	91.4
240	100.7	98.5	100.3	100.3	92.4	96.8	98	3.2	3.2	2.5	95.6	100.7
300	105.5	104.7	106.2	105.5	99.0	103.1	104	2.7	2.6	2.1	101.9	106.1
360	108.6	108.2	108.8	108.0	103.6	106.7	107	2.0	1.8	1.6	105.7	108.9
420	109.9	109.5	110.3	108.8	106.8	108.5	109	1.3	1.2	1.0	108.0	110.0
480	110.8	109.4	110.5	108.6	107.1	109.0	109	1.3	1.2	1.1	108.2	110.3
540	110.7	110.5	110.9	109.6	108.0	109.9	110	1.1	1.0	0.9	109.1	110.8
600	110.5	111.0	110.7	108.7	108.0	109.3	110	1.2	1.1	1.0	108.7	110.7
720	110.7	110.5	110.8	109.3	108.3	109.5	110	1.0	0.9	0.8	109.1	110.6

Table 3.33 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (01N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	01N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCI, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	50	3.7	7.5	3.0
120	40	1.4	3.6	1.1	73	3.8	5.2	3.1
180	51	1.4	2.7	1.1	89	3.6	4.1	2.9
240	61	2.6	4.2	2.0	98	3.2	3.2	2.5
300	69	1.7	2.5	1.4	104	2.7	2.6	2.1
360	76	1.8	2.3	1.4	107	2.0	1.8	1.6
420	82	2.5	3.0	2.0	109	1.3	1.2	1.0
480	87	1.8	2.1	1.5	109	1.3	1.2	1.1
540	92	1.5	1.6	1.2	110	1.1	1.0	0.9
600	96	2.2	2.3	1.8	110	1.2	1.1	1.0
720	101	1.9	1.9	1.6	110	1.0	0.9	0.8

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	288.4
60	24.2		
120	33.1		
180	37.0		
240	37.4		
300	35.4		
360	31.2		
420	26.7		
480	21.9		
540	18.3		
600	13.9		
720	9.2		
	f1	37	
	f2	21	

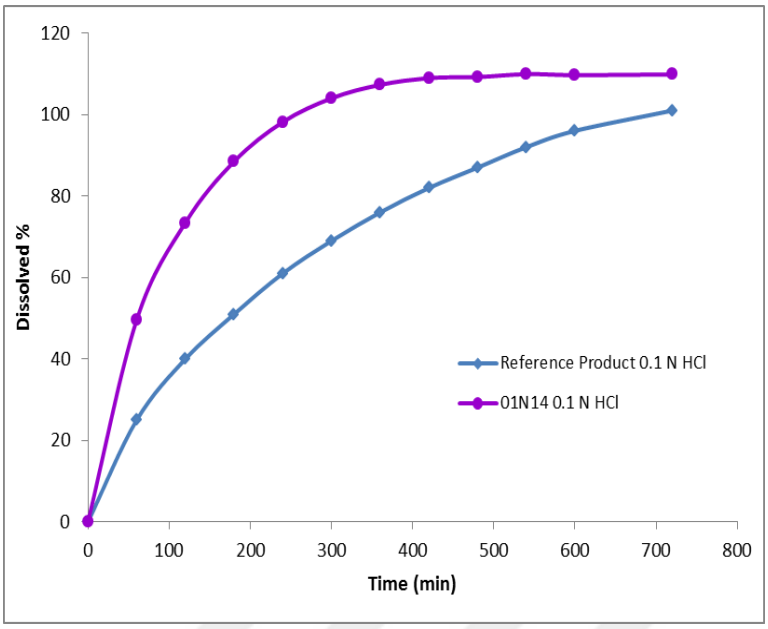


Figure 3.1 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 01N14 vs Reference Product

The obtained f2 value, dissolution test results and the dissolution profile comparison of 01N14 batch numbered formulation trial versus reference product showed us that these tablets were dissolving faster than reference product. The reason of these can be both amounts of excipients or type of the extended release agent.

Because of the obtained f1 and f2 values being below the acceptable limits, it was decided that this formulation procedure should be improved. Table 3.34 shows the dissolution test results of Niacin 500 mg ER Tablet-Capsule (Batch no: 02N14) for the same conditions (0.1 N HCI, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C). The comparative graph for this test was shown in Figure 3.2. f1 was found to be 43, while f2 was found to be 18 for second formulation trial. The comparative dissolution profile shows that very rapid dissolution was observed for test product i.e. more than 50% of drug was released within 1 hour time point (Table 3.35). These results show us extended release agent couldn't extent the release.

Table 3.34 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 02N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 02N14
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	56.6	62.0	64.5	64.8	55.8	56.3	60	4.2	7.1	3.4	56.6	63.4
120	81.6	85.7	87.7	87.9	79.4	81.3	84	3.6	4.3	2.9	81.0	86.8
180	95.5	97.8	99.8	100.0	92.6	95.3	97	2.9	3.0	2.3	94.5	99.1
240	103.0	104.2	106.1	106.6	100.7	102.8	104	2.2	2.1	1.8	102.1	105.7
300	106.8	107.4	109.9	109.2	105.8	106.8	108	1.6	1.5	1.3	106.4	108.9
360	108.6	109.1	111.0	110.5	108.5	108.4	109	1.1	1.0	0.9	108.5	110.2
420	110.1	109.9	111.6	110.8	109.4	108.7	110	1.0	0.9	0.8	109.3	110.9
480	110.6	110.3	111.7	111.0	110.1	109.1	110	0.9	0.8	0.7	109.8	111.2
540	110.2	110.3	112.1	110.8	110.4	109.0	110	1.0	0.9	0.8	109.7	111.3
600	109.3	110.0	111.5	110.9	110.1	109.3	110	0.9	0.8	0.7	109.5	110.9
720	110.3	110.2	112.3	110.9	110.5	109.1	111	1.0	0.9	0.8	109.7	111.4

Table 3.35 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (02N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	02N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	60	4.2	7.1	3.4
120	40	1.4	3.6	1.1	84	3.6	4.3	2.9
180	51	1.4	2.7	1.1	97	2.9	3.0	2.3
240	61	2.6	4.2	2.0	104	2.2	2.1	1.8
300	69	1.7	2.5	1.4	108	1.6	1.5	1.3
360	76	1.8	2.3	1.4	109	1.1	1.0	0.9
420	82	2.5	3.0	2.0	110	1.0	0.9	0.8
480	87	1.8	2.1	1.5	110	0.9	0.8	0.7
540	92	1.5	1.6	1.2	110	1.0	0.9	0.8
600	96	2.2	2.3	1.8	110	0.9	0.8	0.7
720	101	1.9	1.9	1.6	111	1.0	0.9	0.8

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	333.1
60	34.6		
120	43.6		
180	45.4		
240	43.2		
300	39.0		
360	33.3		
420	27.8		
480	23.2		
540	18.9		
600	14.4		
720	9.9		
	f1	43	
	f2	18	

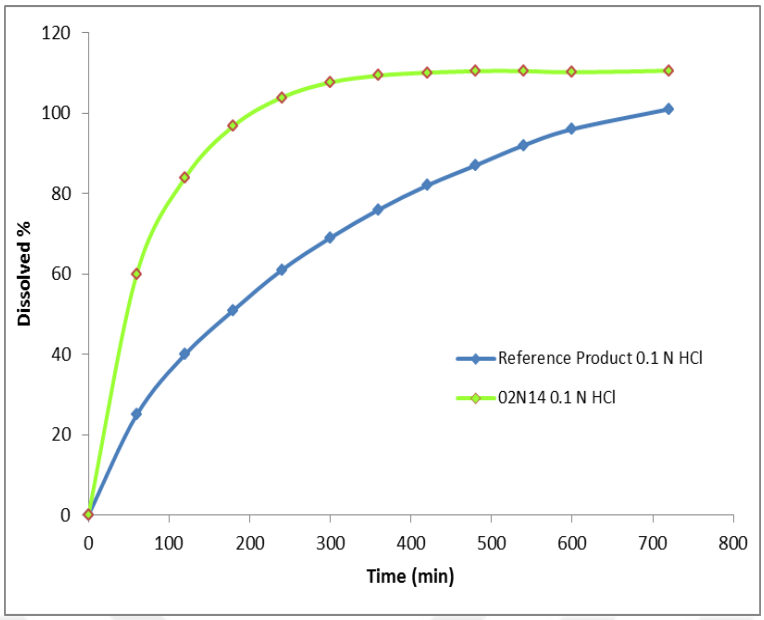


Figure 3.2 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 02N14 vs Reference Product

In addition, for second formulation trial didn't give acceptable f2 value, so that it was continued with new formulation experiments. The next second formulation trials included less amount of extended release agent (Hydroxypropyl methylcellulose) to observe the effect of extended release agent. Table 3.36 shows the dissolution test results of Niacin 500 mg ER Tablet-Capsule (Batch no: 03N14) for the same conditions (0.1 N HCI, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C). The comparative graph for this test in 0.1 N HCl medium was shown in Figure 3.3, from this dissolution graph it was observed that incomplete drug release was observed for test product in 0.1 N HCl dissolution media. f1 value was found to be 37, while f2 was found to be 21 for this formulation trial which are not found in acceptable ranges. Table 3.37 illustrates the detailed comparative test results. These low f values depend on the both extended release agent and incompatible excipient amounts.

Table 3.36 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 03N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 03N14
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	60.3	62.7	55.9	27.9	50.6	53.4	52	12.5	24.2	10.0	41.8	61.8
120	84.7	85.7	80.7	53.8	73.3	79.5	76	11.9	15.6	9.5	66.8	85.8
180	97.5	97.8	94.4	70.1	87.4	94.4	90	10.6	11.7	8.5	81.8	98.7
240	104.8	104.3	102.8	81.5	96.7	103.0	99	9.0	9.1	7.2	91.7	106.0
300	107.5	108.0	107.2	90.0	102.4	107.1	104	7.0	6.8	5.6	98.1	109.3
360	109.1	108.9	109.1	96.7	106.3	108.6	106	4.9	4.6	3.9	102.5	110.4
420	109.7	109.0	109.8	101.0	107.2	108.9	108	3.4	3.1	2.7	104.9	110.3
480	109.9	109.2	109.6	104.6	108.1	109.2	108	2.0	1.8	1.6	106.9	110.0
540	110.3	109.9	109.7	107.1	108.0	109.9	109	1.3	1.2	1.0	108.1	110.2
600	109.7	109.6	109.8	108.3	108.7	109.2	109	0.6	0.6	0.5	108.7	109.7
720	110.1	109.8	110.4	108.4	108.9	109.6	110	0.8	0.7	0.6	108.9	110.1

Table 3.37 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (03N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	03N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCI, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	52	12.5	24.2	10.0
120	40	1.4	3.6	1.1	76	11.9	15.6	9.5
180	51	1.4	2.7	1.1	90	10.6	11.7	8.5
240	61	2.6	4.2	2.0	99	9.0	9.1	7.2
300	69	1.7	2.5	1.4	104	7.0	6.8	5.6
360	76	1.8	2.3	1.4	106	4.9	4.6	3.9
420	82	2.5	3.0	2.0	108	3.4	3.1	2.7
480	87	1.8	2.1	1.5	108	2.0	1.8	1.6
540	92	1.5	1.6	1.2	109	1.3	1.2	1.0
600	96	2.2	2.3	1.8	109	0.6	0.6	0.5
720	101	1.9	1.9	1.6	110	0.8	0.7	0.6

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	291.0
60	26.4		
120	35.9		
180	38.8		
240	38.1		
300	35.1		
360	30.4		
420	25.3		
480	21.1		
540	17.5		
600	13.4		
720	8.9		
	f1	37	
	f2	21	

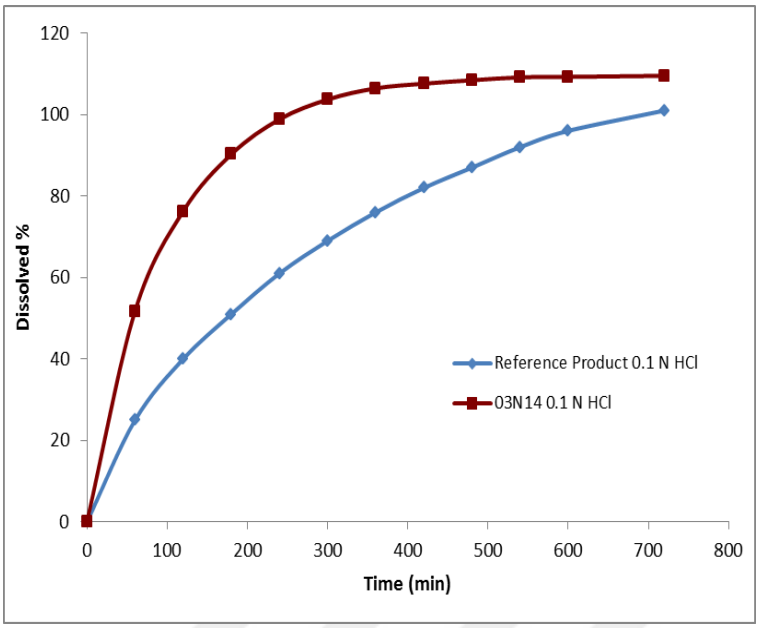


Figure 3.3 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 03N14 vs Reference Product

After three different formulations with different amount of extended release agent and obtained low f2 values it was seen the type of the extended release agent or the type of manufacturing process should be changed for better dissolution results and f2 values. As the design of experiment test results were below the limits it was decided to try new excipients and formulation techniques until getting promising f2 values, and then make a new design pattern for the best formulation. For this purpose it was decided to change the type of extended release agent, HPMC K100 M CR was used in the formulation instead of HPMC K100 M. Dissolution test results and comparative graph for fifth formulation were presented in Table 3.38 and Figure 3.4, respectively. f1 was found to be 35, while f2 was found to be 23 for this formulation trial which are not in agreement with the acceptable ranges. Table 3.39 presents the comparative test results.

