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GEBZE TECHNICAL UNIVERSITY

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FIRAT POTUR

A THESIS SUBMITTED FOR THE DEGREE OF

MASTER OF SCIENCE

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GEBZE TEKNİK ÜNİVERSİTESİ
FEN BİLİMLERİ ENSTİTÜSÜ

SUDA ÇÖZÜNEN FARKLI FİLM KAPLAMA POLİMERLERİNİN MULTİVİTAMİN İLAÇ TABLETLERİ ÜZERİNDEKİ ETKİLERİ

FIRAT POTUR
YÜKSEK LİSANS TEZİ
KİMYA MÜHENDİSLİĞİ ANABİLİM DALI

DANIŞMANI
PROF. DR. H. YILDIRIM ERBİL

GEBZE
2016

GEBZE TEKNİK ÜNİVERSİTESİ	**YÜKSEK LİSANS JÜRİ ONAY FORMU**

GTÜ Fen Bilimleri Enstitüsü Yönetim Kurulu'nun 08/06/2016 tarih ve 2016 / 36 sayılı kararıyla oluşturulan jüri tarafından 15/06/2016 tarihinde tez savunma sınavı yapılan Fırat POTUR'un tez çalışması Kimya Mühendisliği Anabilim Dalında YÜKSEK LİSANS tezi olarak kabul edilmiştir.

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SUMMARY

In this thesis study; the stability of multivitamin tablets against moisture was maintained by coating them with a new polymeric coating solution. The original coating solution of the multivitamin tablets was an Opadry-200 solution, which contains polyvinyl alcohol (PVA) as the main polymer and in order to substitute this Opadry-200 solution, hydroxyl propyl cellulose (HPC), hydroxyl propyl methylcellulose (HPMC) and pure (PVA) polymers were used to prepare the film coating solutions.

The contents of the multivitamin tablets were not changed during all the experiments and the amount of riboflavin and folic acid inside tablets were remained same. Firstly, the moisture analysis of all the film coating materials were carried out in incubators and all the moisture content (% water) results were found to be below 5.0%. After that, the viscosities of the polymeric film coating solutions were found to be between 110-130 mPas after adjusting their solid contents. Later, standard filter papers were coated with film coating solutions and water vapor permeability tests through polymeric films were performed after drying. The amount of water vapor transferred through the unit area of the coated filter paper in one hour was measured and results obtained between 5.86 g/m^2h^{-1} to 8.98 g/m^2h^{-1}. After that, the weight increases of the film coated tablets from the humidity present in the medium were measured and the absorbed water amounts were determined. According to the polymer type, the absorbed water amounts were changed between 9.03 g/m^2h^{-1} to 13.55 g/m^2h^{-1}. It was seen that the water vapor permeability results of film coated tablets fits well with the coated filter paper results. Afterwards, the moisture contents of film coated tablets were determined with a Karl-Fischer titration equipment. The weights and lengths of the film coated multivitamin tablets were also measured and finally dissolution analysis of film coated multivitamin tablets performed in order to determine the performance of final product in the human body. Finally, it was found that PVA and HPC were found as the best polymers having high moisture barrier properties very near to Opadry-200 solution, and the most unsuitable polymer was found to be HPMC 6-cps.

Key Words: Film Coating, Water Vapor Permeability (WVP), Moisture Content (MC).

ÖZET

Multivitamin tabletlerin yeni bir polimerik bir çözelti ile kaplanarak neme karşı stabilitelerin sağlanması bu tez çalışması kapsamında incelenmiştir. Multivitamin tabletlerin orijinal film kaplama çözeltisi, polivinil alkol (PVA) ana polimeri içeren Opadry-200'dür ve bu tez kapsamında Opadry-200'ün yerini tutmak üzere yeni film kaplama çözeltileri hazırlamak için kullanılan polimerler; hydroxyl propyl cellulose (HPC), hydroxyl propyl methylcellulose (HPMC) ve saf (PVA) olarak sıralanmıştır.

Tüm çalışmalar boyunca multivitamin tabletlerin içerikleri değişmemiştir ve riboflavin ve folic acid değerleri sabit tutulmuştur. Bunun için de film kaplama çözeltilerinin sadece ana polimerleri değiştirilmiş, diğer tüm malzemeler ve miktarları hep aynı bırakılmıştır. İlk olarak, film kaplama malzemelerinin nem değerlerine bakılmış ve tüm malzemelerin % 5.0'dan daha düşük nem değerlerine sahip oldukları görülmüştür. Ardından konsantrasyonları ayarlanmış film kaplama çözeltilerinin viskozite değerlerine bakılmış ve sonuçların 110 mPas ile 130 mPas arasında değiştikleri gözlemlenmiştir. Bundan sonra, kaplanan polimer filmlerin su buharı geçirgenliklerini karşılaştırmak amacıyla standart filtre kağıtları polimerik film kaplama çözeltileri ile kaplanmış ve bunlardan bir saatte birim alandan transfer edilen su buharı miktarlarının 5.86 g/m^2h^{-1} ile 8.98 g/m^2h^{-1} aralığında olduğu tespit edilmiştir. Daha sonra, film kaplanmış tabletlerin ağırlık artışı takip edilerek ortamdaki nemden absorplanan su miktarı saptanmıştır. Bu miktarlar polimerin cinsine göre 9.03 g/m^2h^{-1} ile 13.55 g/m^2h^{-1} arasında değişmektedir. Hem filtre kağıdı kaplamalarından, hem de tablet kaplamlarından elde edilen su buharı geçirgenlikleri sonuçları birbirleriyle uyumludur. Ayrıca film kaplı tabletlerin nem içeriklerine Karl-Fischer cihazı ile bakılmıştır. Film kaplama prosesinin tablet üzerindeki fiziksel etkilerinii gözlemlemek amacıyla film kaplı tabletlerin ağırlık ve uzunluk ölçümleri, ayrıca insan vücudundaki performansını gözlemlemek amacıyla da çözünme hızı analizleri gerçekleştirilmiştir. Opadry-200'e en yakın nem geçirmezlik özelliğine sahip olan polimer kaplamaların PVA ve HPC oldukları, en uygun olmayan polimerin ise HPMC 6-cps olduğu saptanmıştır.

Anahtar Kelimeler: Film Kaplama, Su Buharı Geçirgenliği (SBG), Nem İçeriği (Nİ).

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LIST of ABBREVIATIONS and ACRONYMS

Abbreviations and Acronyms		**Explanations**
µm	:	Micrometer
mm	:	Milimeter
^{o}C	:	Degree Celcius
mPas	:	Milipascal Second
ASTM	:	American Society for Testing and Materials
AFM	:	Atomic Force Microscopy
API	:	Active Pharmaceutical Ingredient
BSI	:	British Standards
CPS	:	Centi Poise
DIN	:	German Institute for Standardization
EC	:	Ethyl Cellulose
HPC	:	Hydroxyl Propyl Cellulose
HPLC	:	High Performance Liquid Chromatography
HPMC	:	Hydroxyl Propyl Methylcellulose
ISO	:	International Organization for Standardization
MFFT	:	Minimum Film Forming Temperature
MVTR	:	Moisture Vapor Transmission Rate
PEG	:	Polyethylene Glycol
PMMA	:	Poly Methyl Methacrylate
PVA	:	Polyvinyl Alcohol
RH	:	Relative Humidity
RPM	:	Round Per Minute
SEM	:	Scanning Electron Microscopy
UV	:	Ultra Violet
WVT	:	Water Vapor Transmission

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1. INTRODUCTION

Drug is a chemical substance used in the treatment, cure, prevention, or diagnosis of diseases or used to enhance physical or mental well-being. Tablets may be defined as the solid unit dosage form of drugs with or without suitable diluents and prepared either by molding or compression. They comprise a mixture of active substances and excipients usually in powder form, pressed or compacted from a powder into a solid dose. Film coatings are applied onto the surface of a tablet as a thin polymeric film in order to provide taste masking, moisture and light protecting and improving mechanical resistance of the product. Aqueous coating of oral solid dosage forms has been preferred instead of solvent based coatings because of safety, environmental and economic reasons.

Active pharmaceutical ingredient (API) in a tablet dosage form must be stable in order to ensure its efficacy and safety for the patient until the end of its shelf life. Stability of drug and its API mostly effected from hydrolysis, thermal degradation, oxidation, microorganisms light or any other chemical reactions. Moisture can cause hydrolysis which may destabilize the active substance in a tablet. In order to minimize the sorption of environmental water vapor and prevent the hydrolytic drug degradation; conventional polymer moisture barrier coatings are currently applied to the oral solid dosage forms. Commonly used polymeric film formers for moisture protective coatings include; hydroxyl propyl cellulose (HPC), hydroxyl propyl methylcellulose (HPMC), polyvinyl alcohol (PVA), ethyl cellulose (EC) and poly methyl methacrylate (PMMA).

The purpose of this thesis study is to develop better film coating formulations for moisture protection of multivitamin tablets. The formulation of the main ingredients such as riboflavin and folic acid of the multivitamin drug were not changed during the experimental work. The commercial film coating solution for this drug (Opadry-200) contains polyvinyl alcohol (PVA) polymer of 35 % by weight. We tested the success of alternative hydrophilic polymers such as hydroxyl propyl cellulose (HPC), hydroxyl propyl methylcellulose (HPMC) and 100 % polyvinyl alcohol (PVA) instead of Opadry-200 form film coating solution. Different film coating solutions were prepared having different viscosity and density grades and their coating properties examined. Moisture uptake tests were performed for these film coatings after the tablet coating process in order to observe differences between

original and other film coating solutions. Water vapor permeability tests were also performed for different polymeric coatings and the results were compared using time versus water weight gain plots. The same tests were performed per unit area for film coated tablets which were coated with different polymeric coating solutions.

In summary, the water vapor permeability, water uptake, viscosity and density parameters were measured and reported in this thesis in order to develop a good polymeric barrier coating which can be used in the tablet industry. The most effective film coating solution according to coating ability, appearance of the tablet, protecting the active ingredient for longer times was determined to be polyvinyl alcohol (PVA) based film coating solution.

2. LITERATURE REVIEW

2.1. Coating of Tablets by Polymeric Films

2.1.1. General Description of Tablet Production

Tablet is defined as the composition of active substance and other excipients in a pharmaceutical dosage form. According to world health organization; active pharmaceutical ingredient (API) is explained as "A substance used in a finished pharmaceutical product, intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings". In order to ensure the efficacy and safety of API for the patient until the end of its shelf life with the other excipients, tablet dosage form need to be stable. With the compression of API and other excipients such as binders, disintegrants, lubricants, diluents, flavors and colorants tablets can be produced. Types of tablets differs like film coated tablet, sugar coated tablet, enteric coated tablet, effervescent tablets and so on. Advantages of the tablets are; low cost of for all the dosage forms, easy to package and ship, suitable to large scale production and they have the best combined properties of chemical, mechanical and microbiological stability of all the oral forms [Bhowmik et al., 2014].

2.1.2. Purpose of Film Coating on a Tablet

The main purpose of film coating on a tablet is ensuring its stability in shelf life period of the product. The thickness of the film coating varies between 20 and 100 μm. Primarily; polymer, plasticizer, pigments and solvents are incorporated in a film coating solution. Beside stability, film coatings are applied for several reasons; protection against moisture and light, taste masking, improving product appearance and mechanical resistance, modifying drug release and so on. The earliest process which was used as a pharmaceutical coating is the application of sugar coating with a long process time, needing high temperature and excessive moisture. Afterwards, solvent based film coatings were used but several issues were raised with safety, environmental and economic disadvantages. In order to eliminate these disadvantages; aqueous film coatings are started to be used in pharmaceutical

industry. However, since tablets may contain moisture sensitive drugs or excipients, the use of water soluble materials raises concerns about the physical and chemical stability of the coated tablets [Bharadia et al., 2014].

2.1.3. Mechanism of Aqueous Film Coating

Linda A. Felton reviewed the mechanism of film formation. [Felton 2013] Initially the polymeric solution was in the dissolved state and this solution was sprayed on to the substrate surface with a spray atomization process. The polymer chains interpenetrate and pass into a gel state with the evaporation of the solution then form a solid film with further drying. The overview of the film formation process is given in Figure 2.1. The most important issue in the film formation process is the rate of solvent evaporation. If a solvent evaporates too slowly, the substrates become over-wetted and, in extreme cases, begin to dissolve. If a solvent evaporates too quickly, the polymer containing droplets may dry before either impinging on the substrate surface or spreading on the tablet surface. Besides the evaporation process, viscosity is another key variable in the coating operations. When the viscosity of the solution increases, then the concentration of the polymer solution increases. The molecular weight of the polymer affects the solution viscosity and higher molecular weight grades exhibiting higher viscosities [Felton, 2013].

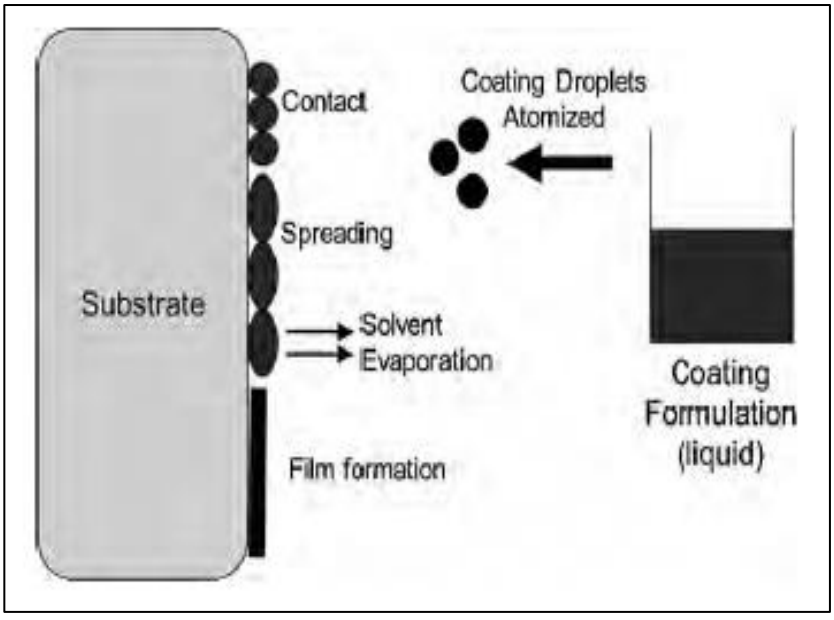

Figure 2.1: Overview of the film formation process.

2.1.4. Ingredients of Film Coating Solutions

Main ingredients in solutions to be used for tablet coating are polymers, plasticizers, colorants, and solvents. Mostly used polymers in the film coating applications are either cellulose derivatives, such as the cellulose ethers, or acrylic polymers and copolymers. Occasionally encountered are high molecular weight polyethylene glycols, polyvinyl pyrrolidone, polyvinyl alcohol and some waxy materials. Plasticizers are generally added to film coating formulations to modify the physical properties of the polymer to make it more usable. Polyols, such as polyethylene glycol, organic esters, such as diethyl phthalate and glycerides are the examples. Colorants in a film coating solution are water insoluble colors named as pigments. Pigments are tend to be more chemically stable to light, provide better opacity and optimize the impermeability of a given water vapor. Examples of colorants are iron oxide pigments, titanium dioxide and aluminum lakes. Both of the two types of solvents are used in film coating applications. Mostly preferred ones are water based instead of organic based solvents. The venting of organic solvent vapor into the atmosphere is ecologically unacceptable and removal of hazardous waste is expensive. Also the storage and quality control costs are comparatively high. As the safety point; organic solvents provide explosion, fire and toxic hazards to plant operators [Cole et al., 2002].

2.1.5. Polymeric Solutions Used In Tablet Coating

Different film coating solutions were prepared to coat tablets in order to compare the effect of polymers used, under constant coating process variables and with aqueous based solvents. Some of the ingredients added to film coating formulations are; magnesium silicate, titanium dioxide, polyethylene glycol, methacrylic acid copolymer, sunset yellow and sodium bicarbonate. As an anticaking agent to improve powder flow in tablet compression talc powder was used. Magnesium silicate ($MgSiO_3$) when hydrated is most commonly known as "talc". Plasticizer were used as polyethylene glycol, in film coating solutions, solid grades of polyethylene glycol can be used for the film-coating of tablets or can be useful as hydrophilic polishing materials. Methacrylic acid copolymer, also known as methacrylic acid - ethyl acrylate copolymer is an excipient used in pharmaceutical

manufacturing. Carbonic acid monosodium salt (sodium bicarbonate) generally used in the pharmaceutical formulations for the source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation. As colorant, titanium dioxide and sunset yellow chemicals were used in order to provide better opacity [Rowe et al., 2009].

2.1.6. Structural Formula of Used Polymers

Coating properties and performance of the finished product mostly effected from the type of the polymer and coating process. Polymers are the main ingredients of the coating formulations and affect the main characteristic of finished product's coating. Chemical structure of the polymers affects the mechanical and permeability properties of the coated tablets; molecular weight of polymers affects the physicochemical property of the final coating. Structural formula and properties of the used polymers are given below [Porter et al., 2009].

Polyvinyl alcohol (PVA); is a water-soluble synthetic polymer represented by the formula $(C_2H_4O)_n$. The value of n for the commercially available materials lies between 500 and 5000, equivalent to a molecular weight range of approximately 20.000–200.000. Structural formula of the PVA is given in Figure 2.2. [Kadajji et al., 2011].

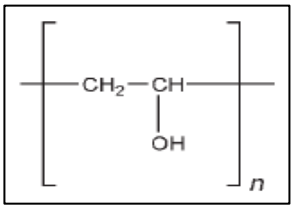

Figure 2.2: Structural formula of polyvinyl alcohol (PVA).

Hydroxypropyl methylcellulose (HPMC); available in several grades depend on viscosity and extent of substitution. Depending upon the viscosity grade, concentrations of 2–20% (w/w) are used for film-forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film-coating solutions. Structural formula of the HPMC is given in Figure 2.3. [Kadajji et al., 2011].

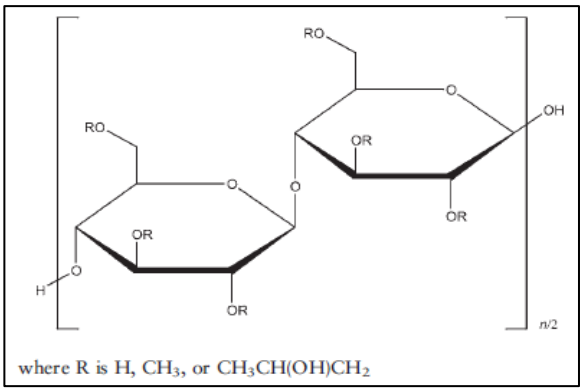

Figure 2.3: Structural formula of Hydroxypropyl methylcellulose (HPMC).

Hydroxypropyl cellulose (HPC); is primarily used in tableting as a binder and film coating formulations. Hydroxypropyl cellulose is commercially available in a number of different grades that have various solution viscosities. Molecular weight has a range of 50.000–1.250.000. Structural formula of the HPC is given in Figure 2.4. [Kadajji et al., 2011].

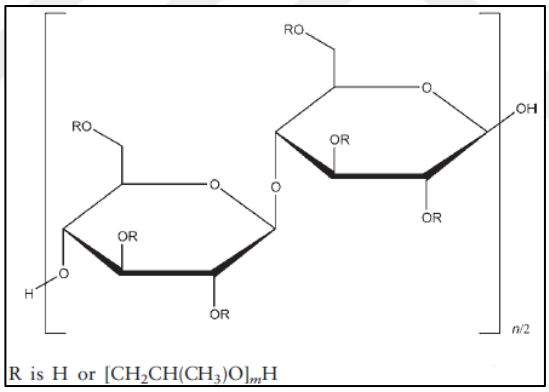

Figure 2.4: Structural formula of Hydroxypropyl cellulose (HPC).

2.2. Moisture Protection for Polymeric Film Coated Tablets

Joshi et al., in 2013 has studied film coatings for taste masking and moisture protection. The most important point for drug tablets was to ensure stability of products until the end of shelf-lives. Hydrolysis, oxidation, thermal degradation, light, microorganisms and other chemical reactions directly affect the active ingredients inside the tablets. The most important problem of these factors was the effect of moisture and accompanying hydrolysis reactions. With the increase of the internal moisture, the structure or chemical properties of the drugs started to degrade. Also humidity affects the glass transition temperature of the polymeric coating and

reduces the stability of the tablet. In 1990, Ahlneck and Zografi performed a study about the molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state. They investigated mechanism of water-solid interactions, molecular disorder in crystalline solids and drug-excipient interactions and to understand how water behaves in such systems as a plasticizer [Ahlneck et al., 1990].

According to the study of S. Joshi; the motion of a water molecule from surface to inside of tablet can be explained as a three step process: First of all, water molecules are absorbed to the film surface. Secondly, water diffusion starts into the inside of the tablet through the membrane coating and finally water molecules settled between the film and tablet surface and degradation starts. The permeability of the polymer film affects the diffusion velocity and interaction throughout the film coating [Joshi et al., 2013].

Water vapor permeability depends on the polarity of the polymer. If the diffused molecule's structural similarity with the polymer is high then the permeability or diffusion coefficients will be high. The quantity of absorbed moisture with the polymer shows the solubility coefficient of water in it. Fick's first law explained the quantity of diffused water vapor for film coating depending on time; surface area of tablet, diffusion coefficient and thickness of the film factors that affect the absorbtion of water into the tablet. Dissolution of drug inside the human body started at mouth, ongoing with stomach or small intestine and contend to blood. The drug should be diffused completely it these sections. The kinetics of dissolution mechanism must be proper for gaining maximum effect from active substance of the drug. In order to ensure providing higher efficacy from drug beside film coating polymer, also other ingredients should be chosen appropriately [Joshi et al., 2013].