Table 3.38 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 05N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 03N14
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	60.3	62.7	55.9	27.9	50.6	53.4	52	12.5	24.2	10.0	41.8	61.8
120	84.7	85.7	80.7	53.8	73.3	79.5	76	11.9	15.6	9.5	66.8	85.8
180	97.5	97.8	94.4	70.1	87.4	94.4	90	10.6	11.7	8.5	81.8	98.7
240	104.8	104.3	102.8	81.5	96.7	103.0	99	9.0	9.1	7.2	91.7	106.0
300	107.5	108.0	107.2	90.0	102.4	107.1	104	7.0	6.8	5.6	98.1	109.3
360	109.1	108.9	109.1	96.7	106.3	108.6	106	4.9	4.6	3.9	102.5	110.4
420	109.7	109.0	109.8	101.0	107.2	108.9	108	3.4	3.1	2.7	104.9	110.3
480	109.9	109.2	109.6	104.6	108.1	109.2	108	2.0	1.8	1.6	106.9	110.0
540	110.3	109.9	109.7	107.1	108.0	109.9	109	1.3	1.2	1.0	108.1	110.2
600	109.7	109.6	109.8	108.3	108.7	109.2	109	0.6	0.6	0.5	108.7	109.7
720	110.1	109.8	110.4	108.4	108.9	109.6	110	0.8	0.7	0.6	108.9	110.1

Table 3.39 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (05N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	05N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCI, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	46	1.7	3.7	1.4
120	40	1.4	3.6	1.1	70	1.9	2.7	1.5
180	51	1.4	2.7	1.1	85	1.7	2.0	1.3
240	61	2.6	4.2	2.0	95	1.5	1.5	1.2
300	69	1.7	2.5	1.4	102	1.3	1.3	1.0
360	76	1.8	2.3	1.4	106	1.0	1.0	0.8
420	82	2.5	3.0	2.0	108	0.7	0.6	0.5
480	87	1.8	2.1	1.5	109	0.6	0.5	0.4
540	92	1.5	1.6	1.2	110	0.8	0.8	0.7
600	96	2.2	2.3	1.8	110	0.6	0.6	0.5
720	101	1.9	1.9	1.6	110	0.5	0.5	0.4

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	270.9
60	20.8		
120	29.6		
180	33.9		
240	34.7		
300	33.5		
360	29.8		
420	26.0		
480	21.9		
540	18.0		
600	13.7		
720	9.2		
	f1	35	
	f2	23	

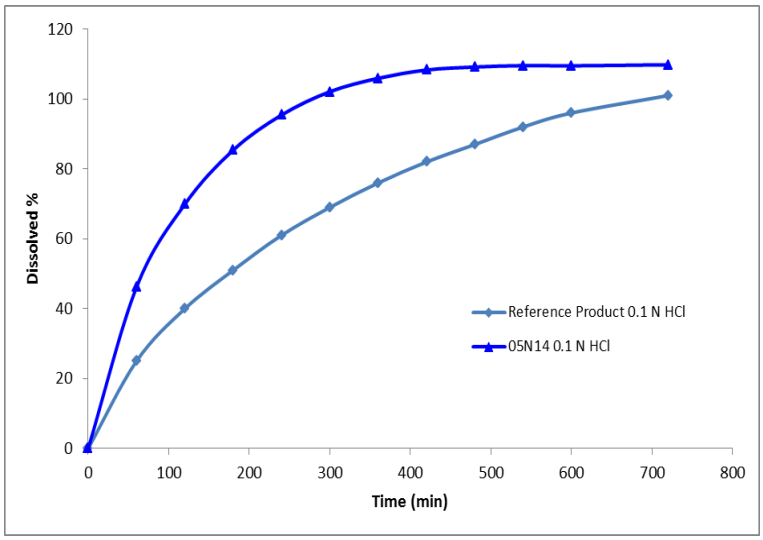


Figure 3.4 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 05N14 vs Reference Product

Although five different formulations were attempted to enhance the f2 value, unfortunately, low f2 values were obtained for all cases. We chose dry granulation technique in the first place because of its easy applicability and low cost. Obtained f2 values after different formulations via dry granulation technique suggest that manufacturing process should be dramatically changed for our formulations. Because of that slugging process was used with the same formulation as sixth formulation trail. Slugging is a direct compression method and in this process powder blend is compacted by applying a force onto the powder, which in general causes a considerable size enlargement.

Table 3.40 shows the dissolution test results and Table 3.41 shows the f2 calculation of Niacin 500 mg ER Tablet-Capsule produced via slugging process (Batch no: 06N14) for 0.1 N HCl dissolution medium. The comparative graph with the reference product for this test was shown in Figure 3.5.

Table 3.40 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 06N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 06N14
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	45.1	45.1	45.1	45.2	43.4	43.5	45	0.9	1.9	0.7	43.9	45.3
120	68.6	69.0	68.5	68.5	65.4	67.5	68	1.3	2.0	1.1	66.9	69.0
180	84.3	84.7	84.4	83.9	80.8	83.6	84	1.4	1.7	1.1	82.5	84.8
240	94.8	95.2	95.0	94.2	91.4	94.4	94	1.4	1.5	1.1	93.0	95.3
300	101.6	101.8	101.3	100.9	99.0	101.0	101	1.0	1.0	0.8	100.1	101.7
360	104.9	104.5	104.9	104.6	103.7	105.2	105	0.5	0.5	0.4	104.2	105.0
420	107.4	107.1	106.9	106.3	106.3	107.5	107	0.5	0.5	0.4	106.5	107.3
480	107.7	108.4	108.0	107.4	107.7	108.1	108	0.4	0.3	0.3	107.6	108.2
540	108.5	108.1	107.5	108.1	108.1	108.5	108	0.4	0.3	0.3	107.8	108.4
600	108.8	108.8	107.9	108.3	108.2	108.7	108	0.4	0.3	0.3	108.2	108.7
720	108.7	108.6	108.0	108.2	108.3	108.5	108	0.3	0.2	0.2	108.2	108.6

Table 3.41 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (06N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	06N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	45	0.9	1.9	0.7
120	40	1.4	3.6	1.1	68	1.3	2.0	1.1
180	51	1.4	2.7	1.1	84	1.4	1.7	1.1
240	61	2.6	4.2	2.0	94	1.4	1.5	1.1
300	69	1.7	2.5	1.4	101	1.0	1.0	0.8
360	76	1.8	2.3	1.4	105	0.5	0.5	0.4
420	82	2.5	3.0	2.0	107	0.5	0.5	0.4
480	87	1.8	2.1	1.5	108	0.4	0.3	0.3
540	92	1.5	1.6	1.2	108	0.4	0.3	0.3
600	96	2.2	2.3	1.8	108	0.4	0.3	0.3
720	101	1.9	1.9	1.6	108	0.3	0.2	0.2

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	255.3
60	19.2		
120	27.6		
180	32.1		
240	33.4		
300	32.3		
360	28.5		
420	24.6		
480	20.6		
540	16.5		
600	12.6		
720	7.8		
	f1	33	
	f2	24	

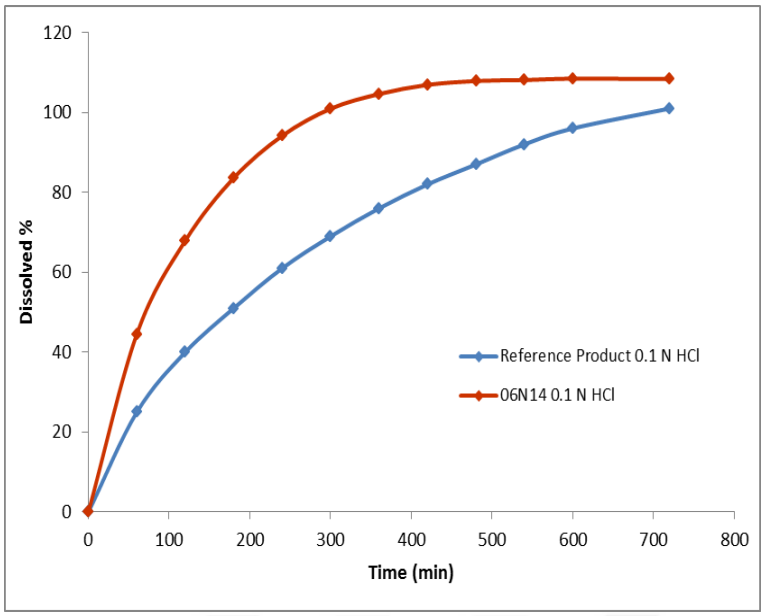


Figure 3.5 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 06N14 vs Reference Product

After the dissolution analyses were completed f1 was found to be 33, while f2 was found to be 24 for 06N14 series which couldn't supply acceptable f2 value. According to obtained f2 values below 50 it was decided that slugging process didn't affect the dissolution rate for Niacin 500 mg ER Tablet-Capsule. So that it was decided to change the formulation type from dry granulation to wet one. Wet granulation forms by binding the powder together with an adhesive, instead of by compaction. Bridges are developed between the particles and the tensile strength of bonds increases as amount of liquid added is increased. Also controlled release agent (HPMC) starts to swell with water and binding properties become more effective. After detecting acceptable dissolution results fractional factorial design for tablet formulation via wet granulation would be planned.

With the first formulation trial via wet granulation technique, consistent values couldn't be obtained. Table 3.42 shows the dissolution test results of Niacin 500 mg ER Tablet-Capsule (Batch no: 07N14) produced by wet granulation. The comparative graph for this test was shown in Figure 3.6. f1 was found to be 18, while f2 was found to be 35 for this formulation trial (Table 3.43) which are not also in agreement with the acceptable ranges. However, dissolution profile of this formulation was closer than the previous formulation trials to the reference product. So that it was decided to proceed with wet granulation technique.

Table 3.42 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 07N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 07N14
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	48.0	47.7	49.1	42.8	35.1	41.1	44	5.4	12.2	4.3	39.7	48.3
120	67.9	66.4	67.9	60.4	51.9	59.4	62	6.3	10.1	5.1	57.3	67.4
180	79.5	77.1	79.3	71.3	62.8	71.0	74	6.5	8.8	5.2	68.3	78.7
240	87.2	84.5	86.8	78.9	70.7	79.1	81	6.3	7.8	5.0	76.2	86.2
300	92.3	89.3	91.6	84.5	76.4	84.5	86	6.0	6.9	4.8	81.7	91.2
360	95.4	92.4	95.0	88.3	80.8	88.3	90	5.5	6.1	4.4	85.6	94.4
420	95.8	93.9	96.6	90.5	84.0	90.8	92	4.6	5.0	3.7	88.2	95.6
480	97.6	94.6	97.3	91.9	86.2	91.8	93	4.3	4.6	3.4	89.8	96.6
540	97.5	94.8	97.6	91.9	87.1	92.4	94	4.0	4.3	3.2	90.4	96.7
600	98.4	95.3	98.0	92.4	87.8	92.8	94	4.0	4.2	3.2	90.9	97.3
720	98.8	95.2	97.7	92.5	88.4	92.8	94	3.8	4.1	3.1	91.2	97.3

Table 3.43 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (07N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	07N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCI, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	44	5.4	12.2	4.3
120	40	1.4	3.6	1.1	62	6.3	10.1	5.0
180	51	1.4	2.7	1.1	74	6.5	8.8	5.2
240	61	2.6	4.2	2.0	81	6.3	7.7	5.0
300	69	1.7	2.5	1.4	86	6.0	6.9	4.8
360	76	1.8	2.3	1.4	90	5.5	6.1	4.4
420	82	2.5	3.0	2.0	92	4.6	5.1	3.7
480	87	1.8	2.1	1.5	93	4.3	4.6	3.4
540	92	1.5	1.6	1.2	94	4.0	4.3	3.2
600	96	2.2	2.3	1.8	94	4.0	4.2	3.2
720	101	1.9	1.9	1.6	94	3.8	4.1	3.1

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	140.4
60	18.6		
120	22.0		
180	22.0		
240	20.5		
300	17.8		
360	13.9		
420	9.6		
480	5.9		
540	1.9		
600	1.7		
720	6.4		
	f1	18	
	f2	35	

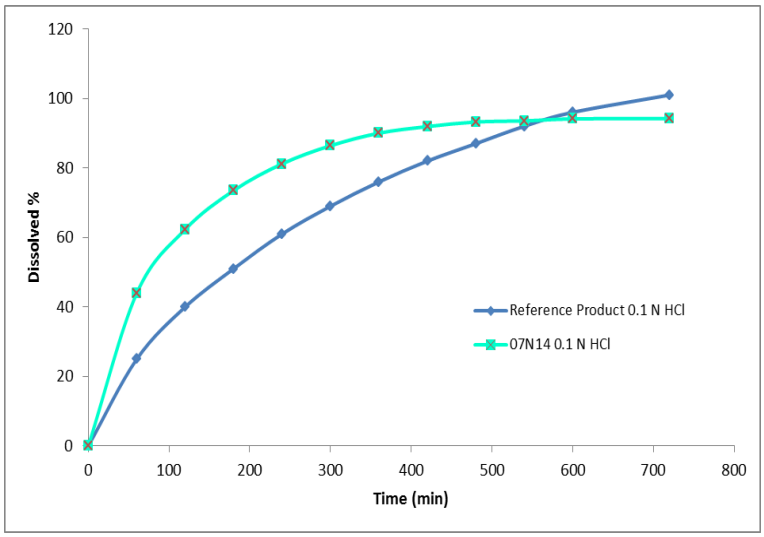


Figure 3.6 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 07N14 vs Reference Product

After the promising dissolution profile test results of wet granulation method experiments were carried out with such like previous formulation. It was expected that changing the HPMC K100 M CR amount in the formulation from 135 mg/tablet to 150 mg/tablet would increase the f2 value. Table 3.44 shows the dissolution test results of this formulation. But when f1 and f2 calculations were performed for dissolution studies, f1 was found to be 27 while, f2 was found to be 28 for 08N14 series as shown in Table 3.45. The comparative graph for this test was shown in Figure 3.7.

Table 3.44 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 08N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 08N14
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	44.4	43.1	43.3	41.6	40.0	41.2	42	1.6	3.8	1.3	41.0	43.6
120	65.2	63.2	63.7	60.7	59.1	61.1	62	2.3	3.6	1.8	60.4	64.0
180	79.5	77.5	78.2	74.6	72.9	75.4	76	2.5	3.2	2.0	74.4	78.3
240	90.2	87.7	88.3	84.4	83.3	85.8	87	2.6	3.0	2.1	84.5	88.7
300	97.5	95.5	95.9	91.6	91.0	93.2	94	2.6	2.7	2.1	92.0	96.2
360	102.8	100.7	100.9	96.8	96.7	98.5	99	2.5	2.5	2.0	97.4	101.4
420	106.1	103.9	104.1	100.1	100.8	102.0	103	2.3	2.2	1.8	101.0	104.6
480	106.8	105.7	106.1	103.0	103.3	104.5	105	1.6	1.5	1.2	103.7	106.1
540	109.5	107.2	107.3	104.0	105.3	105.4	106	2.0	1.8	1.6	104.9	108.0
600	108.9	107.5	108.0	104.6	106.4	105.8	107	1.6	1.5	1.3	105.6	108.1
720	109.3	108.5	108.9	105.0	107.2	106.6	108	1.6	1.5	1.3	106.3	108.9

Table 3.45 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (08N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	08N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	42	1.6	3.8	1.3
120	40	1.4	3.6	1.1	62	2.3	3.6	1.8
180	51	1.4	2.7	1.1	76	2.5	3.2	2.0
240	61	2.6	4.2	2.0	87	2.6	3.0	2.1
300	69	1.7	2.5	1.4	94	2.6	2.7	2.1
360	76	1.8	2.3	1.4	99	2.5	2.5	2.0
420	82	2.5	3.0	2.0	103	2.3	2.2	1.8
480	87	1.8	2.1	1.5	105	1.6	1.5	1.2
540	92	1.5	1.6	1.2	106	2.0	1.8	1.6
600	96	2.2	2.3	1.8	107	1.6	1.5	1.3
720	101	1.9	1.9	1.6	108	1.6	1.5	1.3

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	209.2
60	16.9		
120	21.8		
180	24.9		
240	25.9		
300	25.5		
360	23.3		
420	20.5		
480	17.6		
540	14.8		
600	11.0		
720	7.0		
	f1	27	
	f2	28	

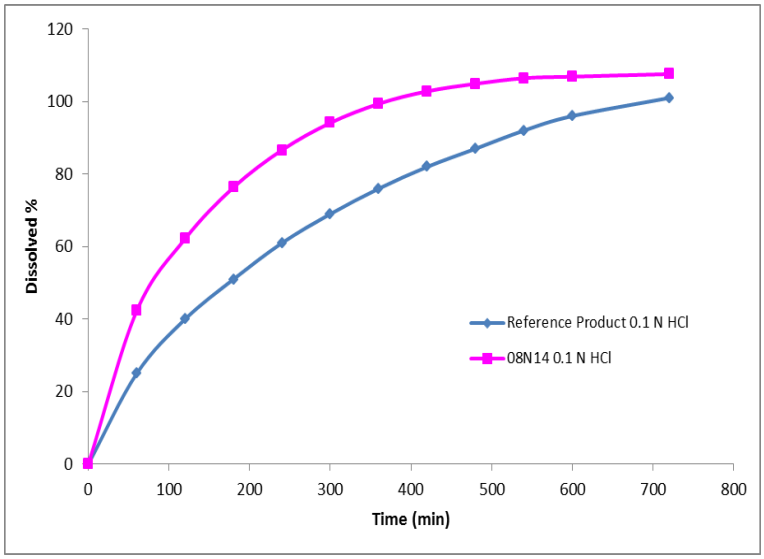


Figure 3.7 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 08N14 vs Reference Product

Because of increasing HPMC K100 M CR amount didn't increase enhance the f2 value as expected; it was decided to change the type of extended release agent which is the most expressive component of controlled release type formulations. Combination of Carboxymethyl Cellulose, HPMC K100 LV (7HF) and HPMC K100 M CR was used for the next formulation. Generally combination of extended release agents aren't preferred for formulations but can be used in some specific circumstances. The dissolution results of this formulation trial were tabulated in Table 3.46 and comparative graph for this test was shown in Figure 3.8 for 0.1 N HCl medium.