2.2.1. Types of Polymeric Solutions Used For Moisture Stability

O. Bley and coworkers in 2009 performed an investigation about protection of moisture sensitive drugs with aqueous polymer coatings, importance of coating and curing conditions. In order to increase the shelf life and ensure the stability of drugs, the proper coating and packaging materials should be implemented. Generally HPC, HPMC, PVA, ethyl cellulose, shellac and polymethyl methacrylate (PMMA) type polymers are used as alternatives for these type drug coatings. For increasing the

yield of the coating, stabilizing agents and preservatives must be added to the coating solutions. Film coating polymer can be directly affected by the moisture.

In order to compare the film coating solutions; they selected polyvinyl alcohol PVA (Opadry AMB), polyvinyl alcohol - polyethylene glycol PVA-PEG copolymer (Kollicoat IR), hydroxypropylmethyl cellulose HPMC (Methocell E5, Sepifilm LP010, Sepifilm LP761, Sepifilm LP770), ethyl cellulose (EC)) (Aquacoat ECD) and Polymethacrylate - Polymethylmethacrylate (PMA-PMMA) copolymer (Eudragit EPO). Tablet coatings were performed under same conditions as; 15 rpm spinning vessel, inlet air velocity: 130 m^3/h, syringe diameter of spray gun: 1.2 mm and spraying pressure: 1.3 bar. After the coating procedure film coated tablets stayed at 60^oC chambers about 3-24 hour time periods. If the absorbed amount of moisture or entering humidity inside tablet increases, then the properties of film coating polymer solution decreases directly. They compared aqueous polymeric film coating solutions under different coating and curing conditions for getting the most proper solution [Bley et al., 2009].

Yadav and Ansari in 2013 studied the moisture barrier application of selected commercial coating systems. They underlined the point that effecting from moisture can happen both during the production process or afterwards while the finished products were reserved. Absorbed moisture could be directly affects the physical or chemical properties of tablet. In order to compare polymeric solutions they perceived different type of polymers and ingredients for moisture effected aspirin tablets under same coating and conservation conditions. Also the performed water uptake tests for drugs then listed the advantages and disadvantages of different type of solutions with different ingredients [Yadav et al., 2013].

2.2.2. Specific Types of Polymers and Solutions to Impart Moisture Transport Resistance

Abbaspour, Makhmalzadeh and Jalali in 2010 performed the study of free films and coated tablets based on hydroxypropyl methyl cellulose (HPMC) and microcrystalline cellulose, aimed for improve stability of moisture sensitive drugs. They explained as the hydrolysis was the dominant process in degradation of drugs, for improving the moisture resistance and mechanical strength this moisture effect must be minimized. With the original coating solution they observed appropriate

results and they tried to find the most favorable solution and characteristics. In the end, they reported the results with different analytical tests which were performed for original and other coating solutions [Abbaspour et al., 2010].

Siepmann and coworkers studied to adjust the desired drug release patterns from ethylcellulose coated dosage forms. They compared the ethylcellulose polymer coated tablets which has lower permeability with different hydroxypropyl methylcellulose coated tablets in order to get desired dissolved stage of the drug inside the human body. They intended to find a coating solution with lower viscosity and higher permeability and more moisture resistant film. They used Theophyline as the model drug [Siepmann et al., 2007].

Shun Por Li and coworkers studied the evaluation of the film coating properties of a hydroxy ethyl cellulose with hydroxyl propyl methylcellulose polymer system. They used Ibuprofen tablets as the model drug and prepared coating formulations with hydroxyethyl cellulose and hydroxyl propyl methylcellulose polymer systems. Polymer amounts in the film coating solutions were kept constant during their trials as % 6 (w/w). HEC and HPMC polymers having different viscosity and molecular weight were mixed and tested to found optimum film coating formulation with the best resistance to moisture and appropriate solubility properties in dissolution medium. They had difficulties in coating procedures with solutions having high viscosities [Li Shun et al., 2002].

G. Perfetti and coworkers reviewed the relation between surface roughness of free films and process parameters in spray coating. They highlighted that spray coating has proper and repeatable results than other techniques. Film coatings were prepared with aqueous based polymeric solutions and properties of these formulations were investigated. Coating amounts were not changed as % 3 (w/w) and polymers were hydroxypropylmethyl cellulose HPMC and PVA. Flow rate of spraying during trials were remained stable as 1.2 ml/min and critical process parameters were described as the distance between of spray nozzle and coating vessel, air pressure of spray nozzle, speed of rotation of coating vessel. These parameters were varied during trials for different film coating solutions in order to found the most proper condition. The results demonstrated that the spray apparatus was a capable method to obtain reproducible free sprayed films with surfaces having various uniformity and/or smoothness depending on the set of processing parameters. Figure of the coating pan is given in Figure 2.5. [Perfetti et al., 2011].

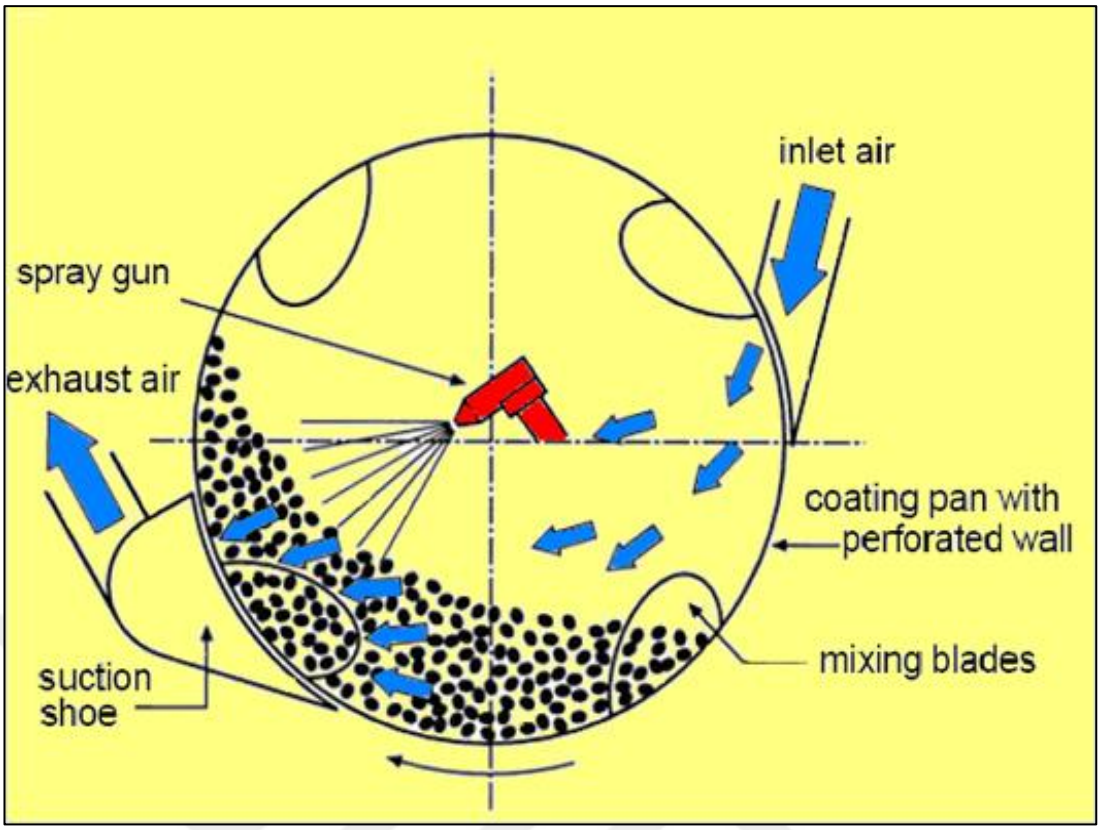

Figure 2.5: Scheme of the coating pan.

There is an inlet air entrance on the top and an exhaust air drive on the other side of the coating pan for controlling temperature and humidity inside the pan. Mixing plates are used for mixing the tablets in order to separate coating solution homogenously to product. Velocity and the amount of film coating solution are controlled by the spray gun which is stayed at the middle of the coating pan [Perfetti et al., 2011].

2.3. Reasons of Polymer Selection for Moisture Stability of Multivitamin Tablets

2.3.1. Film Coated Multivitamin or Vitamin Tablets and Their Properties

Drug stability means the ability of the pharmaceutical dosage form to maintain the physical, chemical, therapeutic and microbial properties during the time of storage and usage by the patient. It is measured by the rate of changes that take place in the pharmaceutical dosage forms. Vitamins are the one of the most effected

product in the group of pharmaceuticals. A multivitamin product contains more than one vitamin and may be supplemented by a number of minerals or trace elements. The stability problems are usually very much greater with liquid drug forms than with solid forms because chemical interactions and hydrolysis cannot be avoided in the presence of water. As the chemical structures of the vitamins differ, a distinction has to be made between the problems of physical and chemical stability. In solid drug forms the most important factors for the chemical stability are the content of free water in the formulation and the adsorption of water from the atmospheric humidity. All other influences almost always are connected with this factor [Bühler, 2001].

Tablets included riboflavin and folic acid vitamins as main ingredients except film coating solutions. Kollidon, ludipress, magnesium stearate and nicotinamide materials involved in tablet solutions as binder. Detailed properties of vitamins are given below.

Riboflavin named as vitamin B_2, to be composed of ribitole and lumichrome. Degradated under visible and UV light. Riboflavin is a yellow-orange solid substance with poor solubility in water. High dose riboflavin appears to be useful alone or along with beta-blockers in the prevention of migraine and combination with UV light has been shown to be effective in reducing the ability of harmful pathogens found in blood products to cause disease. Chemical structure of this vitamin was given in Figure 2.6. [Bühler, 2001], [DeRitter, 1982].

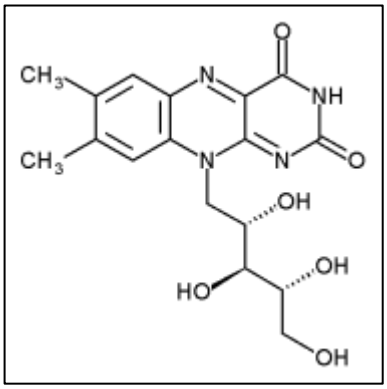

Figure 2.6: Structural formula of Riboflavine.

Folic acid (Folat-polisin, $C_{19}H_{19}N_7O_6$) included in group B vitamins (B9). Folic acid is a form of the water-soluble vitamin B9. All B vitamins help the body convert food (carbohydrates) into fuel (glucose), which is used to produce energy. Folic acid

is crucial for proper brain function and plays an important role in mental and emotional health. Pregnant women need more folic acid to lower the risk of neural tube birth defects, including cleft palate, spina bifida, and brain damage. Chemical structure of this vitamin is given in Figure 2.7. [Bühler, 2001], [DeRitter, 1982].

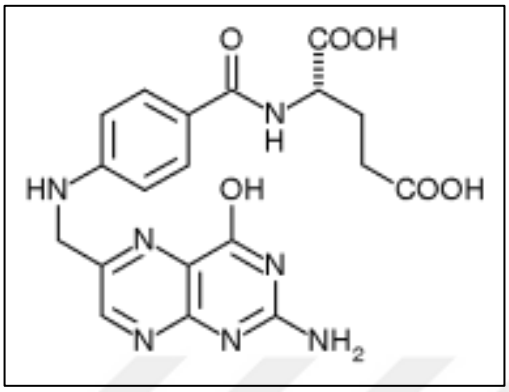

Figure 2.7: Structural formula of Folic Acid.

Nicotinamide, also known as niacinamide and nicotinic amide, is the amide of nicotinic acid (vitamin B3/niacin). Nicotinamide is a water-soluble vitamin and is part of the vitamin B group. Nicotinamide has anti-inflammatory actions. These may be of benefit to patients with inflammatory skin conditions. This vitamine increases the biosynthesis of ceramides in human keratinocytes in vitro and enhances the epidermal permeability barrier in vivo. It is stable under light, oxidation and heat medias. Chemical structure of this vitamin is given in Figure 2.8 [Bühler, 2001].

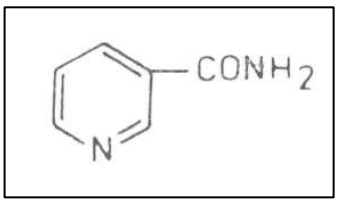

Figure 2.8: Structural formula of Nicotinamide.

Ludipress material used as additive ingredient in tablet formulations. It is tasteless and odorless, effective for maintaining product uniformity without dissolving. Ludipress is composed of Lactose monohydrate, Povidone K30 (Kollidon® 30) and Crospovidone (Kollidon CL). Kollidon VA 64 is vinylpyrrolidone-vinyl acetate copolymers which are soluble both in water and in alcohols. They are used in the pharmaceutical industry as binder in tablets, as

granulating agents, as retarding and as film former. Magnesium stearate exists as a salt form and is useful for its lubricating properties for capsules and tablets in industry. It is used to help prevent pharmaceutical ingredients from adhering to industry equipment. Magnesium stearate may be derived from both plant and animal sources [Bühler, 2001].

Vitamins are group of organic compounds. Small amounts of these compounds are enough for the normal functioning of the human body. On natural food sources they can be easily extracted. According to their fat or water solubility two groups of vitamins can be classified and totally thirteen vitamins are recognized in human nutrition. However, it is sometimes difficult to obtain enough of a particular nutrient from food. Special circumstances, such as pregnancy or reduced absorption by older people, can lead to higher needs for various nutrients. Even though fortification of foods has done its best to close these gaps, taking a multi-vitamin can be a wise strategy to ensure getting enough. The collection of more than one vitamin in a tablet drug called multivitamin tablet [Marshall, 1983].

Vitamins are the one of the pharmaceutical product that directly affected from the thermal or moisture degradation. Beside these factors, light or microorganisms may affect the stability of vitamins and multivitamins. As the scope of this thesis evaluating the moisture effect on multivitamin tablets different polymeric solutions were prepared and experimented on same multivitamin tablets. Additionally in the literature there are many sources about stability of multivitamins and effect of different aqueous based polymeric solutions on moisture.

2.4. Water Vapor Permeability of Polymers and Its Measurement Methods

2.4.1. General Information on Water Vapor Permeability and Measurement

Vapor permeability is a material's ability to allow water "vapor" to pass. In many industries like; food, pharmaceuticals and packaging moisture sensitive products are producing and permeability of preventative films important. There are many techniques to measure vapor permeability or moisture vapor transmission rate (MVTR). Gravimetric or equipment used techniques are still using range from loss of moisture by mass to very low transmission rates. Standard methods can be listed like;

International Organization for Standardization (ISO), American Society for Testing and Materials (ASTM), British standards (BSI), German Institute for Standardization (DIN) and so on. The conditions under which the measurements are made have very important effects on the results. Both the temperature of and humidity gradient across the sample need to be measured, controlled and recorded with the result. A MVTR result without specifying these conditions is almost meaningless. Certainly no two results can be compared unless the conditions are known. The most common international unit for the MVTR is g/m²/day [ASTM, 1995]. This ASTM method includes two basic processes which are water wetting method and the desiccant method. Main purpose of these methods are providing the measurement of permeance. In the water wetting method, one side of the specimen was wetted, and in the desiccant method; low humidity on one side and high humidity on the other side of the coating was maintained.

In the desiccant method; test specimen is sealed to the open mouth of the test dish containing desiccants, and the sample placed in a controlled humidity and temperature place. Periodic weightings were determined and the rate of water vapor through the sample into the desiccant was calculated.

In the water wetting method; periodic weigh of the sample determine the rate of vapor movement from the distilled water containing dish through the controlled temperature and humidity. A simple apparatus is used to obtain reliable values of water vapor transfer through permeable and semi permeable materials. Values obtaining from results may be used in design, manufacture and marketing of product. Testing conditions like humidity and temperature must be selected most closely approach the conditions of use in order to use the selected product for proper utilization. While any set of conditions may be used and those conditions reported, standard conditions that have been useful. Calculation of water vapor transmission is given below [ASTM, 1995].

$$WVT = \frac{G}{t}/A = \mathrm{G/tA} \tag{2.1}$$

- G = weight change, grains (from the straight line)
- t = time during which G occurred
- G/t = slope of the straight line
- A = test area (cup mouth area)

2.4.2. Specific Studies on Water Vapor Permeability of Polymers Used in Film Coating

Effects of temperature and humidity on the barrier properties of biaxially oriented polypropylene (PP) and polyvinyl alcohol (PVA) films study was performed by Chen Mo and coworkers [Mo Chen et al., 2014]. Water vapor permeability and oxygen permeability are two of important parameters for packaging materials that shelf life and general quality of the product directly affected from these factors. They reported that humidity and temperature directly affected the permeability performance of packaging materials. They performed tests at $10^oC – 45^oC$ with 50 % RH or at 23^oC with 35 % - 90 % RH intervals. The environmental condition was 50 ± 5 RH and 23 ± 1^oC also for the films $50cm^2$ water vapor transmission effective areas was perceived. Water vapor transmission rate and oxygen transmission rate measurements were performed for different films at various parameters. For polyvinyl alcohol (PVA) films; when RH increased the oxygen transmission rate and water vapor transmission rates were exponentially increased. Increased temperature also effect the water vapor transmission rate of PVA positively and increased, however oxygen transmission rate was decreased. For the polypropylene (PP) films with the increased temperature water vapor transmission rate and oxygen transmission rates were increased but with increased RH, water vapor transmission rate was increased and oxygen transmission rate was decreased. They concluded in their study that RH variation was more effective than temperature variation [Mo Chen et al., 2014].

Moisture sorption and permeability characteristics of polymer films, implications for their use as barrier coatings for solid dosage forms containing hydrolysable drug substances was studied by Mwesigwa et al., in 2007. In their work, they used a model Aspirin tablet which the content and quantity was not changed during their studies. The purpose of their study was to view the differences between different film coating materials on the Aspirin tablets. Uncoated and coated Aspirin tablet cores were exposed to 75% RH at 25^oC for 4 months to enable the assessment of the ability of the coatings to prevent moisture uptake and aspirin degradation. They used poly (methacrylic acid ethyl acrylate) copolymer (Eudragit L30 D-55, Evonik), poly(butyl methacrylate (2-dimethylaminoethyl, methacrylate methyl methacrylate copolymer (Eudragit EPO, Evonik), a polyvinyl alcohol (PVA)

and xanthan gum-based preformulated coating system (Opadry AMB, Colorcon, Dartford, UK); and a hypromellose-based preformulated coating system (Sepifilm LP 014, Seppic, Paris La Defense cedex, France). They found that Eudragit EPO was the least permeable coating followed by Opadry AMB, Eudragit L30 D-55 and Sepifilm LP. No direct relationship was found between the amounts of moisture sorbed and the permeability characteristics of the films. They also showed that the ability to prevent hydrolysis in the coated tablet cores was not the result of preventing moisture uptake into the core. Adhesion between the coating and the core is of great significance to film coating applications as loss of adhesion may compromise the ability of the coating to provide mechanical protection to the substrate. They concluded their study as "no direct relationship was found between the amounts of moisture sorbed and the permeability characteristics of the applied films". All coated cores they tried achieved a net reduction in the amount of moisture sorbed. According to their studies they showed that the ability to prevent hydrolysis in the coated tablet cores was not the result of preventing moisture uptake in the core. According to this study, in some cases the result of permeability characteristics of film coating materials are not the only effective factor on explaining the moisture barrier characteristics of film coatings. Beside permeability, diffusion, solubility coefficient factors, application of film coating on tablet, environmental factors like humidity and temperature and used materials in film coating solutions are other important factors that affect the moisture barrier quality of film coatings [Mwesigwa et al., 2007].

Measurement of water vapor transmission rate in highly permeable films study was performed by Y. Hu and coworkers. They carried out ASTM E 96 method for highly permeable films and compared the area effect on water vapor transmissions and various materials in the cup test. They concluded that the high water vapor flux through the more permeable films caused a reduction in the driving force for water vapor transmission [Hu et al., 2000].

2.5. Water Vapor Permeability of Film Coated Tablets

2.5.1. Relation Between Water Vapor Permeability and Moisture Content of a Tablet

Chad R. Dalton and coworkers performed a study about processing and storage effects on water vapor sorption by some model pharmaceutical solid dosage formulations [Dalton et al., 1997]. Water is an important parameter that effect the stability and unity of products and they reported that several analytical water detection techniques with different sensitivity. The purposes of their tests are water sorption behavior identification with determining the water content of tablets of the different formulation. They also compared the different analytical methods and processing operations in order to predict the accuracy of water content. They used Karl Fischer analysis as identification of the moisture, loss on drying analysis and moisture balance for different formulations. They performed these analytical tests in different environment RH values. Additionally they changed the temperature values that tablets exposed. They concluded that all the techniques used in their study for water content determinations were found to be reproducible when carefully performed. If the content of the formulations were changed then the water uptake of materials were varied. When they evaluated the RH and temperature effect on the moisture sorption; they determined that the temperature effects on water sorption were small however different RH values directly affect the moisture sorption behavior [Dalton et al., 1997].

2.5.2. Methods Used for Water Vapor Permeability Measurement of Film Coated Tablets

Shawn A. Kucera and coworkers published the “physical aging in pharmaceutical polymers and the effect on solid oral dosage forms stability” study in 2013 [Kucera et al., 2013]. They investigated the factors that influence physical aging and methods used to stabilize or prevent physical aging; plasticisers, curing and storage conditions of product, excipients, addition of high glass transition temperature polymers are directly affect the physical aging and the stability of the tablet drug. They showed that RH and temperature during storage also affect the aging. They explained the formation of thin films according to Figure 2.9.