According to obtained dissolution study test results, the f1 and f2 values were calculated and f1 was found to be 36, while f2 was found to be 22 for 09N14 series as shown in Table 3.47. Obtained f1 and f2 values showed us that this type of extended release agent combination wasn't suitable for our tablet formulation.

Table 3.46 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 09N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 09N14
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	51.4	48.5	52.2	52.7	53.3	47.5	51	2.4	4.7	1.9	49.0	52.8
120	73.0	69.9	75.0	73.8	75.7	68.5	73	2.9	3.9	2.3	70.4	74.9
180	87.1	84.6	89.7	87.2	89.8	82.8	87	2.8	3.2	2.2	84.6	89.1
240	96.0	94.4	99.0	96.2	99.2	92.3	96	2.7	2.8	2.1	94.1	98.3
300	102.3	101.3	105.2	102.0	105.2	99.6	103	2.2	2.2	1.8	100.8	104.4
360	106.0	105.2	109.1	105.6	109.1	103.6	106	2.2	2.1	1.8	104.7	108.2
420	108.5	107.6	110.7	107.9	111.9	106.6	109	2.0	1.9	1.6	107.3	110.5
480	107.8	108.9	110.9	108.0	112.4	107.4	109	2.0	1.8	1.6	107.6	110.8
540	109.7	109.1	110.9	109.7	112.4	108.2	110	1.5	1.3	1.2	108.8	111.2
600	109.1	109.8	111.3	109.0	112.7	108.3	110	1.7	1.5	1.3	108.7	111.4
720	109.7	109.5	111.3	109.6	113.1	108.8	110	1.6	1.4	1.3	109.1	111.6

Table 3.47 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (09N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	09N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCI, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	51	2.4	4.7	1.9
120	40	1.4	3.6	1.1	73	2.9	3.9	2.3
180	51	1.4	2.7	1.1	87	2.8	3.2	2.2
240	61	2.6	4.2	2.0	96	2.7	2.8	2.1
300	69	1.7	2.5	1.4	103	2.2	2.2	1.8
360	76	1.8	2.3	1.4	106	2.2	2.1	1.8
420	82	2.5	3.0	2.0	109	2.0	1.9	1.6
480	87	1.8	2.1	1.5	109	2.0	1.8	1.6
540	92	1.5	1.6	1.2	110	1.5	1.3	1.2
600	96	2.2	2.3	1.8	110	1.7	1.5	1.3
720	101	1.9	1.9	1.6	110	1.6	1.4	1.3

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	283.8
60	25.6		
120	32.3		
180	35.4		
240	35.5		
300	34.0		
360	30.3		
420	26.6		
480	21.9		
540	18.4		
600	14.2		
720	9.7		
	f1	36	
	f2	22	

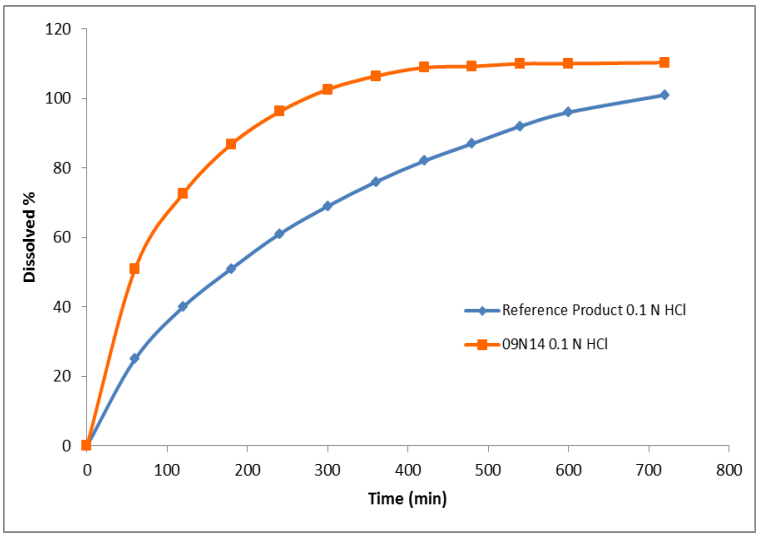


Figure 3.8 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 09N14 vs Reference Product

The next formulation contains combination of HPMC E4M and HPMC K100 M CR as extended release agent. Table 3.48 illustrates the test results of dissolution profile study while, Figure 3.9 shows the comparative test results with the reference product dissolution profile and Table 3.49 shows the f1-f2 results of this formulation (10N14). f1 and f2 values were obtained below the acceptable the limits. Thus, combination of HPMC E4M and HPMC K100 M CR as extended release agent does not have any impact on the dissolution similarity factor of this drug product.

Ega and Siddoju (2016) used similar type of methocel (Methocel K4M CR) in their study via wet granulation method in order to achieve required extended release profile. Although according to their study the experimental formulation compared well with commercial products and met the proposed standards for controlled release products, the use of HPMC E4M didn’t performed well in this study rather displaying un-expected results.

Table 3.48 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 10N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 10N14
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**			**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0
60	46.3	43.9	37.9	43	4.3	10.1	4.9	37.8	47.6
120	68.7	64.4	57.2	63	5.8	9.2	6.6	56.9	70.0
180	82.0	78.4	70.6	77	5.8	7.6	6.6	70.4	83.6
240	90.8	88.4	80.8	87	5.2	6.0	5.9	80.8	92.6
300	97.4	95.7	88.6	94	4.7	5.0	5.3	88.6	99.2
360	102.4	100.8	94.6	99	4.1	4.2	4.7	94.6	103.9
420	104.8	104.0	98.7	103	3.3	3.2	3.8	98.7	106.3
480	106.4	106.5	101.4	105	2.9	2.8	3.3	101.5	108.1
540	107.4	107.6	102.6	106	2.8	2.7	3.2	102.7	109.1
600	107.8	108.4	104.4	107	2.2	2.0	2.4	104.4	109.3
720	109.5	109.4	105.3	108	2.4	2.2	2.7	105.4	110.8

Table 3.49 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (10N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	10N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	43	4.3	10.1	4.9
120	40	1.4	3.6	1.1	63	5.8	9.2	6.6
180	51	1.4	2.7	1.1	77	5.8	7.6	6.6
240	61	2.6	4.2	2.0	87	5.2	6.0	5.9
300	69	1.7	2.5	1.4	94	4.7	5.0	5.3
360	76	1.8	2.3	1.4	99	4.1	4.2	4.7
420	82	2.5	3.0	2.0	103	3.3	3.2	3.8
480	87	1.8	2.1	1.5	105	2.9	2.8	3.3
540	92	1.5	1.6	1.2	106	2.8	2.7	3.2
600	96	2.2	2.3	1.8	107	2.2	2.0	2.4
720	101	1.9	1.9	1.6	108	2.4	2.2	2.7

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	210.7
60	17.3		
120	23.1		
180	25.5		
240	25.9		
300	25.3		
360	23.2		
420	20.2		
480	17.5		
540	14.3		
600	11.0		
720	7.4		
	f1	27	
	f2	21	

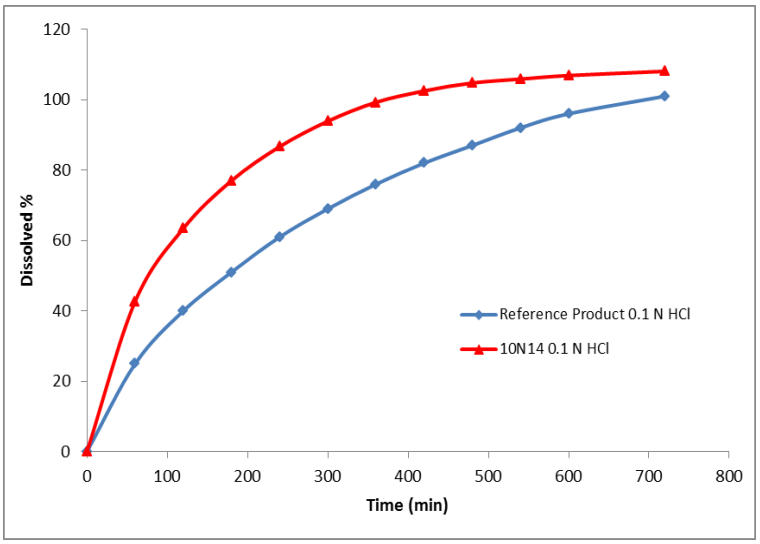


Figure 3.9 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 10N14 vs Reference Product

When the results, calculated according to the dissolution profile study performed in 0.1 N HCl medium shown in the Table 3.49, have been examined, it was seen that the combined extended release agent used in the production of the product has not provided the expected f2 enhancement. Since proper f2 value couldn't be obtained with this formulation, it was decided to perform a new mini formulation trial consist of only K100 M CR as extended release agent. 11N14 batch numbered Niacin 500 mg ER Tablet-Capsule formulation test results were illustrated in Table 3.50 and dissolution profile graph vs reference product was shown in Figure 3.10.

f1 and f2 values were calculated and f1 was found to be 16, while f2 was found to be 32 for this series (Table 3.51). Increase in f2 value implies that this dissolution profile was closer to reference product dissolution profile. Also decrease at first hour in dissolution results proved us that extended release of the product can be deemed to be successful.

Table 3.50 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 11N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 11N14
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)				**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0
60	23.3	19.6	22.1	22	1.9	8.7	2.1	19.5	23.8
120	36.9	29.8	33.6	33	3.6	10.6	4.0	29.4	37.5
180	47.9	38.1	42.4	43	4.9	11.5	5.6	37.2	48.4
240	56.9	45.0	49.9	51	6.0	11.8	6.8	43.8	57.4
300	64.2	51.0	56.7	57	6.6	11.6	7.5	49.8	64.8
360	70.5	56.4	62.6	63	7.1	11.2	8.0	55.2	71.2
420	75.7	61.1	67.8	68	7.3	10.7	8.3	59.9	76.5
480	80.3	65.5	72.7	73	7.4	10.2	8.4	64.5	81.2
540	83.9	69.5	76.6	77	7.2	9.4	8.1	68.5	84.8
600	87.1	73.0	80.5	80	7.1	8.8	8.0	72.2	88.2
720	91.8	79.4	86.8	86	6.7	7.3	7.1	78.9	93.1

Table 3.51 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (11N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	11N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	22	1.9	8.7	2.1
120	40	1.4	3.6	1.1	33	3.6	10.6	4.0
180	51	1.4	2.7	1.1	43	4.9	11.5	5.6
240	61	2.6	4.2	2.0	51	6.0	11.8	6.8
300	69	1.7	2.5	1.4	57	6.6	11.6	7.5
360	76	1.8	2.3	1.4	63	7.1	11.2	8.0
420	82	2.5	3.0	2.0	68	7.3	10.7	8.3
480	87	1.8	2.1	1.5	73	7.4	10.2	8.4
540	92	1.5	1.6	1.2	77	7.2	9.4	8.1
600	96	2.2	2.3	1.8	80	7.1	8.8	8.0
720	101	1.9	1.9	1.6	86	6.2	7.3	7.1

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	127.5
60	3.7		
120	6.9		
180	8.7		
240	10.1		
300	11.3		
360	12.9		
420	14.1		
480	14.5		
540	15.0		
600	15.6		
720	14.6		
	f1	16	
	f2	32	

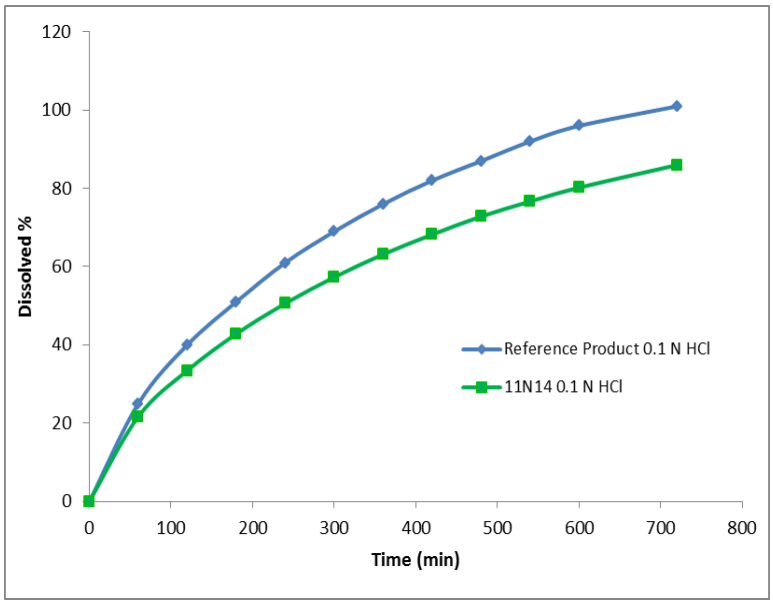


Figure 3.10 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 11N14 vs Reference Product

11N14 numbered Niacin 500 mg ER Tablet-Capsule formulation test results were promising. After having been realized that the increased amount of HPMC K100M CR positively affect the f2 value, the same formulation was repeated with more amount of granule to be sure. Table 3.52 displays the dissolution results of this formula (Batch number: 12N14) and dissolution profile graph vs reference product was illustrated in Figure 3.11. Based on obtained dissolution profile test results f1 was found to be 6, while f2 was found to be 61 for this series (Table 3.53). f2 value of this production was with in between the limits so that it was decided to compose design pattern of DoE according to this formulation.

Table 3.52 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 12N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 12N14
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	21.4	25.3	19.5	22.5	25.4	22.8	23	2.3	10.0	1.8	21.0	24.6
120	35.0	39.8	32.1	36.4	39.9	37.7	37	3.0	8.1	2.4	34.4	39.2
180	45.7	51.0	42.2	47.5	51.2	49.3	48	3.5	7.2	2.8	45.0	50.6
240	54.5	60.3	50.8	56.6	60.5	59.1	57	3.8	6.7	3.0	53.9	60.0
300	62.0	68.0	58.1	64.5	68.4	67.4	65	4.1	6.3	3.3	61.5	68.0
360	68.4	74.7	64.5	71.1	75.0	74.5	71	4.2	5.9	3.4	68.0	74.8
420	74.0	80.3	70.2	77.0	80.7	80.6	77	4.3	5.6	3.4	73.7	80.6
480	78.8	85.2	75.1	81.9	85.5	85.9	82	4.4	5.3	3.5	78.6	85.6
540	82.8	89.2	79.4	86.2	89.6	90.3	86	4.4	5.1	3.5	82.8	89.7
600	86.4	92.7	83.1	89.8	93.0	94.1	90	4.3	4.8	3.5	86.4	93.3
720	92.1	97.7	98.9	95.5	98.1	99.8	97	2.8	2.9	2.2	94.8	99.3

Table 3.53 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (12N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	12N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	23	2.3	10.0	1.8
120	40	1.4	3.6	1.1	37	3.0	8.1	2.4
180	51	1.4	2.7	1.1	48	3.5	7.2	2.8
240	61	2.6	4.2	2.0	57	3.8	6.7	3.0
300	69	1.7	2.5	1.4	65	4.1	6.3	3.3
360	76	1.8	2.3	1.4	71	4.2	5.9	3.4
420	82	2.5	3.0	2.0	77	4.3	5.6	3.4
480	87	1.8	2.1	1.5	82	4.4	5.3	3.5
540	92	1.5	1.6	1.2	86	4.4	5.1	3.5
600	96	2.2	2.3	1.8	90	4.3	4.8	3.5
720	101	1.9	1.9	1.6	97	2.8	2.9	2.2

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	47.5
60	2.6		
120	3.5		
180	3.7		
240	3.8		
300	3.9		
360	4.7		
420	5.2		
480	5.2		
540	5.4		
600	6.0		
720	3.6		
	f1	6	
	f2	61	

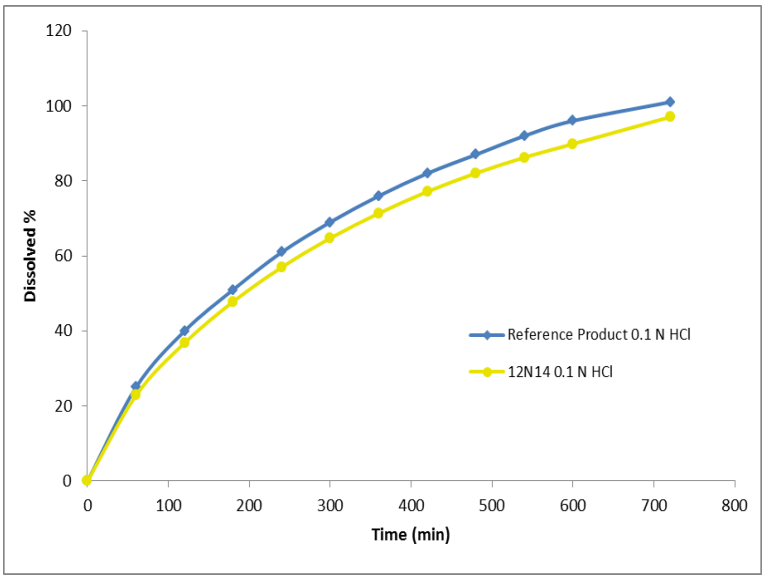


Figure 3.11 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 12N14 vs Reference Product

For the first formulation of DoE lower amount of HPMC K100 M CR was used and according to results of this batch DoE pattern requires to be developed or modified. Table 3.54 shows the dissolution test results of Niacin 500 mg ER Tablet-Capsule (Batch no: 13N14) for the same conditions. The comparative graph for this test was shown in Figure 3.12.

Also the f1 and f2 calculations were performed for dissolution studies, test results of second batch of reference product were considered for these calculations as well and f1 was found to be 2, while f2 was found to be 80 for 13N14 series. Table 3.55 shows the graph of comparative test results. Despite the fact that lower amount of HPMC K100 M CR was used surprisingly higher f2 value was obtained. The reason of this could be the use of second batch of Niacin for this formulation. Even though the API and the origin of API were supplied from same sources, particle size of the API can be different and this can cause different dissolution profile.

Table 3.54 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 13N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 13N14
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	24.1	29.2	27.4	26.3	24.6	29.3	27	2.2	8.3	1.8	25.0	28.6
120	37.7	44.3	42.7	41.1	38.3	44.5	41	2.9	7.1	2.3	39.1	43.8
180	51.3	55.7	54.2	52.5	51.0	55.9	53	2.2	4.0	1.7	51.7	55.2
240	61.7	64.7	63.4	61.8	61.2	65.0	63	1.6	2.6	1.3	61.7	64.3
300	70.4	72.3	71.1	69.5	69.8	72.6	71	1.3	1.8	1.0	69.9	72.0
360	77.6	78.6	77.5	75.9	75.9	78.8	77	1.3	1.6	1.0	76.4	78.4
420	83.1	83.7	82.7	81.3	81.6	84.1	83	1.1	1.4	0.9	81.9	83.6
480	87.8	88.2	87.1	85.8	86.6	88.4	87	1.0	1.2	0.8	86.5	88.1
540	91.8	91.7	90.9	89.5	90.9	92.0	91	0.9	1.0	0.7	90.4	91.9
600	94.5	94.4	93.7	92.4	93.0	94.7	94	0.9	1.0	0.7	93.0	94.5
720	97.7	97.9	97.3	96.0	97.9	98.2	98	0.8	0.8	0.6	96.9	98.1

Table 3.55 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (13N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	13N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCI, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	27	2.2	8.3	1.8
120	40	1.4	3.6	1.1	41	2.9	7.1	2.3
180	51	1.4	2.7	1.1	53	2.2	4.0	1.7
240	61	2.6	4.2	2.0	63	1.6	2.6	1.3
300	69	1.7	2.5	1.4	71	1.3	1.8	1.0
360	76	1.8	2.3	1.4	77	1.3	1.6	1.0
420	82	2.5	3.0	2.0	83	1.1	1.4	0.9
480	87	1.8	2.1	1.5	87	1.0	1.2	0.8
540	92	1.5	1.6	1.2	91	0.9	1.0	0.7
600	96	2.2	2.3	1.8	94	0.9	1.0	0.7
720	101	1.9	1.9	1.6	98	0.8	0.8	0.6

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	16.5
60	1.5		
120	1.1		
180	1.9		
240	2.2		
300	2.3		
360	1.3		
420	0.5		
480	0.0		
540	0.5		
600	2.0		
720	3.1		
	f1	2	
	f2	80	

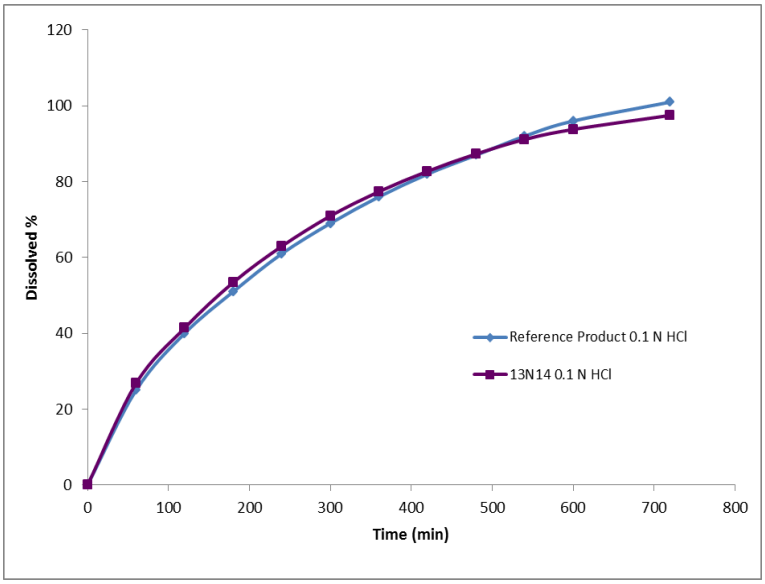


Figure 3.12 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 13N14 vs Reference Product

13N14 batch numbered tablets showed similar dissolution profile compared to the test results of reference product better than expectation. It was, therefore, planned to determine behavior of HPMC K100 M CR with lower amount. For second part of DoE HPMC K100 M CR amount was decreased, while Lactose Monohydrate amount was increased and amount of Avicel PH 102 was kept the same as in the previous formulation. Tablets were pressed and dissolution profile experiment was performed with second trial of DoE formulation study (Batch number: 14N14).

The dissolution results of 14N14 batch numbered Niacin 500 mg ER Tablet-Capsule were tabulated in Table 3.56 for 0.1 N HCl medium. The comparative graph for this test was shown in Figure 3.13, from the below dissolution data, it is observed that complete dissolution was observed with this formulation in the 0.1 N HCl dissolution media. The f1 and f2 calculations were performed for dissolution studies, second batch of reference product was considered for the calculations and f1 was found to be 3, f2 was found to be 70 as presented in Table 3.57.

Table 3.56 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 14N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 14N14
Number of units	6
Dissolution conditions	0.1 N HCI, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	24.5	29.8	26.8	30.5	28.0	29.3	28	2.2	7.9	1.8	26.4	29.9
120	42.7	43.5	45.0	43.1	44.5	47.6	44	1.8	4.0	1.4	43.0	45.8
180	56.5	57.8	55.4	58.6	57.5	56.9	57	1.1	1.9	0.9	56.2	58.0
240	67.5	64.7	63.4	61.8	64.7	65.0	65	1.9	2.9	1.5	63.0	66.0
300	73.5	68.0	69.5	72.5	74.2	73.0	72	2.5	3.4	2.0	69.8	73.8
360	80.5	77.6	78.5	73.5	77.6	80.2	78	2.5	3.2	2.0	76.0	80.0
420	82.5	83.2	85.6	85.4	81.7	82.5	83	1.6	2.0	1.3	82.2	84.8
480	87.0	83.5	91.0	92.5	87.4	85.2	88	3.4	3.9	2.7	85.0	90.5
540	95.6	96.7	91.5	92.6	90.2	90.4	93	2.7	2.9	2.2	90.6	95.0
600	98.4	89.7	97.9	99.5	100.2	99.5	98	3.9	4.0	3.1	94.4	100.7
720	101.5	99.6	98.5	102.5	101.3	99.9	101	1.5	1.5	1.2	99.4	101.7

Table 3.57 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (14N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	14N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	28	2.2	7.9	1.8
120	40	1.4	3.6	1.1	44	1.8	4.0	1.4
180	51	1.4	2.7	1.1	57	1.1	1.9	0.9
240	61	2.6	4.2	2.0	65	1.9	2.9	1.5
300	69	1.7	2.5	1.4	72	2.5	3.4	2.0
360	76	1.8	2.3	1.4	78	2.5	3.2	2.0
420	82	2.5	3.0	2.0	83	1.6	2.0	1.3
480	87	1.8	2.1	1.5	88	3.4	3.9	2.7
540	92	1.5	1.6	1.2	93	2.7	2.9	2.2
600	96	2.2	2.3	1.8	98	3.9	4.0	3.1
720	101	1.9	1.9	1.6	101	1.5	1.5	1.2

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	26.0
60	2.8		
120	4.1		
180	5.6		
240	3.8		
300	3.2		
360	1.9		
420	1.2		
480	0.5		
540	1.2		
600	1.7		
720	0.1		
	f1	3	
	f2	70	

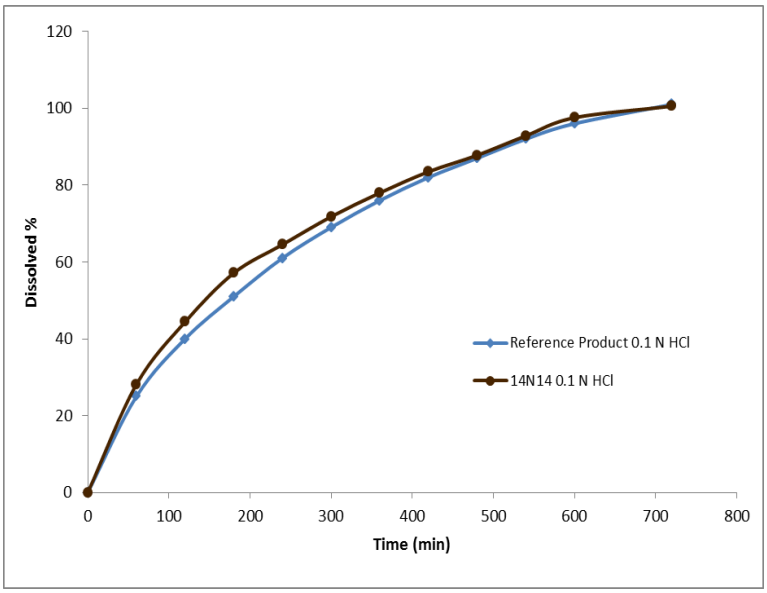


Figure 3.13 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 14N14 vs Reference Product

Lower f2 value was obtained with the second formulation of DoE than the first formulation trial. The reason behind the lower f2 values, compared to the first formulation, was thought to be the reduced controlled release agent amount, when HPMC amount get lower binding capacity might get lower. For the third formulation amount of HPMC K100 M CR was kept the same as the second one, Lactose Monohydrate and Avicel PH 102 amount were decreased. After wet granulation process tablets were pressed and dissolution profile experiment was performed. The results of dissolution profile study were shown in Table 3.58 and the comparative graph of 15N14 batch numbered Niacin 500 mg ER Tablet-Capsule was shown in Figure 3.14.

According to dissolution study test results f1 and f2 calculations were performed, second batch of reference product was considered for the calculations and f1 was found to be 6, f2 was found to be 60 as shown in Table 3.59.

Table 3.58 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 15N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 15N14
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	28.7	32.5	30.6	30.4	28.7	29.5	30	1.4	4.8	1.2	28.9	31.2
120	43.2	45.7	46.5	42.3	45.6	44.1	45	1.6	3.7	1.3	43.3	45.9
180	58.0	59.3	57.5	57.6	58.5	58.7	58	0.7	1.2	0.6	57.7	58.8
240	66.5	67.5	67.9	69.1	66.4	65.3	67	1.3	2.0	1.1	66.0	68.2
300	74.5	75.0	74.9	73.2	75.6	72.3	74	1.2	1.7	1.0	73.3	75.2
360	79.5	82.5	83.7	79.5	82.6	80.2	81	1.8	2.2	1.5	79.9	82.8
420	87.6	87.0	86.4	82.5	90.1	87.8	87	2.5	2.9	2.0	84.9	88.9
480	90.5	91.7	90.6	89.2	92.5	91.9	91	1.2	1.3	1.0	90.1	92.0
540	95.0	94.7	93.2	94.0	95.2	94.9	95	0.8	0.8	0.6	93.9	95.1
600	98.2	98.0	100.2	98.9	98.2	97.0	98	1.1	1.1	0.9	97.6	99.3
720	100.9	101.3	102.7	102.9	103.1	102.5	102	0.9	0.9	0.7	101.5	103.0

Table 3.59 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (15N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	15N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	30	1.4	4.8	1.2
120	40	1.4	3.6	1.1	45	1.6	3.7	1.3
180	51	1.4	2.7	1.1	58	0.7	1.2	0.6
240	61	2.6	4.2	2.0	67	1.3	2.0	1.1
300	69	1.7	2.5	1.4	74	1.2	1.7	1.0
360	76	1.8	2.3	1.4	81	1.8	2.2	1.5
420	82	2.5	3.0	2.0	87	2.5	2.9	2.0
480	87	1.8	2.1	1.5	91	1.2	1.3	1.0
540	92	1.5	1.6	1.2	95	0.8	0.8	0.6
600	96	2.2	2.3	1.8	98	1.1	1.1	0.9
720	101	1.9	1.9	1.6	102	0.9	0.9	0.7

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	48.4
60	4.7		
120	4.2		
180	6.8		
240	6.4		
300	5.6		
360	5.2		
420	4.6		
480	3.8		
540	2.9		
600	2.6		
720	1.6		
	f1	6	
	f2	60	

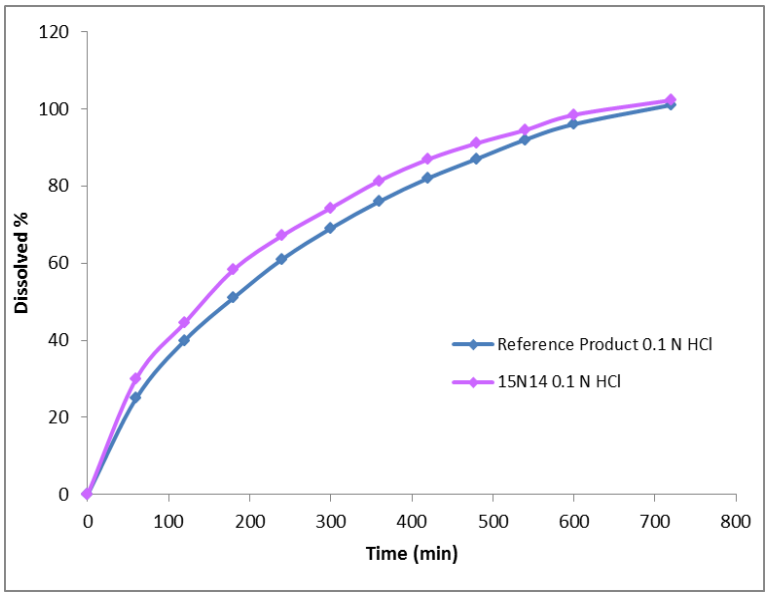


Figure 3.14 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 15N14 vs Reference Product

As shown in Table 3.59 f2 value of third formulation trial was obtained the lowest but still in agreement with the acceptable ranges. This value showed us decreasing amount of HPMC K100 M CR, Lactose Monohydrate and Avicel PH 102 negatively affect the dissolution profile. For last part of DoE experiment HPMC K100 M CR amount and Lactose Monohydrate amount were increased, Avicel PH 102 was decreased again. After tablets were pressed and dissolution profile experiment was performed detailed comparisons were made with reference product.