In the first stage, the aqueous film coating dispersion was sprayed and deposited on the tablet surface and water is removed at a constant rate. Later, water evaporation is ongoing and polymer particles become closer to each other. During the third stage, the formation of the film is completed and water evaporation stops. Stability or drug release rate change was assumed to be affected from physical aging or the gradual coalescence of the polymeric film [Kucera et al., 2013].

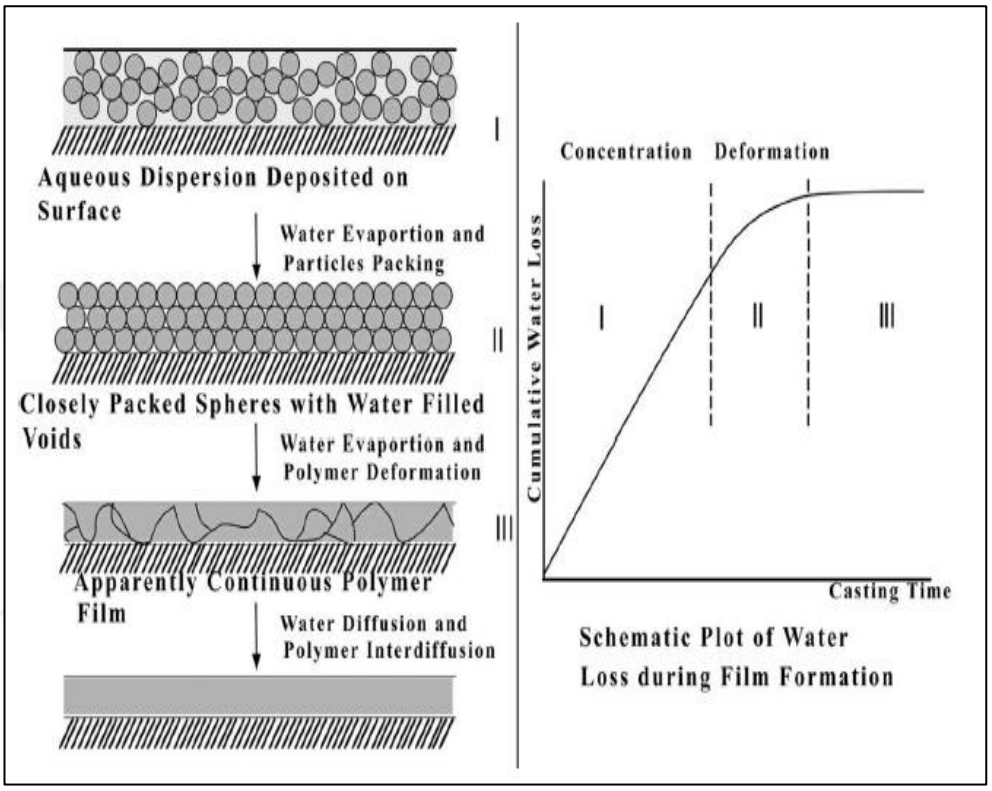

Figure 2.9: The formation of thin films from polymeric lattices occurs with the simultaneous evaporation of water.

2.5.3. Methods Used for Water Vapor Permeability Measurement of Polymer Coated Filter Papers

Porter and Felton in 2010 published a review article about "techniques to assess film coatings and evaluate film coated products". They explained the number of experimental techniques in order to determine the physical, mechanical, adhesive, thermal and permeability properties of free and applied films. These techniques are used in order to better understand the film coating process and prevent manufacturing, coating and performance problems [Porter et al., 2010].

They used mechanical assessment techniques and applied stress analysis with tensile stress and puncture stress analysis of polymers. Then they used film adhesion technique in order to show the stability factor of the drug products. They used differential scanning calorimetry (DSC) technique for determination of the glass transition temperature of the film coating polymers and also they used minimum film forming temperature (MFFT) for determination of cause coalescence of a polymeric dispersion to form a film. They also used microscopy analytical techniques for digital imaging for surface analysis of film coated products such as scanning electron microscopy (SEM) and atomic force microscopy (AFM) for determining coating surface and roughness characteristics. They used water vapor permeability and water vapor transmission through free films in order to determine water transfer across film coatings. They also measured the oxygen permeability of the free films [Porter et al., 2010].

3. EXPERIMENTAL

3.1. Materials

In this thesis work, riboflavine and folic acid vitamins, nicotinamide, Ludipress, Kollidon VA 64 and magnesium stearate materials were obtained from Zentiva Health Products Company, Turkey. All of these materials are HPLC grade. Average weight multivitamin tablets are 180 mg and content of these tablets was not changed during the laboratory studies. Weight and percentage of tablet materials are given in Table 3.1.

Table 3.1: Ingredient of Multivitamin Tablets.

Material	Amount (mg)	Percentage (%)
Riboflavine	2.16	1.2 %
Folic Acid	2.70	1.5 %
Nicotinamide	21.06	11.7 %
Ludipress	145.98	81.1 %
Kollidon VA 64	7.20	4.0 %
Magnesium Stearate	0.90	0.5 %
Total	180 mg	100 %

Polyvinyl alcohol (PVA), hydroxypropyl methylcellulose (HPMC) -3 Cps, hydroxypropyl methylcellulose (HPMC) -5 Cps, hydroxypropyl methylcellulose (HPMC) -6 Cps and hydroxypropyl cellulose (HPC) polymers were the main film coating polymers which were used in this study.

The ingredients added to film coating formulations are magnesium silicate, titanium dioxide, polyethylene glycol, methacrylic acid copolymer, quinoline yellow and sodium bicarbonate. Main film coating polymers and ingredients were obtained from Zentiva Health Products Company, Turkey. The weight percentage of film coating materials were not changed during studies and content of the film coating solution is given in Table 3.2.

Table 3.2: Content of the Film Coating Solution.

Content	Material Name	% w/w
1	MAIN POLYMER	35.00
2	TITANIUM DIOXIDE	22.00
3	TALC	23.88
4	MACROGOL/PEG	12.00
5	METHACRYLIC ACID COPOLYMER	4.00
6	QUINOLINE YELLOW	3.00
7	SODIUM BICARBONATE	0.12

3.2. Methods and Instrumentation

3.2.1. Preparation of Multivitamin Tablets

Ingredients of multivitamin tablets (Table 3.1.) were mixed in the powder mixer equipment and pressed with the tablet pressing machine. Total amount of the ingredient powder was 18 kg and approximately 100.000 multivitamin tablets were prepared in order to be used in the laboratory trials. Average weights of these tablets were around 180 mg.

3.2.2. Preparation of Polymeric Film Coating Solutions

Polymeric film coating solutions contain seven different materials which were given in Table 3.2. Six different film coating solutions were prepared. Only main polymer was changed in the film coating solutions and the others were kept constant in all studies. Original film coating solution of multivitamin tablets was Opadry-200 and obtained from Zentiva Health Products Company, Turkey.

120 g. of powdered film coating mixture were prepared by adding each material to polyethylene nylon bags. 36 g. of main polymer, 32.4 g. of titanium dioxide, 28.66 g. of Talc, 14.4 g. of Macrogol PEG, 4.8 g. of methacrylic acid copolymer, 3.6 g. of quinolone yellow and 144 mg. of sodium bicarbonate were separately added and mixed about 5 minutes in solid form.

After 120 g. of polymeric solid powdered mixture was obtained, than this mixture slowly poured into 480 ml of pure water in 10 minutes. The solution was

mixed about 20 minutes with a mechanical stirrer, at 80^{o}C in order to obtain homogenous mixture. Finally, 6 different polymeric solutions were obtained having a volume of 600 ml containing 20 % polymeric mixtures and 80 % of pure water.

3.2.3. Moisture Analysis of Film Coating Materials

Moisture analysis of the film coating materials was performed at 105^{o}C and 45^{o}C in incubators. Firstly, approximately 1g of each material weighed at automatic balance equipment. These materials were polymers and other ingredients of film coating solutions as; PVA, HPMC-3 Cps, HPMC-5 Cps, HPMC-6 Cps and HPC polymers, titanium dioxide, Talc, Macrogol PEG, methacrylic acid copolymer, quinolone yellow and sodium bicarbonate. Afterwards these materials except sodium bicarbonate were put in 105^{o}C incubator and kept there about 2 hours. Sodium bicarbonate was kept at 45^{o}C incubator two days because of its structure. These materials were removed from the chamber and kept in a desiccator about 5 minutes. After that, the final weighs of materials were noted. Moisture percentages of materials were calculated according formula 3.1.

$$\% \text{ water} = \frac{\text{Ws} - \text{Ws}'}{\text{Ws}} \text{x } 100 \qquad (3.1)$$

- W_s = weight of the material before incubator
- $W_s{}'$ = weight of the material after incubator

3.2.4. Viscosity Analysis of Film Coating Solutions

Viscosity analysis performed with a Brookfield Viscometer (Spindle 62 / 60 Rpm) at 25^{o}C. At the first step, the viscosity of original solution Opadry-200 was determined. After that, other polymeric film coating solution viscosities were measured. All solutions contain 20 % of polymeric material and 80 % of water. Later, 6, 8, 12 and 20 g of polymers were dissolved in 80 ml water and their viscosities were measured in order to compare the effect of the amount of polymers on the final viscosities of the solutions.

3.2.5. Film Coating of Multivitamin Tablets

The tablets were film coated using a pilot scale side vented, perforated pan coating apparatus (GS PELLEGRINI HT/M 003 / HT 2195). Photo of the film coating apparatus used in this thesis study is given in Figure 3.1.

Figure 3.1: Photo of the film coating apparatus.

The process parameters and the user controllable constant setting ranges were presented in Table 3.3. Each coating batch was comprised of 1.5 kg of tablets. The amount of coating solution was 600 g. The tablets were preheated for 10 minutes and dried for 5 minutes after spraying. The tablets were stored in closed polyethylene bags at controlled conditions of 25± 2^{o}C and 60% relative humidity after the film coating.

Table 3.3: Process Parameters of Film Coating Application.

Process Parameter	Ranges
Pan Temperature	40-43^{o}C
Inlet Air Temperature	60-65^{o}C
Outlet Air Temperature	60-65^{o}C
Spraying Air Pressure	4-6 psi
Rotating Speed of Pan	12-15 rpm
Flow Rate of Coating Solution	5-6 g/minute

3.2.6. Water Vapor Permeability Analysis

ASTM E 96 water vapor permeability tests were performed for the film coating solutions and film coated tablets at 25 ± 2^{o}C room temperature and 65 % relative humidity conditions in closed desiccators. Aluminum cups having 10 cm diameters and around 9-10 g in weight were used. Whatman 589/1 filter papers having cellulose structure were used in order to form a test layer on the cups after dipping into the coating solution. Photo of the filter paper was given in Figure 3.2. The filter papers were 12.5 cm in diameters, 0.95 g in weight and 0.15 mm in width. Silica gels were used as desiccants in the aluminum cups and were dried at 105^{o}C about 3 hours prior to the water vapor permeability tests.