Table 3.60 shows the dissolution test results of Niacin 500 mg ER Tablet-Capsule (Batch no: 16N14) for 0.1 N HCl medium. The comparative graph for this test was illustrated in Figure 3.15. Also the f1 and f2 calculations were performed for this last formulation trial, second batch of reference product was considered for these calculations and f1 was found to be 1, while f2 was found to be 94 (Table 3.61). This calculated f2 value showed us the last formulation was the most similar to the reference product. According to information so far, the last trial was chosen as the final formula.

Table 3.60 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (Batch no: 16N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 16N14
Number of units	6
Dissolution conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	27.4	27.1	25.5	27.1	25.7	25.6	26	0.9	3.4	0.7	25.7	27.1
120	41.5	41.5	38.8	40.2	38.8	38.7	40	1.3	3.4	1.1	38.8	41.0
180	53.5	52.8	49.6	50.6	49.5	49.3	51	1.8	3.6	1.5	49.4	52.3
240	62.9	62.4	59.0	59.8	58.8	58.5	60	1.9	3.2	1.5	58.7	61.8
300	70.6	70.6	67.4	67.8	67.1	66.7	68	1.8	2.6	1.4	67.0	69.8
360	77.2	77.9	75.2	75.2	74.6	74.3	76	1.5	1.9	1.2	74.6	76.9
420	83.1	84.9	81.5	81.9	81.5	81.2	82	1.4	1.7	1.1	81.2	83.5
480	88.1	90.3	86.8	87.8	87.6	87.4	88	1.2	1.4	1.0	87.0	89.0
540	92.1	94.4	91.1	92.2	92.9	92.6	93	1.1	1.2	0.9	91.7	93.4
600	95.0	97.1	94.5	95.7	97.3	97.0	96	1.2	1.2	1.0	95.1	97.1
720	98.7	99.4	99.0	99.7	101.5	101.3	100	1.2	1.2	1.0	99.0	100.9

Table 3.61 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) (16N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	16N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	0.1 N HCl, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	25	1.0	3.9	0.8	26	0.9	3.4	0.7
120	40	1.4	3.6	1.1	40	1.3	3.4	1.1
180	51	1.4	2.7	1.1	51	1.8	3.6	1.5
240	61	2.6	4.2	2.0	60	1.9	3.2	1.5
300	69	1.7	2.5	1.4	68	1.8	2.6	1.4
360	76	1.8	2.3	1.4	76	1.5	1.9	1.2
420	82	2.5	3.0	2.0	82	1.4	1.7	1.1
480	87	1.8	2.1	1.5	88	1.2	1.4	1.0
540	92	1.5	1.6	1.2	93	1.1	1.2	0.9
600	96	2.2	2.3	1.8	96	1.2	1.2	1.0
720	101	1.9	1.9	1.6	100	1.2	1.2	1.0

Reference/Test product

Time (min)	**(R-T)**	**SR**	780.3
0	0	**S(R-T)**	5.8
60	1.0		
120	0.4		
180	0.6		
240	0.5		
300	0.3		
360	0.4		
420	0.0		
480	0.7		
540	0.9		
600	0.3		
720	0.7		
	f1	1	
	f2	94	

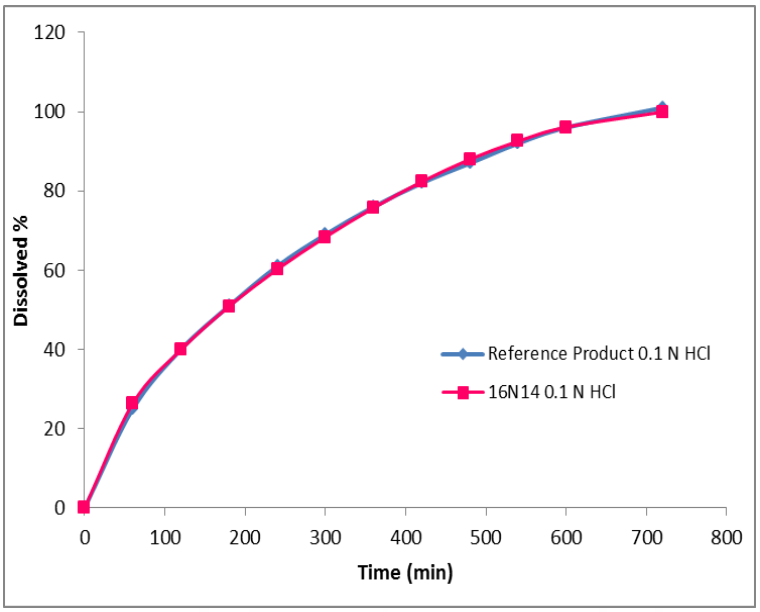


Figure 3.15 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 16N14 vs Reference Product

Figure 3.16 illustrates the comparative dissolution graphs of all formulation trials (except 04N14) for Niacin 500 mg ER Tablet-Capsule and reference product. Also Figure 3.17 shows comparative dissolution graphs of DoE series of Niacin 500 mg ER Tablet-Capsule and reference product.

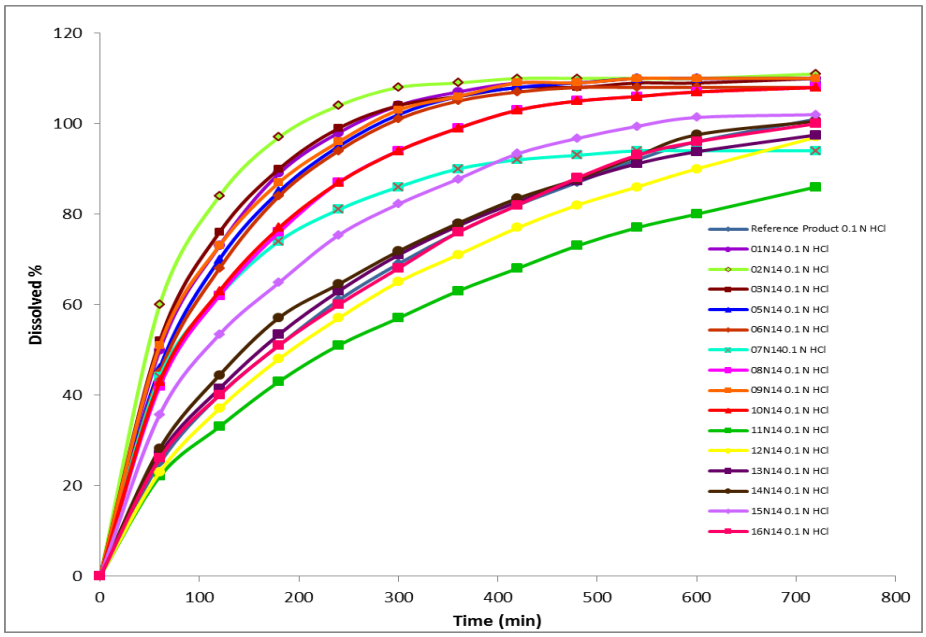


Figure 3.16 Dissolution profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 01-16N14 vs Reference Product

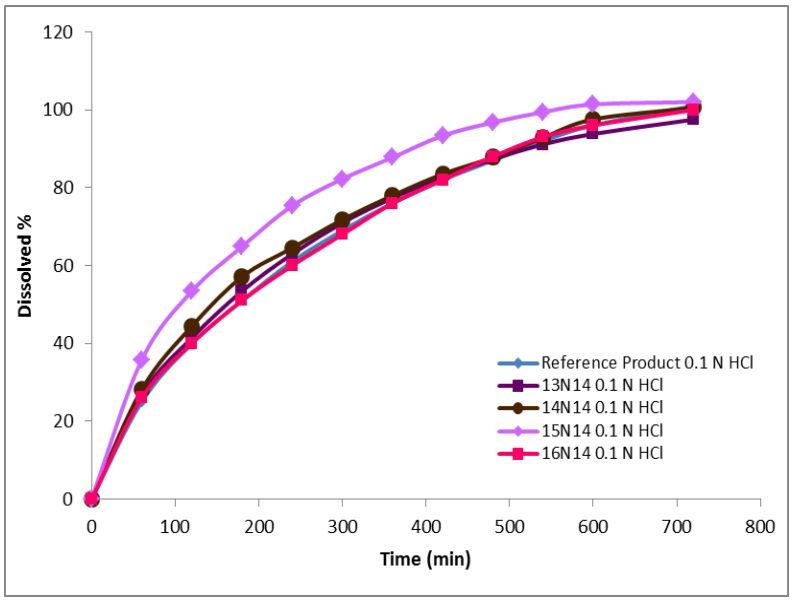


Figure 3.17 Dissolution profiles of Niacin 500 mg ER Tablet-Capsule (pH 1.2) 13N14-16N14 vs Reference Product

Table 3.62 summarizes comparison of the f2 values for four Niacin 500 mg ER Tablet-Capsule obtained from dissolution profile studies in 0.1 N HCl medium. Similar dissolution profile test results were obtained for 0.1 N HCl medium. But f2 value of 16N14 numbered formulation was obtained higher which means the most appropriate formulation for this study was this formulation compared to reference product.

Table 3.62 Comparative f2 values of Niacin 500 mg ER Tablet-Capsule

	Trial no			
	13N14	**14N14**	**15N14**	**16N14**
f2 value	80	70	60	94

In the second part of comparison studies different dissolution medium test results should be compared. 6 tablets of both reference product and formulated product were placed into dissolution vessels and analyzed for percentage of dissolved drug.

The dissolution test results of two batches of reference product were tabulated in Table 3.63 and 3.64 in pH 4.5 acetate buffer medium, respectively.

Also 16N14 batch numbered Niacin 500 mg ER Tablet-Capsule samples were analyzed by employing the same method in pH 4.5 acetate buffer medium. Table 3.65 shows the dissolution test results of Niacin 500 mg ER Tablet-Capsule (Batch no: 16N14) for in pH 4.5 acetate buffer medium. The comparative graph for this test was illustrated in Figure 3.18. According to calculated dissolution test results f1 was found to be 4, while f2 was found to be 78 (Table 3.66) in which second batch of reference product was considered for the calculations. These results showed us f2 value was in agreement with the acceptable ranges also for this medium.

Table 3.63 Dissolution profile of Niascor 500 mg ER Tablet (pH 4.5 acetate buffer) (Batch no: 1803201)

Product name	Niascor 500 mg ER Tablet - 1803201
Number of units	6
Dissolution conditions	pH 4.5 acetate buffer, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	14.0	15.1	14.2	15.2	14.2	14.4	15	0.5	3.5	0.4	14.1	14.9
120	21.9	23.3	22.0	23.0	22.3	22.7	23	0.6	2.5	0.4	22.1	23.0
240	35.1	36.2	35.0	36.0	35.5	35.9	36	0.5	1.4	0.4	35.2	36.0
360	46.2	47.2	46.1	46.9	46.6	47.0	47	0.4	1.0	0.4	46.3	47.0
480	55.9	56.8	55.8	56.5	56.2	56.6	56	0.4	0.7	0.3	56.0	56.6
600	64.5	65.3	64.3	64.8	64.7	65.1	65	0.4	0.6	0.3	64.5	65.1
720	72.0	72.9	71.9	72.3	72.2	72.7	72	0.4	0.5	0.3	72.0	72.6

Table 3.64 Dissolution profile of Niascor 500 mg ER Tablet (pH 4.5 acetate buffer) (Batch no: 1803202)

Product name	Niascor 500 mg ER Tablet - 1803202
Number of units	6
Dissolution conditions	pH 4.5 acetate buffer, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	11.5	12.7	12.3	11.5	11.1	10.9	12	0.7	6.0	0.6	11.1	12.2
120	20.3	21.3	22.5	20.5	19.7	21.5	21	1.0	4.8	0.8	20.2	21.8
180	29.0	30.1	27.0	27.5	28.2	30.2	29	1.3	4.6	1.1	27.6	29.7
240	34.9	35.8	37.2	33.9	34.2	36.2	35	1.3	3.6	1.0	34.4	36.4
300	42.3	39.5	41.8	39.2	41.5	44.2	41	1.9	4.5	1.5	39.9	42.9
360	48.5	47.9	50.1	47.6	46.9	47.0	48	1.2	2.5	0.9	47.1	48.9
420	53.2	55.4	54.3	50.7	52.8	52.5	53	1.6	3.0	1.3	51.9	54.4
480	58.6	59.3	57.6	57.1	56.5	58.3	58	1.0	1.8	0.8	57.1	58.7
540	62.4	60.5	59.7	62.5	63.7	64.5	62	1.8	2.9	1.5	60.7	63.7
600	66.3	67.4	65.2	67.8	63.2	64.5	66	1.8	2.7	1.4	64.3	67.1
720	75.3	76.5	70.5	74.7	75.2	70.9	74	2.5	3.4	2.0	71.8	75.9

Table 3.65 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 4.5 acetate buffer) (Batch no: 16N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 16N14
Number of units	6
Dissolution conditions	pH 4.5 acetate buffer, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	9.8	10.5	10.9	11.2	10.1	10.3	10	0.5	4.9	0.4	10.1	10.9
120	20.5	22.3	21.9	23.0	21.4	20.9	22	0.9	4.3	0.7	20.9	22.4
180	32.4	29.2	28.7	31.9	30.5	31.5	31	1.5	4.9	1.2	29.5	31.9
240	36.7	39.2	38.5	39.2	36.1	38.5	38	1.3	3.5	1.1	37.0	39.1
300	43.1	45.6	40.7	44.5	43.5	46.8	44	2.1	4.8	1.7	42.3	45.7
360	50.5	51.2	50.4	49.2	48.9	49.5	50	0.9	1.8	0.7	49.2	50.7
420	54.5	57.4	53.2	54.9	53.0	56.7	55	1.8	3.3	1.4	53.5	56.4
480	59.5	60.2	61.3	59.2	59.7	60.1	60	0.7	1.2	0.6	59.4	60.6
540	64.5	63.2	63.5	60.9	63.5	65.9	64	1.6	2.6	1.3	62.3	64.9
600	67.2	65.9	69.1	66.5	65.9	66.7	67	1.2	1.8	1.1	65.9	67.8
720	74.6	74.8	74.9	76.5	77.1	77.9	76	1.4	1.8	1.1	74.9	77.1