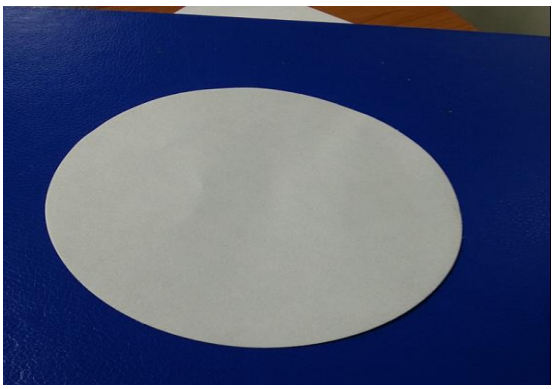

Figure 3.2: Photo of the filter paper.

At the first step; filter papers were dipped into film coating solutions and kept there for 5 minutes to absorb the coating materials. Then, the impregnated filter papers were dried overnight at room temperature. Empty aluminum cups were

weighed and a constant weight of 20 g of silica gels was added to the cups. Dried filter papers were placed over the cups which were filled with desiccants. In order to ensure the moisture transfer, through only the filter paper, the sides of the filter paper touching the aluminum cups were closed with a melted wax. Photo of the aluminum cup was given in Figure 3.3.

Figure 3.3: Photo of the aluminum cup.

Weights of the cups were noted and the cups were kept at 23-25^{o}C and 65 % relative humidity conditions in closed desiccators. In 0.4 hours period weight of the cups measured till the weights remain constant value. The calculation of water vapor transmission through the polymer coated filter paper is given below.

$$WVT = \frac{G}{t}/A = \text{G/tA} \tag{3.2}$$

- G = weight change, grains (from the straight line)
- t = time during which G occurred
- G/t = slope of the straight line
- A = test area (cup mouth area)

3.2.7. Water Vapor Permeability Analysis of Film Coated Tablets

Water vapor permeability analysis performed for film coated tablets. Same tablets were coated with six different coating solutions where only main polymer was changed in these solutions. Six trials were performed in order to define the effect of water vapor permeability at film coated tablets. In each trial 5 film coated tablets were dried at 105^{o}C chambers about 2 hours at the first step. After that, weight

measurements of the 5 tablets were conducted and recorded. Then the weights of the film coated tablets were measured in 1 hour time periods till the weights remain constant value. During film coated tablet water vapor permeability studies, they were kept at 23-25^{o}C room temperature and 65 % relative humidity conditions in closed desiccators.

3.2.8. Moisture Content of Film Coated Tablets

The moisture contents of film coated tablets were determined with a Karl-Fischer titration equipment. Film coated tablets were transformed into powder form in mortars and 0.5 g of tablet powder was used in all studies. Reagent (titrant) added to a burette and the reagent included alcohol, SO_2, a base and I_2. Powdered tablet sample added to the titration vessel and the vessel started to stir. The instrument was zeroed by titrating undesired moisture in the system. The addition of the reagent started from the burette while stirring. When the endpoint was reached, the electrode detected no change in current upon addition of more reagent. By knowing how much titrant was added, the water content of the film coated tablets calculated and the results were given as % water. Figure of the Karl-Fischer equipment is given in Figure 3.4.

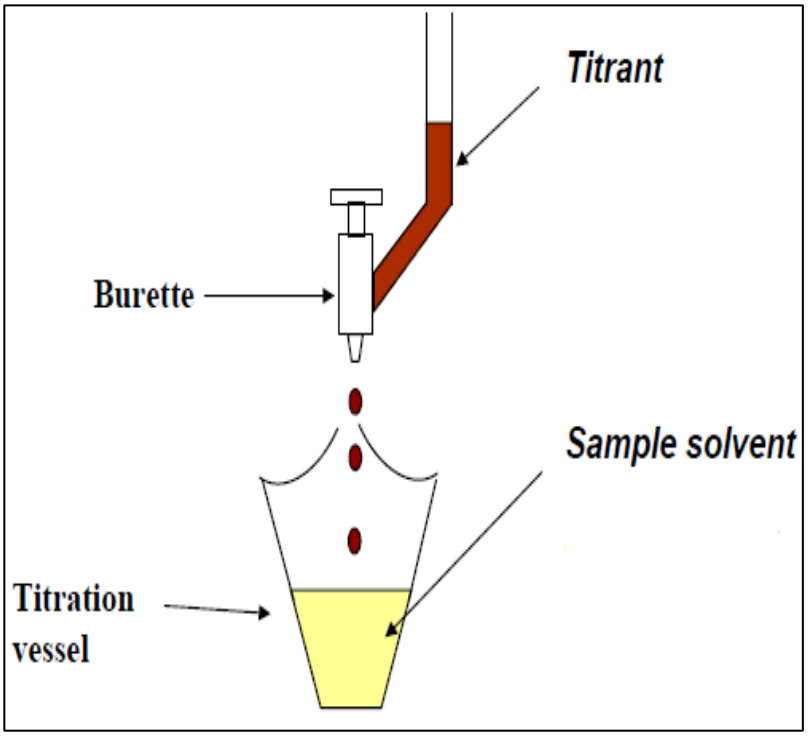

Figure 3.4: Karl-Fischer Equipment.

These tests were performed in 6 hours, 24 hours and 48 hours for all film coated tablets and the results were compared with the filter paper water vapor permeability method results.

3.2.9. Surface Area Measurements of Film Coated Tablets

Surface areas of film coated tablets were determined according to the formulas given below and used to explain the results of water vapor permeability and water uptake analysis per unit area. Scheme of the tablet is given in Figure 3.5. r_b is the contact radius of A_1 part of the tablet, h_1 and h_2 are the heights of A_1 and A_2 parts. Area of the region A_1 is equal to A_3.

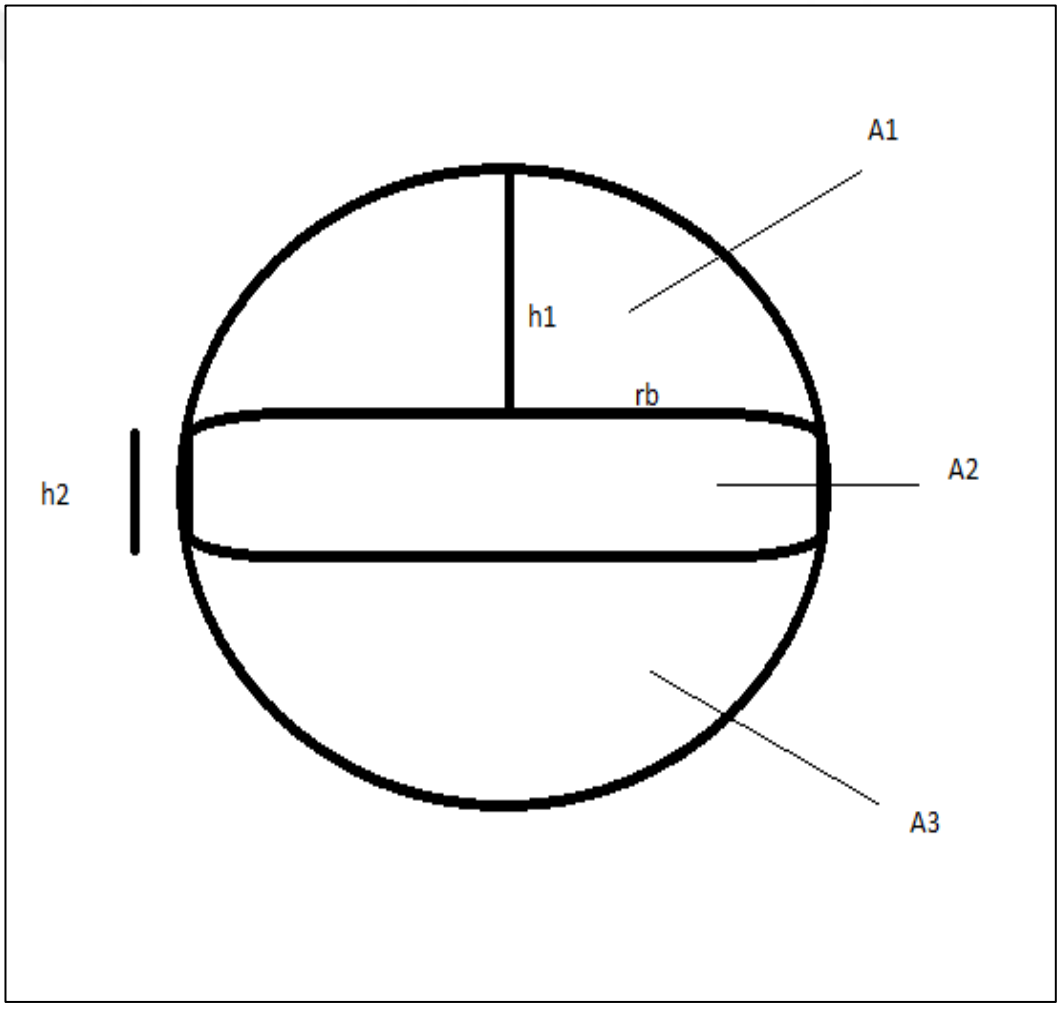

Figure 3.5: Scheme of the film coated tablet.

Contact radius of A_1 is equal to 4mm (r_b =4mm), height of the A_2 part is equal to 2mm (h_2 = 2 mm), height of the A_1 and A_3 parts is equal to 0.75mm (h1 =

0.75mm) and the total heights of A_1 and A_2 parts are equal to 3.5mm ($2h_1 + h_2 = 3.5$ mm). Calculations were performed according to below formulas.

$$A_1 = A_3 = \pi (r_b^2 + h_1^2) \quad (3.3)$$

$$A_2 = 2 \pi r_b h_2 \quad (3.4)$$

$$A_{TOTAL} = 2 \pi (r_b^2 + h_1^2) + 2 \pi r_b h_2 \quad (3.5)$$

$$A_{TOTAL} = 2 \pi [(r_b^2 + h_1^2) + r_b h_2] \quad (3.6)$$

A_{TOTAL} = 2*3.14 [$(0.004m)^2$ + $(0.00075m)^2$ + (0.004*0.002)] and total area was found as 0.000155 m^2 (A_{TOTAL} = 0.000155 m^2).

3.2.10. Weight and Length Measurements of Film Coated Tablets

The weights and lengths of the film coated tablets and uncoated tablets were measured in order to compare the film coating performance of solutions. 10 tablets were used for each study and average weights and lengths were reported. Automatic balance equipment Mettler Toledo ML model was used for weight measurements. An electronic compass was used for length measurements.