Table 3.66 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 4.5acetate buffer) (16N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	16N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	pH 4.5 acetate, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	12	0.7	6.0	0.6	10	0.5	4.9	0.4
120	21	1.0	4.8	0.8	22	0.9	4.3	0.7
180	29	1.3	4.6	1.1	31	1.5	4.9	1.2
240	35	1.3	3.6	1.0	38	1.3	3.5	1.1
300	41	1.9	4.5	1.5	44	2.1	4.8	1.7
360	48	1.2	2.5	0.9	50	0.9	1.8	0.7
420	53	1.6	3.0	1.3	55	1.8	3.3	1.4
480	58	1.0	1.8	0.8	60	0.7	1.2	0.6
540	62	1.8	2.9	1.5	64	1.6	2.6	1.3
600	66	1.8	2.7	1.4	67	1.2	1.8	1.0
720	74	2.5	3.4	2.0	76	1.4	1.8	1.1

Reference/Test product

Time (min)	**(R-T)**	**SR**	498.9
0	0	**S(R-T)**	19.7
60	1.2		
120	0.7		
180	2.0		
240	2.7		
300	2.6		
360	2.0		
420	1.8		
480	2.1		
540	1.4		
600	1.2		
720	2.1		
	f1	4	
	f2	78	

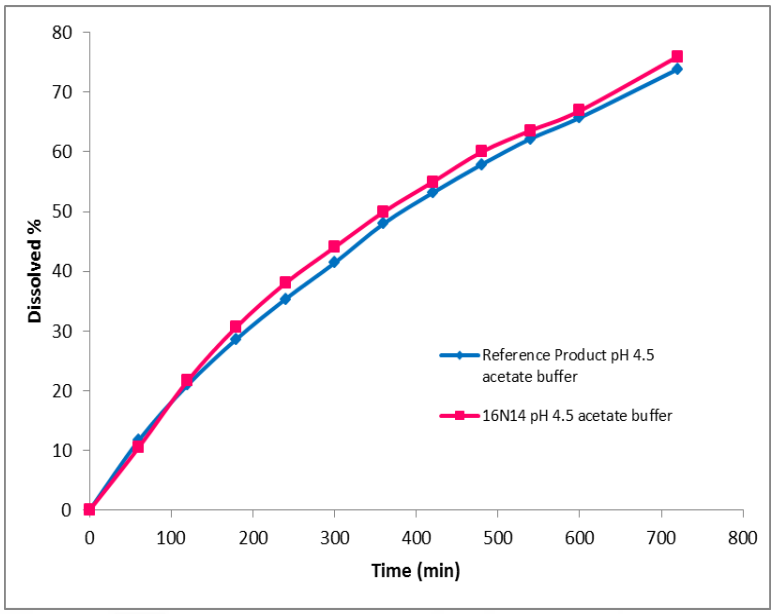


Figure 3.18 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 4.5 acetate buffer) 16N14 vs Reference Product

For the next step 6 tablets of both reference product and formulated product were placed into dissolution vessels filled with pH 6.8 phosphate buffer medium and analyzed for percentage of dissolved drug with different intervals.

The dissolution test results of reference products were tabulated in Table 3.67 and 3.68 in pH 6.8 phosphate buffer medium. Also 16N14 batch numbered Niacin 500 mg ER Tablet-Capsule samples were analyzed by employing the same method in pH 6.8 phosphate buffer medium. Table 3.69 summarizes the dissolution test results of Niacin 500 mg ER Tablet-Capsule (Batch no: 16N14) for in pH 6.8 phosphate buffer medium. The comparative graph was illustrated in Figure 3.19. Also the f1 and f2 values were calculated with regard to obtained dissolution study data, second batch of reference product was considered for these calculations and f1 was found to be 11, while f2 was found to be 59 as shown in Table 3.70. These results proved us f2 value was in agreement with the acceptable ranges also for this medium.

Table 3.67 Dissolution profile of Niascor 500 mg ER Tablet (pH 6.8 phosphate buffer) (Batch no: 1803201)

Product name	Niascor 500 mg ER Tablet - 1803201
Number of units	6
Dissolution conditions	pH 6.8 phosphate buffer, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	12.8	10.5	14.1	0	0	0	12	1.8	14.6	1.5	11.0	13.9
120	19.3	16.7	20.6	0	0	0	19	2.0	10.5	1.6	17.3	20.5
240	29.3	26.3	30.5	0	0	0	29	2.2	7.5	1.7	27.0	30.4
360	37.2	34.1	38.6	0	0	0	37	2.3	6.3	1.8	34.8	38.5
480	44.0	40.9	45.4	0	0	0	43	2.3	5.3	1.8	41.6	45.3
600	49.9	47.2	51.3	0	0	0	49	2.1	4.2	1.7	47.8	51.1
720	55.3	53.6	56.7	0	0	0	55	1.6	2.8	1.2	54.0	56.4
840	60.4	60.1	61.6	0	0	0	61	0.8	1.3	0.6	60.1	61.3
960	65.2	67.0	66.1	0	0	0	66	0.9	1.4	0.7	65.4	66.8
1080	69.8	73.4	70.6	0	0	0	71	1.9	2.7	1.5	69.8	72.8
1200	74.3	78.8	74.7	0	0	0	76	2.5	3.3	2.0	73.9	77.9
1320	78.9	83.7	78.8	0	0	0	80	2.8	3.5	2.2	78.2	82.7
1440	83.4	87.5	83.0	0	0	0	85	2.5	2.9	2.0	82.6	86.6

Table 3.68 Dissolution profile of Niascor 500 mg ER Tablet (pH 6.8 phosphate buffer) (Batch no: 1803202)

Product name	Niascor 500 mg ER Tablet - 1803202
Number of units	6
Dissolution conditions	pH 6.8 phosphate buffer, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	10.9	11.5	11.2	11.5	10.7	10.1	11	0.5	4.9	0.4	10.6	11.4
120	20.5	20.7	19.8	18.9	19.1	18.2	20	1.0	5.0	0.8	18.8	20.3
180	26.9	25.4	27.2	26.9	24.3	27.0	26	1.2	4.4	0.9	25.3	27.2
240	32.5	31.7	33.5	29.7	30.7	31.2	32	1.3	4.3	1.1	30.5	32.6
300	35.4	38.2	34.5	36.7	36.3	37.5	36	1.4	3.7	1.1	35.4	37.5
360	43.5	40.5	39.4	38.5	39.7	41.5	41	1.8	4.4	1.4	39.1	41.9
420	45.7	46.5	43.5	42.9	44.6	43.1	44	1.5	3.3	1.2	43.2	45.6
480	49.5	50.2	47.5	48.9	46.5	45.4	48	1.9	3.9	1.5	46.5	49.5
540	51.1	52.4	53.4	49.5	50.2	50.0	51	1.5	3.0	1.2	49.9	52.3
600	54.5	53.2	55.6	54.1	53.9	52.9	54	1.0	1.8	0.8	53.3	54.8
720	60.5	62.5	63.7	59.4	58.5	55.4	60	3.0	4.9	2.4	57.6	62.4

Table 3.69 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 6.8 phosphate buffer)

(Batch no: 16N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 16N14
Number of units	6
Dissolution conditions	pH 6.8 phosphate buffer, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	12	12.5	12.7	11.5	13.2	12	12	0.6	4.9	0.5	11.8	12.8
120	23.7	21.0	21.6	21.3	22.0	21.9	22	0.9	4.3	0.8	21.2	22.7
180	28.1	29.3	27.8	26.9	27.9	28.6	28	0.8	2.9	0.6	27.5	28.7
240	34.7	35.2	33.9	34.5	33.9	32.0	34	1.1	3.3	0.9	33.1	34.9
300	41.5	39.7	40.2	40.5	40.7	38.0	40	1.2	3.0	1.0	39.1	41.1
360	44.5	43.7	42.9	44.6	44.9	47.8	45	1.7	3.7	1.3	43.4	46.1
420	48.9	49.2	49.5	50.2	51.7	46.5	49	1.7	3.5	1.4	48.0	50.7
480	56.2	53.5	54.1	54.0	53.9	52.1	54	1.3	2.4	1.1	52.9	55.0
540	57.5	58.3	59.7	60.1	56.5	56.0	58	1.7	2.9	1.3	56.7	59.4
600	62.3	60.7	60.8	62.1	59.7	60.1	61	1.1	1.7	0.8	60.1	61.8
720	65.7	70.2	66.5	64.3	68.1	63.2	66	2.5	3.8	2.0	64.3	68.4

Table 3.70 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (pH 6.8 phosphate buffer) (16N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	16N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	pH 6.8 phosphate, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	11	0.5	4.9	0.4	12	0.6	4.9	0.5
120	20	1.0	5.0	0.8	22	0.9	4.3	0.8
180	26	1.2	4.4	0.9	28	0.8	2.9	0.6
240	32	1.3	4.3	1.1	34	1.1	3.3	0.9
300	36	1.4	3.7	1.1	40	1.2	3.0	1.0
360	40	1.8	4.3	1.4	45	1.7	3.7	1.3
420	44	1.5	3.3	1.2	49	1.7	3.5	1.4
480	48	1.9	3.9	1.5	54	1.3	2.4	1.1
540	51	1.5	3.0	1.2	58	1.7	2.9	1.3
600	54	1.0	1.8	0.8	61	1.1	1.7	0.8
720	60	3.0	4.9	2.4	66	2.5	3.8	2.0

Reference/Test product

Time (min)	**(R-T)**	**SR**	422.8
0	0	**S(R-T)**	47.0
60	1.3		
120	2.4		
180	1.8		
240	2.5		
300	3.7		
360	4.3		
420	5.0		
480	6.0		
540	6.9		
600	6.9		
720	6.3		
	f1	11	
	f2	59	

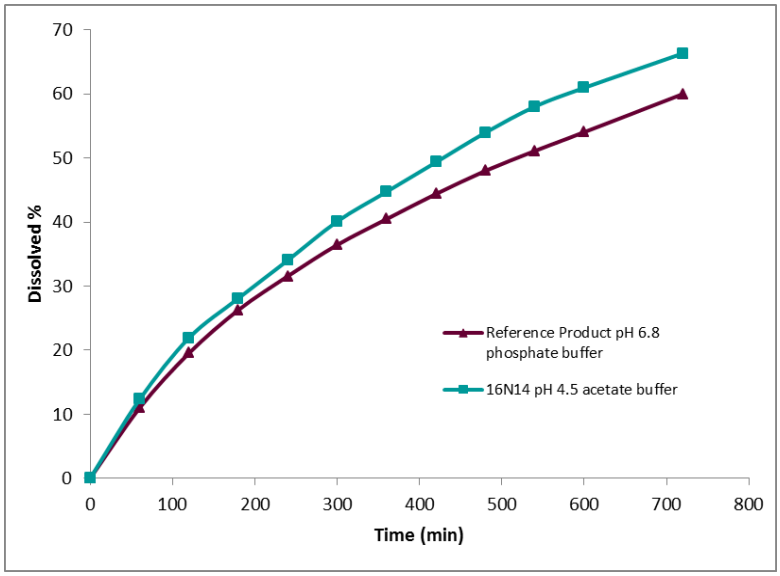


Figure 3.19 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (pH 6.8 phosphate buffer) 16N14 vs Reference Product

As the last comparison experiment, 6 tablets of both reference product and formulated product were placed into dissolution vessels filled with distilled water and analyzed for percentage of dissolved drug with different intervals.

Table 3.71 and 3.72 summarize the dissolution test results of reference products in distilled water. Dissolution test results of 16N14 batch numbered Niacin 500 mg ER Tablet-Capsule samples analyzed with the same method in distilled water medium were illustrated in Table 3.73. The comparative graph was shown in Figure 3.20 and calculated f1 and f2 results were tabulated in Table 3.74. For f1 f2 comparisons, second batch of reference product was considered and f1 was found to be 3, while f2 was found to be 83 which are within the acceptable ranges.

Table 3.71 Dissolution profile of Niascor 500 mg ER Tablet (Distilled water) (Batch no: 1803201)

Product name	Niascor 500 mg ER Tablet - 1803201
Number of units	6
Dissolution conditions	Distilled water, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	12.9	13.8	13.8	13.6	13.1	13.6	13	0.4	2.8	0.3	13.2	13.8
120	21.0	22.2	22.7	22.2	21.2	22.3	22	0.7	3.1	0.5	21.4	22.5
240	34.8	36.5	37.5	36.6	35.0	36.7	36	1.1	2.9	0.8	35.3	37.0
360	46.9	49.0	50.0	49.0	47.3	49.0	49	1.2	2.4	0.9	47.6	49.5
480	57.7	60.3	61.0	59.7	58.4	59.9	60	1.2	2.1	1.0	58.5	60.5
600	67.5	70.3	70.8	69.1	68.4	69.7	69	1.2	1.8	1.0	68.3	70.3
720	76.5	79.1	79.2	77.3	77.3	78.4	78	1.1	1.4	0.9	77.1	78.8
840	84.1	86.4	86.0	84.4	85.0	85.6	85	0.9	1.1	0.7	84.5	86.0
960	90.3	92.1	91.6	90.2	91.4	90.9	91	0.8	0.8	0.6	90.5	91.7
1080	94.5	96.1	95.7	93.9	95.8	95.1	95	0.8	0.9	0.7	94.5	95.9
1200	98.0	99.4	98.7	97.4	98.8	98.0	98	0.7	0.7	0.6	97.8	99.0
1320	100.3	102.2	101.0	99.5	100.9	100.2	101	0.9	0.9	0.7	99.9	101.4
1440	102.0	102.6	102.3	100.7	102.3	101.3	102	0.7	0.7	0.6	101.3	102.4

Table 3.72 Dissolution profile of Niascor 500 mg ER Tablet (Distilled water) (Batch no: 1803202)

Product name	Niascor 500 mg ER Tablet - 1803202
Number of units	6
Dissolution conditions	Distilled water, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	14.5	13.2	12.9	14.1	14.2	13.5	14	0.6	4.6	0.5	13.2	14.2
120	24.5	22.6	23.7	24.6	25.2	24.3	24	0.9	3.7	0.7	23.4	24.9
180	32.5	34.9	30.2	32.8	33.0	32.3	33	1.5	4.6	1.2	31.4	33.8
240	36.9	40.8	40.5	38.7	41.5	37.6	39	1.9	4.8	1.5	37.8	40.8
300	46.2	44.5	43.9	45.6	46.1	45.9	45	0.9	2.1	0.8	44.6	46.1
360	51.5	54.2	51.3	49.9	48.3	51.9	51	2.0	3.9	1.6	49.6	52.8
420	58.2	56.9	57.0	58.3	56.5	56.2	57	0.9	1.5	0.7	56.5	57.9
480	62.9	64.5	65.7	61.9	63.5	62.1	63	1.5	2.3	1.2	62.3	64.6
540	69.2	70.1	67.5	66.3	69.1	67.8	68	1.4	2.0	1.1	67.2	69.4
600	74.5	75.2	72.3	71.8	73.4	72.1	73	1.4	1.9	1.1	72.1	74.3
720	80.9	81.9	83.5	79.6	82.0	80.3	81	1.4	1.7	1.1	80.3	82.5

Table 3.73 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (Distilled water) (Batch no: 16N14)

Product name	Niacin 500 mg ER Tablet - Capsule - 16N14
Number of units	6
Dissolution conditions	Distilled water, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C