3.2.11. Dissolution Analysis of Film Coated Tablets

The dissolved amount of riboflavine and folic acid vitamins was determined with the dissolution analysis. Multivitamin tablets were weighed in an analytical balance individually. The temperature of the dissolution equipment was fixed to 37^oC and the paddle of the instrument was adjusted at 50 rpm. The weighed tablets were placed into vessels and were dissolved in water. After 1 hour, the samples were collected to vials and these vials entered to HPLC equipment in order to measure the dissolved amount of vitamins. Figure of the dissolution equipment is given in Figure 3.6.

Figure 3.6: Varian dissolution equipment.

Dissolution tests were performed for 6 different film coated tablets. Average of the results was given as % dissolved riboflavine and % dissolved folic acid. Calculation of % dissolved materials was according to formula 3.13.

$$(R_{sample} / R_{standard}) \times (C_{standard} / C_{sample}) \times 100 = \% \text{ dissolved amount} \quad (3.13)$$

where;

- R_{sample} = Area of Folic Acid or Riboflavine peak in sample solution
- $R_{standard}$ = Area of Folic Acid or Riboflavine peak in standard solution
- $C_{standard}$ = Concentration of Standard solution
- C_{sample} = Concentration of sample solution

4. RESULTS & DISCUSSIONS

4.1. Moisture Content Results of the Coating Materials

Moisture analysis were performed for the film coating polymers; PVA, HPMC-3CPS, HPMC-5CPS, HPMC-6CPS and HPC polymers, and ingredients of film coating solutions; titanium dioxide, talc, Macrogol PEG, methacrylic acid copolymer, quinolone yellow and sodium bicarbonate. Moisture percentages of the materials were calculated according to formula 3.1 and given in Table 4.1.

Table 4.1: Moisture analysis values of film coating materials.

Material Name	Ws (g)	Ws′ (g)	% water
POLYVINYL ALCOHOL (PVA)	1.0079	0.9869	2.08
HPMC-3CPS	1.0153	0.9930	2.20
HPMC-5CPS	1.0076	0.9846	2.28
HPMC-6CPS	0.9987	0.9824	1.63
HPC	1.0122	0.9905	2.14
TITANIUM DIOXIDE	1.0138	1.0102	0.36
TALC	1.0049	1.0025	0.24
MACROGOL/PEG	1.0036	1.0015	0.21
METHACRYLIC ACID COPOLYMER	1.0098	0.9722	3.72
QUINOLINE YELLOW	1.0100	0.9672	4.24
SODIUM BICARBONATE	1.0217	1.0187	0.29

Ws is the weight of the material before incubation and Ws′ is the material's weight after drying. It can be seen in the above table that all % water results were found to be below 5.0%, and the highest value was found for quinolone yellow (4.24%) and the lowest for macrogol/PEG (0.21%). The water contents of the main polymers (PVA, HPMC-3 CPS, HPMC-5 CPS, HPMC-6 CPS and HPC) were close to each other and all results are similar to the literature results [Dalton, 1997], [Kadajji, 2011], [Raymond C, 2009].

4.2. Viscosities of Film Coating Solutions

Viscosities of the polymer solutions that were used to coat the tablets were measured with a Brookfield Viscometer (Spindle 62 / 60 Rpm) at 25^{o}C. Initially, the viscosity of original coating solution (Opadry-200) was determined. All solutions contain 20% of polymeric materials and 80% of water. Viscosity results of the polymer solutions are given in Table 4.2.

Table 4.2: Viscosity results of film coating materials.

Polymeric Solutions	Viscosity Results (mPas)
Opadry 200	110
Solution 1 (HPMC-3 CPS)	90
Solution 2 (HPMC-5 CPS)	120
Solution 3 (HPMC-6 CPS)	130
Solution 4 (HPC)	180
Solution 5 (PVA)	100

Viscosity value of original solution Opadry-200 found as 110 mPas. This result is in accordance with the literature results which vary between 90 and 180 mPas. [McGinity, 2008]. In order to obtain the original coating solution viscosity value, the concentration of Solution 1 was changed to 25 % polymer content and 75 % water, concentration of Solution 4 was changed to 12 % polymeric material and 88 % water. After adjusting the concentrations, the results of solution viscosities are given in Table 4.3. Viscosities of solutions were now close to original Opadry-200 solution and the effect viscosity difference of polymeric solutions onto the formed films can be neglected after that adjustment. The effect of the weight percentage of the polymer to the viscosity of the final solution was examined and the results are given in Table 4.3.

Table 4.3: Viscosity results of film coating materials (after polymer concentration adjustment of the solution).

Polymeric Solutions	Viscosity Results (mPas)	Concentration (%)
Opadry 200	110	20/80
Solution 1 (HPMC-3 CPS)	115	25/75
Solution 2 (HPMC-5 CPS)	120	20/80
Solution 3 (HPMC-6 CPS)	130	20/80
Solution 4 (HPC)	110	12/88
Solution 5 (PVA)	100	20/80

Afterwards, the viscosity measurements of HPMC-3 CPS, HPMC-5 CPS, HPMC-6 CPS, HPC and PVA polymers at different concentrations were carried out and the viscosity results of these solutions are given in Table 4.4.

Table 4.4: Viscosity results of film coating materials.

	Viscosity (mPas)			
Polymer	6g/80ml	8g/80ml	12g/80ml	20g/80ml
HPMC-3cps	30	55	240	1700
HMPC-5cps	50	110	390	7600
HPMC-6cps	60	115	420	7000
HPC	50	520	2100	25000
PVA	20	35	50	360

According to the results, viscosity value for the hydroxyl propyl cellulose (HPC) polymer was higher than other polymers as increased from 50 mPas to 25000 mPas. The high viscosity values of HPC caused difficulties during the film coating process since it is difficult to spray the highly viscous solutions onto tablets.

4.3. Water Vapor Permeability Results of Film Coatings

4.3.1. Water Vapor Permeability of Filter Papers

The calculation of water vapor transmission through the polymer coated filter paper is given below.

$$WVT = G/tA \quad (4.1)$$

- G = weight change, grains (from the straight line)
- t = time of weight increase
- G/t = slope of the straight line
- A = test area (membrane/air open area in the cup)

Filter paper membrane area which was in contact with air was calculated by considering only the moisture transfer section of the filter paper. Radius of the related section was 0.04 m giving 0.005027 m^2 from Eq.4.2.

$$\text{Area of circular section} = \pi r^2 \quad (4.2)$$

Initially, the water vapor permeability test was performed for only the plain filter paper without swelling in with any film coating solution. Three trials were carried out and the mean values of the weight increase of adsorbed water are given in Figure 4.1.

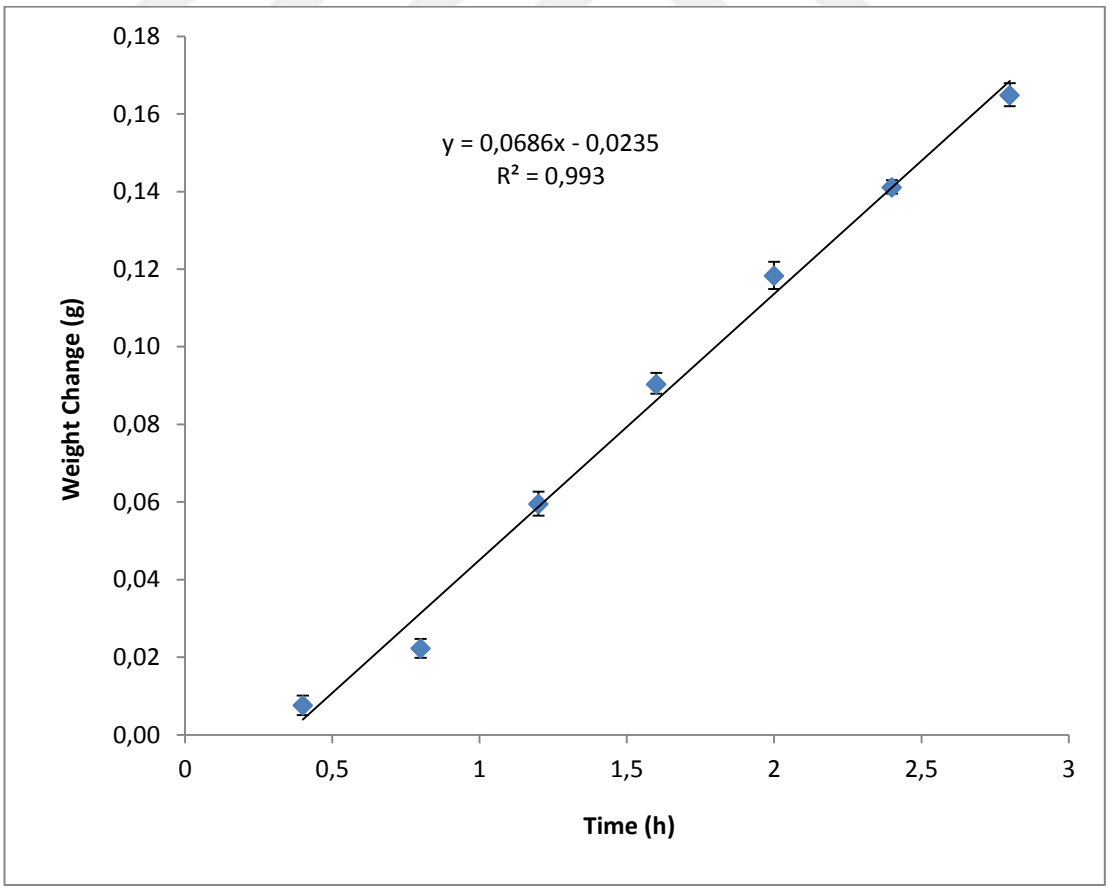

Figure 4.1: Water vapor permeability plot for an uncoated filter paper.

Water vapor permeability result for the uncoated filter paper was calculated according to the slope of the lines and cup mouth area. The average water vapor permeability result for the uncoated filter paper was found to be 13.64 g/m^2h^{-1} as given in Table 4.5.

Table 4.5: Permeability results of filter paper.

Filter Paper Trials	Slope	Permeability (g/m^2h^{-1})
Trial 1	0.0684	13.61
Trial 2	0.0686	13.65
Trial 3	0.0687	13.67
Average		13.64

In order to check the feasibility of our test system for the water vapor permeability tests, another study was performed where we measured the permeability of a sheet which is made up from the polypropylene polymer as a reference. The water vapor permeability of polypropylene sheets was reported to be between 0.4 – 0.8 g/m^2h^{-1} in the literature [Mo Chen, 2014]. Three samples were prepared and tests performed for the PP sheets and the results were given in Figure 4.2.