Time (min)	**Dissolved %**						**Average (%)**	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval**		
	1.Tb.	**2.Tb.**	**3.Tb.**	**4.Tb.**	**5.Tb.**	**6.Tb.**				**C.I (%95)**	**Lower Limit**	**Upper Limit**
0	0	0	0	0	0	0	0	0	0	0	0	0
60	12.3	11.7	12.1	11.9	11.6	12.6	12	0.4	3.1	0.3	11.7	12.3
120	23.5	22.9	21.7	22.9	23.6	24.1	23	0.8	3.6	0.7	22.5	23.8
180	32.0	33.5	30.9	30.0	29.5	30.3	31	1.5	4.8	1.2	29.8	32.2
240	39.5	38.1	38.0	39.6	37.3	36.9	38	1.1	2.9	0.9	37.3	39.1
300	45.6	46.3	42.9	41.8	43.5	44.2	44	1.7	3.8	1.3	42.7	45.4
360	53.7	51.2	49.5	49.2	50.3	47.3	50	2.2	4.3	1.7	48.5	51.9
420	57.8	56.1	55.2	54.9	54.8	57.1	56	1.2	2.2	1.0	55.0	57.0
480	62.3	63.5	60.4	59.8	60.2	60.0	61	1.5	2.5	1.2	59.8	62.2
540	68.5	64.5	63.1	67.1	68.0	66.1	66	2.1	3.2	1.7	64.5	67.9
600	73.5	68.2	74.8	71.0	70.2	69.0	71	2.6	3.6	2.1	69.1	73.2
720	80.5	79.5	84.3	80.1	76.5	79.1	80	2.5	3.2	2.0	78.0	82.0

Table 3.74 Comparative Dissolution Profiles of Niacin 500 mg ER Tablet-Capsule (Distilled water) (16N14) with Reference Product

Reference (R) Product Name	**Niascor 500 mg ER Tablet**
Active Pharmaceutical Ingredients	Niacin

Test (T) Product Name	**Niacin 500 mg ER Tablet-Capsule**
Batch number	16N14
Active Pharmaceutical Ingredients	Niacin

Number of sample points	6
Dissolution Conditions	Distilled water, 900 mL, 100 rpm, pedal with sinker, 37 °C ± 0.5 °C
Active Pharmaceutical Ingredients	Niacin

Time (min)	**DISSOLVED %**							
	Niascor 500 mg ER Tablet				**Niacin 500 mg ER Tablet-Capsule**			
	Average (%)	**Standard Deviation**	**Relative Standard Deviation (%)**	**Confidence Interval (%95)**	**Average (%)**	**Standard Deviation**	**Relative Standard Deviation %**	**Confidence Interval (%95)**
0	0	0	0	0	0	0	0	0
60	14	0.6	4.6	0.5	12	0.4	3.1	0.3
120	24	0.9	3.7	0.7	23	0.8	3.6	0.7
180	33	1.5	4.6	1.2	31	1.5	4.8	1.2
240	39	1.9	4.8	1.5	38	1.1	2.9	0.9
300	45	0.9	2.1	0.8	44	1.7	3.8	1.3
360	51	2.0	3.9	1.6	50	2.2	4.3	1.7
420	57	0.9	1.5	0.7	56	1.2	2.2	1.0
480	63	1.5	2.3	1.2	61	1.5	2.5	1.2
540	68	1.4	2.0	1.1	66	2.1	3.2	1.7
600	73	1.4	1.9	1.1	71	2.6	3.6	2.1
720	81	1.4	1.7	1.1	80	2.5	3.2	2.0

Reference/Test product

Time (min)	**(R-T)**	**SR**	549.9
0	0	**S(R-T)**	16.9
60	1.7		
120	1.0		
180	1.6		
240	1.1		
300	1.3		
360	1.0		
420	1.2		
480	2.4		
540	2.1		
600	2.1		
720	1.4		
	f1	3	
	f2	83	

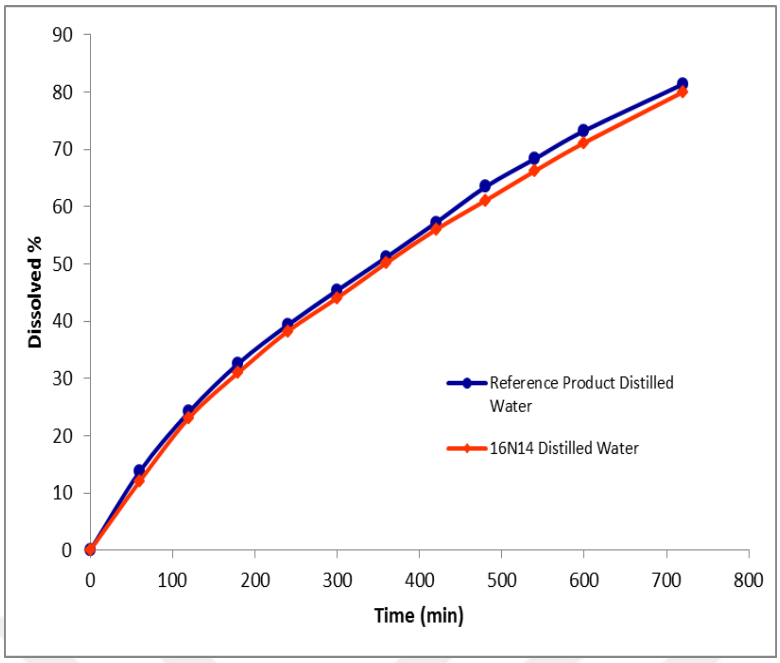


Figure 3.20 Dissolution profile of Niacin 500 mg ER Tablet-Capsule (Distilled water) 16N14 vs Reference Product

4. DISCUSSION

The literature survey showed that Niacin is selective antihyperlipidemic agent improves HDL tolerance in patients with hypercholesterolemia. During this study various factors that likely to affect the performance of the extended release was studied. In order to achieve required extended release profile, tablets were prepared by dry granulation, direct compaction and wet granulation techniques using different formulations. For all the formulations dissolution tests were performed and percentage drug release was calculated.

Three experimental parameters (amount of HPMC E15, HPMC K100M and Avicel PH 102 for the first DoE; amount of HPMC K100 M CR, Lactose Monohydrate and Avicel PH 102 for the second DoE) to optimize formulation of Niacin 500 mg ER Tablet-Capsule were planned to study using the Fractional Factorial Design Methodology matrix. In all experiments, the API (Niacin) and stearic acid amounts were constant. The full experimental plans with respect to their values were listed in Table 2.2 and Table 2.16.

At the beginning of the study, dry granulation method was chosen for the granulation process because of its easy applicability and lower production cost. After many formulation trials, formulation method and the design levels were changed to wet granulation. Nevertheless enough data couldn’t be obtained for factorial design calculations**.** Although Fractional Factorial Design Methodology matrix couldn’t apply, the most appropriate unit formula for production of Niacin 500 mg ER Tablet-Capsule was determined with the obtained dissolution profile data. Acceptable f2 values were gained with wet granulation technique. The reason behind the getting higher f2 values with wet granulation technique is thought to be the increase in the binding capacity of HPMC by swelling in the water.

According to dissolution profile results it is possible to observe that there was a greater f2 value (f2: 80 and f2: 94) when HPMC K100 M CR amount was at the upper level. When HPMC K100 M CR and Lactose Monohydrate amounts were at the upper level the highest f2 value was obtained. At the end of the

formulation trials and their dissolution studies it was proved that the main factor affecting the dissolution rate to be HPMC as the extended release agent.

In conclusion, Niacin 500 mg ER Tablet-Capsule drug products within the scope of this thesis showed similar dissolution profile in different pH media (0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and distilled water) with the corresponding reference drug product Niascor 500 mg ER Tablet. Similarity calculation was performed according to guidance for industry dissolution testing of extended release solid oral dosage forms and after all comparisons unit formula of the 16N14 numbered formulation, consists of 500.0 mg of Niacin, 140.0 mg of HPMC K100M CR, 35.0 mg of Lactose Monohydrate, 13.0 mg of Avicel PH 102 and 5.0 mg of Stearic acid, was chosen as the final formulation for this study.

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7. **FreeZone Innovation,** Case Learnings, İstanbul, 2012
8. **2nd Symposium on Scale-up of Oral Solid Dosage Forms,** GEA, Switzerland, 2011
9. **Oral Dispersible Tablet Development and CR Technology,** IMCD, İstanbul, 2010
10. **Reference Standards and Impurities in Pharmaceutical Industry,** LGC Standards, İstanbul, 2010
11. **Ion Exchange 2008,** Cambridge University, England, 2008

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14. **International Somer Symposium Series-1,** METU, Ankara, 2007

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2. Saba Samatya, Evrim Orhan, Nalan Kabay, Ali Tuncel, "Comparative boron removal performance of monodisperse-porous particles with molecular brushes via "click chemistry" and direct coupling, Original Research, Article Colloids and Surfaces A: Physicochemical and Engineering Aspects

3. M. Arda. E. Orhan, O. Arar, M. Yüksel, N. Kabay, "Removal of Fluoride from Geothermal Water by Electrodialysis" Separation Science and Technology

APPENDICES

Appendix 1 Certificate of nicotinic acid

NICOTINIC ACID

DSM

CERTIFICATE OF ANALYSIS

Productcode : 0409626
Lot No. : 5938
Analysis No. : 03620145

Test	Result	Limits / Specifications	Dimension / Units
Appearance	crystalline powder	Crystalline powder	
Colour	white	White	
Identity	corresponds	Corresponds	
Melting point	236.4	234.0 to 238.0	deg C
Loss on drying	0.02	max. 1.0	%
Sulphated ash (residue on ignition)	<0.05	max. 0.1	%
Heavy metals	<20	max. 20	ppm
Chlorides	<200	max. 200	ppm
Sulphates	<200	max. 200	ppm
Related substances	meets Ph. Eur. requirements	max. 0.5	%
Ordinary impurities	meets USP requirements	max. 2.0	%
Organic volatile impurities	meets USP requirements	meets USP requirements	
Assay (dried)	99.8	99.5 to 100.5	%

This lot was analysed and released by our authorized Quality Control Department and was found to meet the specifications as given above.
The product meets all requirements of the following valid compendia when tested accordingly:
USP,FCC,Ph.Eur.

DSM Nutritional Products Ltd
The Quality Assurance Manager

Schill Roger

Appendix 2 Certificate of Methocel K 100M CR

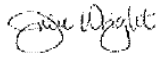
Certificate 5827397 The Dow Chemical Company Page 1
Date: 20.08.2012 Certificate of Analysis Shipped: 17.08.2012

Melanie Kracke
COLORCON LIMITED Fax:
DARTFORD FREIGHT TERMINAL
CROSSWAYS DARTFORD EN DA2 6QJ UNITED KINGDOM
Cust P.O.: 030/50/40157487 Dlvy Note: 71671371 10
Material: METHOCEL* K100M Premium CR
Hydroxypropyl Methylcellulose Spec: 00002684-S
Batch: 1G31012N02 Mfgd: 31.07.2012 Retest Date: 30.07.2017
Ship from: THE DOW CHEMICAL COMPANY BAY CITY MI UNITED STATES

It is hereby certified the material indicated above has been manufactured in accordance with the FDA cGMPs, Kosher guidelines, was inspected and tested in accordance with the conditions and the requirements of current USP, EP and JP for Hypromellose as well as the current specific purity criteria for the food additive Hydroxypropyl Methyl Cellulose (E464) and unless agreed otherwise conforms in all respects to the specification relevant thereto.

Feature	Units	Results 1G31012N02	Limits Minimum	Limits Maximum
Apparent Viscosity Brookfield 2% in water, @ 20degC	mPa.s	105,130	75,000	140,000
Loss on Drying	%	1.9	----	5.0
Residue on Ignition	%	0.5	----	1.5
Ash, Sulfated	%	0.5	----	1.5
pH, 2% in Water	-	7.0	5.0	8.0
Assay, Methoxyl	%	23.0	22.0	24.0
Assay, Hydroxypropoxyl	%	10.6	9.5	11.5
Appearance Opalescence		Passes		
Appearance solution color		Passes		
Particle Size Thru 40 U. S. Std. Sieve	%	99.9	99.0	----
Particle Size Thru 100 U. S. Std Sieve	%	95.1	90.0	----
Particle Size Thru 230 U.S.Std. Sieve	%	61.5	50.0	80.0

This Batch, based on audit testing and process control, is certified to be NMT 20 ppm heavy metals (as Pb) and also meets all specification requirements for harmonized identification tests, residual solvents and microbiological limits.
Batch (Lot) Number manufacture location (char 7-8): 2N = Midland, MI; ND = Bomlitz,Germany; 24 = Plaquemine, LA; 07 = Stade, Germany



Julie Wright, FORTEFIBER, METHOCEL Quality Systems Specialist
For inquiries please contact Customer Service at 1-800-232-2436 (USA).

* Trademark of The Dow Chemical Company

Appendix 3 Certificate of lactose monohydrate

DFE pharma

Issue Day	02-04-14
Sales Order No.	GSO004435
Your P.O. No.	101932OD

IMCD UK Ltd
Times House, Throwley Way
SM1 4AF Sutton
GREAT BRITAIN

CERTIFICATE OF ANALYSIS

Product	: Lactochem ® Fine Powder -Pharmaceutical use
Product code	: 502064
Batch no.	: 679096
Production Date	: 20-02-2014
Retest Date	: 20-02-2017
Description	alpha-lactose monohydrate pharmaceutical grade conform USP / NF, Ph.Eur, JP, current at time of manufacture
Product Description	A white or almost white, odourless, crystalline powder freely but slowly soluble in water, practically insoluble in ethanol.
Residual solvents (CPMP/ICH/283/95 and USP-NF Chapter 467):	No class 1, 2, 3 solvents are used during production

Physical-Chemical data	Specification	Results
Identification	conform USP/NF , Ph.Eur. , JP	conform
Appearance in solution	clear and nearly colourless	passes test
Residue on ignition	Max. 0,1 %	< 0,1 %
Total Water	4,5 - 5,5 %	5,1 %
Loss on drying	Max. 0,5 %	0,1 %
Acidity (0,1 N NaOH)	Max. 0,4 ml	0,3 ml
Specific Optical Rotation (on anhydrous basis)	+54,4° to +55,9°	55,2 °
Absorbance between 210-220 nm (1%, 1cm)	Max. 0,25	< 0,25
Absorbance between 270-300 nm (1%, 1cm)	Max. 0,07	< 0,07
Absorbance at 400 nm (10%, 1cm)	Max. 0,04	< 0,04
Heavy metals	Max. 5 ppm	< 5 ppm

Microbiological data	Specification	Results
TAMC	Max. 100 / g	< 100 cfu / g
Bile tolerant gram neg.bacteria	absent in 1 g	absent
Escherichia coli	absent in 10 g	absent

DMV-Fonterra Excipients GmbH & Co. KG

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BLZ 502 304 00
Account 180989E005
BIC: ABNADEFFFRA
IBAN: DE85502304001809898005
VAT DE 246736318

General partner: DMV-Fonterra Excipients Verwaltungs-GmbH
Directors: Jan Jongsma
Stephen Cajzago
pharma@dfepharma.com
www.dfepharma.com
Stat. seat: Goch
Amtsgericht Kleve HRB 8945

DFE pharma

Issue Day	02-04-14
Sales Order No.	GSO004435
Your P.O. No.	1018320D

IMCD UK Ltd
Times House, Throwley Way
SM1 4AF Sutton
GREAT BRITAIN

Product	: Lactochem ® Fine Powder -Pharmaceutical use	
Product code	: 502064	
Batch no.	: 679096	
Production Date	: 20-02-2014	
Retest Date	: 20-02-2017	
Salmonellae sp.	absent in 5 x 25 g	absent
TYMC	Max. 10 / g	< 10 cfu / g

Particle size distribution (Alpine, Airjet)	Specification	Results
% < 150 micron	Min. 98 %	100 %
% < 75 micron	Min. 80 %	86 %
% < 53 micron	55 - 80 %	73 %

supply from our production site:
FrieslandCampina Domo B.V.
Needseweg 23
7271 AB Borculo
The Netherlands

Release Date: 24-03-2014
by QA , MANGEB
This document has been produced electronically and is valid without a signature

DMV-Fonterra Excipients GmbH & Co. KG

Klever Strasse 187
47574 Goch, Germany
P.O. Box 20 21 20
47563 Goch, Germany
T. +49 2823 9283 770
F. +49 2823 9283 7799
Stat. seat: Goch
Amtsgericht Kleve HRA 3732

Bank:
The Royal Bank of Scotland
BLZ 502 304 00
Account 1809692005
BIC: ABNADEFFRA
IBAN: DE85502304001809692005
VAT DE 246736315

General partner: DMV-Fonterra Excipients Verwaltungs-GmbH
Directors: Jan Jongsma
Stephen Gajzago
pharma@dfepharma.com
www.dfepharma.com
Stat. seat: Goch
Amtsgericht Kleve HRB 3945

Appendix 4 Certificate of Avicel PH 102

M ,ternational
Vallingstown, Little Island
:o. Cork, Ireland
:ustomer Service: + 353-21-435-4133
ax: + 353-21-451-7210

FMC BioPolymer

Certificate of Analysis

1H3C0156
0257

Avicel® Microcrystalline Cellulose, NF, Ph. Eur, JP

Type : PH-102
Lot No : 71248C
Manufacturing Date: 27-Nov-2012
Reevaluation Date: 26-Nov-2016

Customer Purchase Order : 86597OD
Delivery Number : 80540112

tandard	Specification	Lot Analysis
Loss on Drying, %	3.0 - 5.0	3.4
Loose Bulk Density, g/cc	0.28 - 0.33	0.30
DP ,units (ID B USP,EP)(ID 3 JP)	NMT 350	218
P.S.D.,Malvern LD, µm ,d10 (FRC, Ph.eur)	-	35
P.S.D.,Malvern LD, µm ,d50 (FRC, Ph.eur)	-	106
P.S.D.,Malvern LD, µm ,d90 (FRC, Ph.eur)	-	214
Identification A(USP,EP, JP 1)	PASS	Pass
Identification 2 (JP)	PASS	Pass
pH	5.5 - 7.0	6.2
C luctivity,µS/cm	NMT 75	43
Residue on Ignition, %	NMT 0.050	0.003
Water Soluble Substances, mg/5g	NMT 12.5	7.6
Water soluble substances, %	NMT 0.25	0.15
Heavy Metals, % (Pb)	NMT 0.001	Pass
Sol.in Cu Tetramine Hydroxide	Soluble	Pass
Ether Soluble Substances,mg/10g	NMT 5.0	0.1
Air Jet Particle Size, wt. % + 60Mesh	NMT 8.0	0.1
Air Jet Particle Size, wt. % + 200Mesh	NLT 45.0	60.0
Total Aerobic Microbial Count, cfu/gram	NMT 100	Pass
Total Yeast and Mold Count, cfu/gram	NMT 20	Pass
Salmonella Species	Absent in a 10g sample	Pass
Escherichia coli	Absent in a 10g sample	Pass
Staphylococcus aureus	Absent in a 10g sample	Pass
Pseudomonas aeruginosa	Absent in a 10g sample	Pass
Coliform species	Absent in a 10g sample	Pass

torage Conditions: Store at ambient conditions, keep containers sealed, material is hygroscopic.

ertify that as of the date of shipment the product conforms with the current USP / NF, Ph.Eur & JP specifications on the ate of manufacture. This product is manufactured in accordance to GMP as detailed in IPEC GMP guide for Bulk Excipients. MC test methods are used when the test is not listed in the Pharmacopeia.
he Product meets the requirement for Residual Solvents USP < 467 > and ICH Guide Q3C.
SO 9001:2000 Certified Quality System. Refer to package label for Kosher status.
RC.s (Ph.Eur) Hausner Ratio Typical values: For all Avicel PH grades: 1.18 - 1.45.
egree of Crystallinity Typical Values: For all Avicel PH grades, approximately 80% by Intensity and 66% by Area.
ypical Degree of Polymerization range for Avicel PH Microcrystalline Cellulose is 100 to 300.
xpiry date: None, but FMC recommend retesting for Loss on Drying after re-evaluation date listed above.

IT-More than, NMT-Not more than, LT-Less than, NLT-Not less than.

lanufactured under GMPs and Issued by:
MC BioPolymer
Vallingstown, Little Island,
:o. Cork, Ireland

Eileen Dennehy

Eileen Dennehy
Quality Manager

Appendix 5 Certificate of stearic acid

BASF
The Chemical Company

Certificate of Analysis

BASF SE

Please note that the certificates of analysis are also conveniently available online and around the clock at www.worldaccount.basf.com

Fax No 09843982826

BASF Chemtrade GmbH (EMP)

Industriestrasse 20

91593 Burgbernheim

Germany

2012-04-25
E-EMC/OW
QUALITY-CONTROL-EMC@BASF.COM

Certificate No 1328
Page 1 of 5

Inspection Certificate 3.1 according to EN 10204

Speziol® L2SM GF Pharma

25KG Plastics Film Bags
Purchase Order/Customer Product#
646589
50215445

Material	50215445
Order	3007808464 000010
Delivery	3410406859 000010
Lot	0008241191
Lot/Qty	1350.000 KG
Total	1350.000 KG
Transport	D CC 100

Characteristic Method	Unit	Value	Lower Limit	Upper Limit
IDENTIFICATION A Ph.Eur.2.2.18		PASS		
IDENTIFICATION B Ph.Eur.2.5.1		PASS		
IDENTIFICATION C Ph.Eur.2.2.28		PASS		
ACID VALUE MG KOH/G Ph.Eur.2.5.1		206	194	212
APPEARANCE Ph.Eur.2.2.2 I		PASS		
ACIDITY Ph.Eur.1474		PASS		
IODINE VALUE G I/100G Ph.Eur.2.5.4		0,6	-	4,0
FREEZING POINT Ph.Eur.2.2.18	°C	56	53	59
NICKEL Ph.Eur.2.4.31	ppm	< 1	-	1
FATTY ACID < C14 Ph.Eur.2.2.28	%(a)	0,2	-	1,0
FATTY ACID C14:0 Ph.Eur.2.2.28	%(a)	1,1	-	2,0
FATTY ACID C16:0 Ph.Eur.2.2.28	%(a)	44,3	40,0	55,0
FATTY ACID C18:0 Ph.Eur.2.2.28	%(a)	53,4	40,0	60,0

The aforementioned data shall constitute the agreed contractual quality of the product at the time of passing of risk. The data are controlled at regular intervals as part of our quality assurance program. Neither these data nor the properties of product specimens shall imply any legally binding guarantee of certain properties or of fitness for a specific purpose. No liability of ours can be derived therefrom.

This is a computer-generated document. No signature is required.

BASF
The Chemical Company

Certificate of Analysis

BASF SE

Please note that the certificates of analysis are also conveniently available online and around the clock at www.workdaccount.basf.com

Fax No 09843982826

BASF Chemtrade GmbH (EMP)

Industriestrasse 20

91593 Burgbernheim

Germany

2012-04-25
E-EMC/OW
QUALITY-CONTROL-EMC@BASF.COM

Certificate No 1328
Page 3 of 5

Inspection Certificate 3.1 according to EN 10204

Spezial® L2SM GF Pharma

25KG Plastics Film Bags
Purchase Order/Customer Product#
646589
50215445

Material	50215445
Order	3007808464 000010
Delivery	3410406859 000010
Lot	0008241191
Lot/Qty	1350.000 KG
Total	1350.000 KG
Transport	D CC 100

Characteristic Method	Unit	Value	Lower Limit	Upper Limit
MELTING POINT JP	°C	56	56	72
ACID VALUE MG KOH/G JP 1.13	°C	206	194	218
IODINE VALUE G I/100G JP 1.13		0,3	-	4,0
PURITY (1) JP		PASS		
PURITY (2) JP 1.07		PASS		
PURITY (3) JP		PASS		
RESIDUE ON IGNITION JP 2.44	%	0,1	-	0,1
ARSENIC USP/NF (730)	ppm	< 1	-	1
LEAD USP/NF (730)	ppm	< 1	-	1
CADMIUM USP/NF (730)	ppm	< 1	-	1
IRON USP/NF (730)	ppm	< 1	-	1
COPPER USP/NF (730)	ppm	< 1	-	1
NICKEL USP/NF (730)	ppm	< 1	-	1

The aforementioned data shall constitute the agreed contractual quality of the product at the time of passing of risk. The data are controlled at regular intervals as part of our quality assurance program. Neither these data nor the properties of product specimens shall imply any legally binding guarantee of certain properties or of fitness for a specific purpose. No liability of ours can be derived therefrom.

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BASF
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BASF SE

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91593 Burgbernheim

Germany

2012-04-25
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QUALITY-CONTROL-EMC@BASF.COM

Certificate No 1328
Page 5 of 5

Inspection Certificate 3.1 according to EN 10204

Speziol® L2SM GF Pharma

25KG Plastics Film Bags
Purchase Order/Customer Product#
646589
50215445

Material	50215445	
Order	3007808464	000010
Delivery	3410406859	000010
Lot	0008241191	
Lot/Qty	1350.000	KG
Total	1350.000	KG
Transport	D CC 100	

Production date	15.03.2012
Release date	02.04.2012
Retest date	15.03.2014

Appendix 6 Certificate of hard gelatin capsule

TO THE ATTENTION OF:

CAPSUGEL®

CERTIFICATE OF ANALYSIS

The capsules are produced under very carefully controlled conditions. Controls are performed continuously throughout the process and guarantee that capsules conform to the highest quality standards. The capsules described below conform to the specifications as defined in the current edition of the Capsugel "Technical Reference File" for empty hard gelatin capsules.

PRODUCT DESCRIPTION Empty Hard Gelatin Capsules

Customer:		Lot Number:	33800621
Product Name:		Customer Reference:	
Product Code:		Product Size:	00
Manufacturing Date:	05-Mar-2013	Type:	CONI-SNAP
Expiration Date:	Mar 2018		

BODY		**CAP**	
Code:	44.000	Code:	44.000
Name:	WHITE OP.	Name:	WHITE OP.

Body Composition		**Cap Composition**	
Titanium dioxide	2.0000 %	Titanium dioxide	2.0000 %
GELATIN	qsp 100 %	GELATIN	qsp 100 %

Due to the nature of raw materials, their sourcing, and technology improvements, the color composition data indicated are target values and actual values may vary to insure the consistency of lot color. Capsugel supports the expiry date if recommendations for warehousing and transportation are observed (recommended : 15°C - 25°C and 35% - 65% relative humidity)

Ingredient / Reference	E Nr	C.I. Nr	Function	Regulatory References
Titanium dioxide	E171	77891	Opacifier	(EU) 231/2012, 21 CFR, EP, JP, USP/NF
GELATIN			Structure	EP, JP, USP/NF

ANALYTICAL DATA

Characteristics	Test Method	Units	Specifications	Results
Identification of gelatin	CP010		Positive	pass *
Identification of TiO2	CP011		Conforms to composition	pass *
Sulphated ash	CP015	%	Less than 7	pass *
Arsenic	CP017A	ppm	Less than 1	pass *
Cadmium	CP017B	ppm	Less than 0.5	pass *
Lead	CP017C	ppm	Less than 1	pass *
Mercury	CP017D	ppm	Less than 0.1	pass *
Lubricant content	CP019	%	Less than 0.5	0.05 *
Sulphur dioxide	CP020	ppm	Less than 50	2 *
Disintegration time	CP001	min/sec	Less than 15:00	8:11 *
Loss on drying	CP014	%	13.0 to 16.0	14.5
Average weight	CP003	mg	111 to 125	114.6
Total Aerobic Microbial Count	CP031	cfu / g	Less than 1000	45
Escherichia coli	CP033		Absence in 1 gram	pass *
Salmonella	CP034		Absence in 10 gram	pass *
Staphylococcus aureus	CP035		Absence in 1 gram	pass *
Pseudomonas aeruginosa	CP036		Absence in 1 gram	pass *
Total Yeasts/Moulds Count	CP032	cfu / g	Less than 100	< 10 *

*** Reduced frequency testing**

Customer Name: Lot Nr: 33800621

Capsugel hard gelatin capsules are meeting <2 ppm Chromium as defined in the Chinese pharmacopoeia for Vacant Gelatin.
In accordance with ICH Q3C residual solvent guideline , Class 3 Solvents may be used according to good manufacturing practices such that their cumulative value does not exceed 5000ppm or 0.5%, under option 1 as defined in ICH Q3C, USP<467>, and EP General Text 5.4.

Physical Characteristics

This product conforms to established A.Q.L.'s for Physical Attributes.
Appearance - Clean empty capsules, meeting the specified requirements of color and size.
Odor - Free of disagreeable odor.
The reported disintegration time is subjective, and is provided to indicate Pass/Fail status for 15 minutes.
Tests for color, solubility and acidity conform to Japanese Pharmacopeia requirements.

TSE/BSE Regulations

Capsugel can use blends of several pharmaceutical gelatins. When bovine gelatin is used by Capsugel, it is in full compliance with all pharmaceutical regulatory statutes.
Specifically, Capsugel fully complies with the following where applicable:

- Commission Directive 2003/63/EC, compliance is demonstrated by the "Certificate of Suitability".
- Regulation (EC) No 853/2004 on specific hygiene rules for food of animal origin.
- Regulation (EC) No 999/2001 as regards specified risk material, Commission Regulation (EC) No 722/2007.
- United States FDA September 1997 Guidance for Industry.
- United States FDA - 21 CFR Parts 211, 226, 300, 500, 530, 600, 895, and 1271 related to Use of Materials Derived from Cattle in Medical Products.
- United States FDA - 21 CFR Parts 189 and 700 related to Use of Materials Derived From Cattle in Human Food and Cosmetics.
- Japanese Ministry of Health, Labor Welfare (MHLW) - "Food Sanitation Law", No. 10 in MHLW notification on Jan. 16,2004.
- Japanese Ministry of Health, Labor and Welfare - Notification No. 210 of MHLW, issued on May 20, 2003.
- The raw material is derived from healthy animals slaughtered in a slaughterhouse, which have been inspected by an official veterinarian and have been deemed fit for human consumption.

Capsugel currently manufactures capsules under any (or all) of the following Certificates of Suitability:

- Nitta Gelatin R1 CEP 2005-217
- Nitta Gelatin R1 CEP 2004-247
- Nitta Gelatin R1 CEP 2004-320
- Rousselot SAS R1 CEP 2000-027
- Rousselot SAS R1 CEP 2001-332
- Gelita group R1 CEP 2003-172
- PB Gelatins R1 CEP 2002-110
- Sterling Gelatin R1-CEP 2001-211
- PB Leiner R1-CEP 2004-022
- Nitta Gelatin R1-CEP 2000-344

Manufacturing Processes:
No Addition of Preservatives
No Ethylene Oxide Treatment
No Irradiation Treatment

CAPSUGEL - BORNEM
Sophie De Keersmaeker - Quality Assurance
Rijksweg 11 - 2880 Bornem -Belgium
Tel: +32 (0)3 8900588

Digitally approved by Moernaut, Roel (Mar 14 2013, 16:43:39)