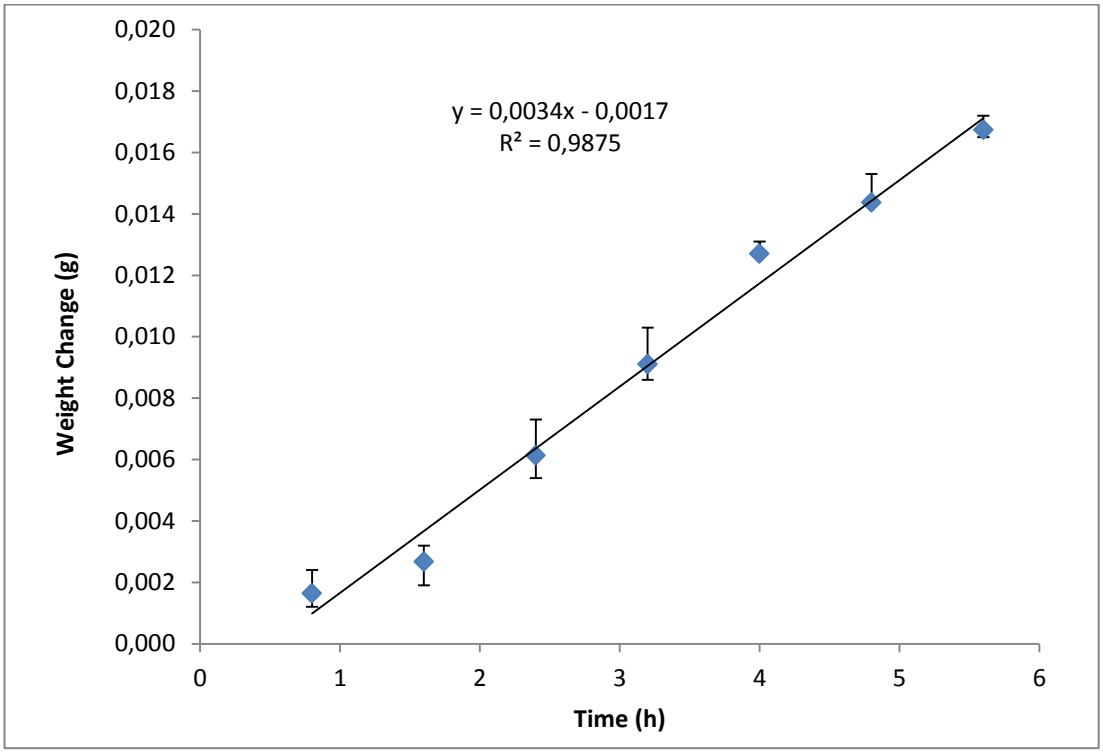

Figure 4.2: Water vapor permeability plot for sheet protector.

The water vapor permeability result for the reference PP sheets was calculated according to the slope of the lines and cup mouth area and given in Table 4.6.

Table 4.6: Permeability results of sheet protector.

Sheet Protector Trials	Slope	Permeability (g/m^2h^{-1})
Trial 1	0.0033	0.66
Trial 2	0.0035	0.70
Trial 3	0.0033	0.66
Average		0.67

For the PP sheet, the average water vapor permeability result was found to be 0.67 g/m^2h^{-1} which is between the 0.4 – 0.8 g/m^2h^{-1} values reported in the literature and demonstrates the success of our water vapor permeability set-up [Mo Chen, 2014]. Afterwards, the permeability tests of the filter papers coated with the original Opadry-200 polymeric solution were performed.

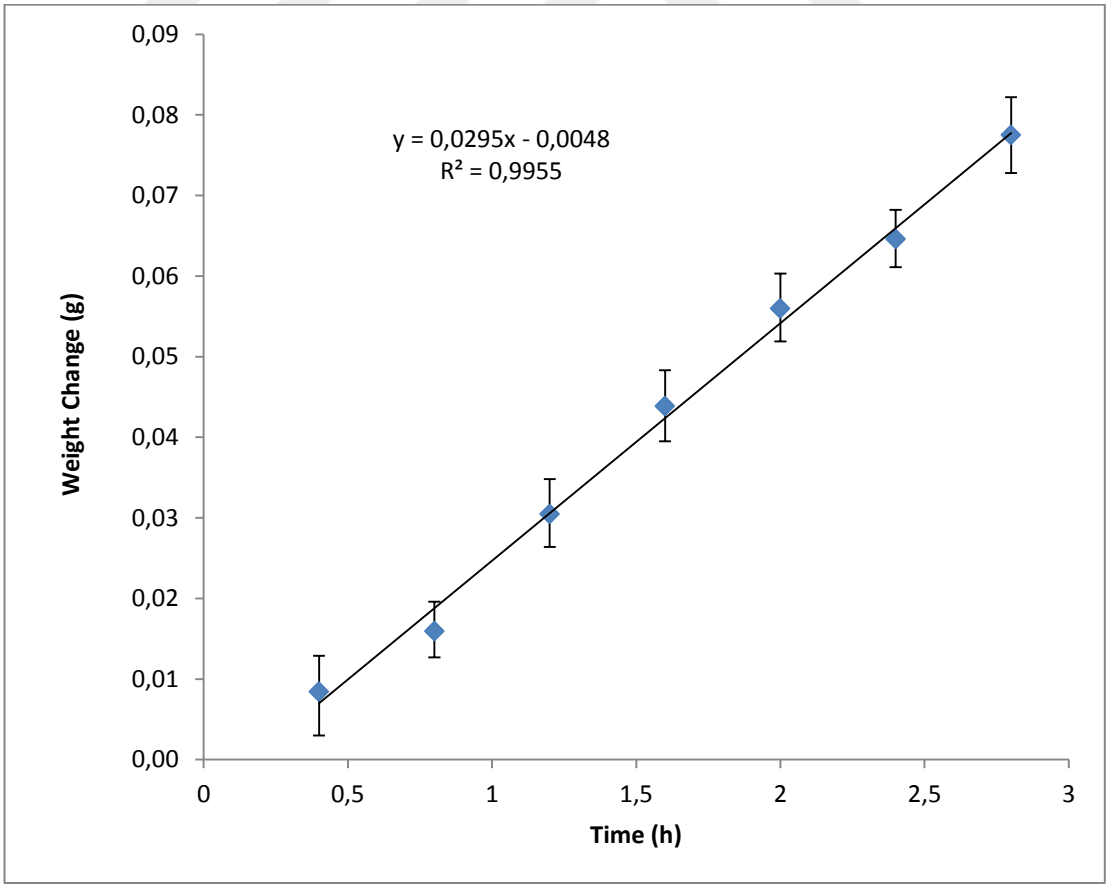

Figure 4.3: Water vapor permeability plot for Opadry-200.

The average water vapor permeability result for the Opadry-200 solution coated filter paper was found to be 5.86 g/m^2h^{-1} as given in Table 4.7.

Table 4.7: Permeability results of Opadry-200.

Opadry-200 Trials	Slope	Permeability (g/m^2h^{-1})
Trial 1	0,0296	5,89
Trial 2	0,0293	5,83
Trial 3	0,0295	5,87
Average		5.86

The average water vapor permeability result was found as 5.86 g/m^2h^{-1} for Opadry-200 coated filter papers. The objective of this study is to achieve similar solution and permeability characteristics to the original Opadry-200 solution. Then the permeability tests were conducted for other film coating solutions after coated onto the filter papers.

Polyvinyl (PVA) alcohol coating solution was used in these tests. As the original Opadry-200 solution contains the PVA polymer as the main ingredient, then the results of the PVA based film coating solution values were expected to be close to the Opadry-200 coating values. Samples of filter papers applied respectively and plots of trials were given in Figure 4.4.

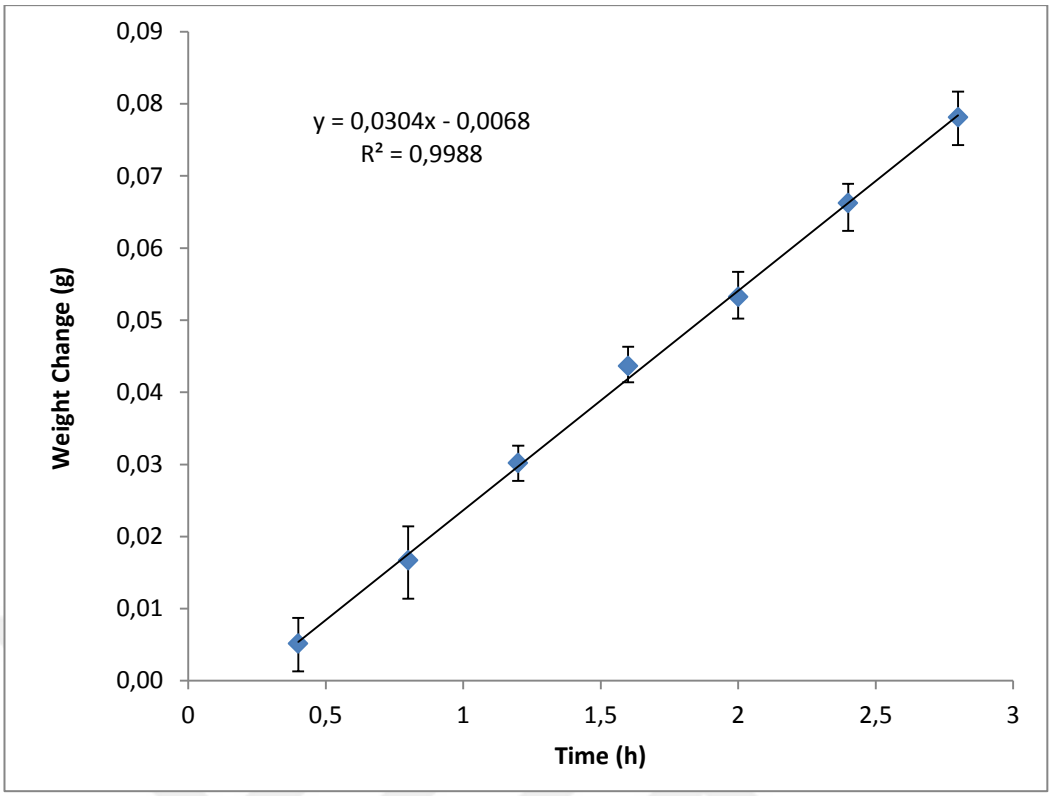

Figure 4.4: Water vapor permeability plot for PVA.

According to the plots, the water vapor permeability results for PVA solution coatings were calculated with the slopes and cup mouth area and given in Table 4.8.

Table 4.8: Permeability results of Polyvinyl Alcohol (PVA).

PVA Trials	Slope	Permeability (g/m^2h^{-1})
Trial 1	0,0307	6,11
Trial 2	0,0304	6,05
Trial 3	0,0302	6,01
Average		6.05

For the polyvinyl alcohol based film coating solution, the average water vapor permeability result was found to be 6.05 g/m^2h^{-1}. This result is very close to the value of Opadry-200 coatings (5.86 g/m^2h^{-1}).

Next trials were conducted for the hydroxyl propyl methyl cellulose based polymeric solutions. HPMC-3 polymer was used for preparing the film coating solution and coated onto the filter papers. Three filter paper tests were used for calculating water vapor permeability and plot was given in Figure 4.5.

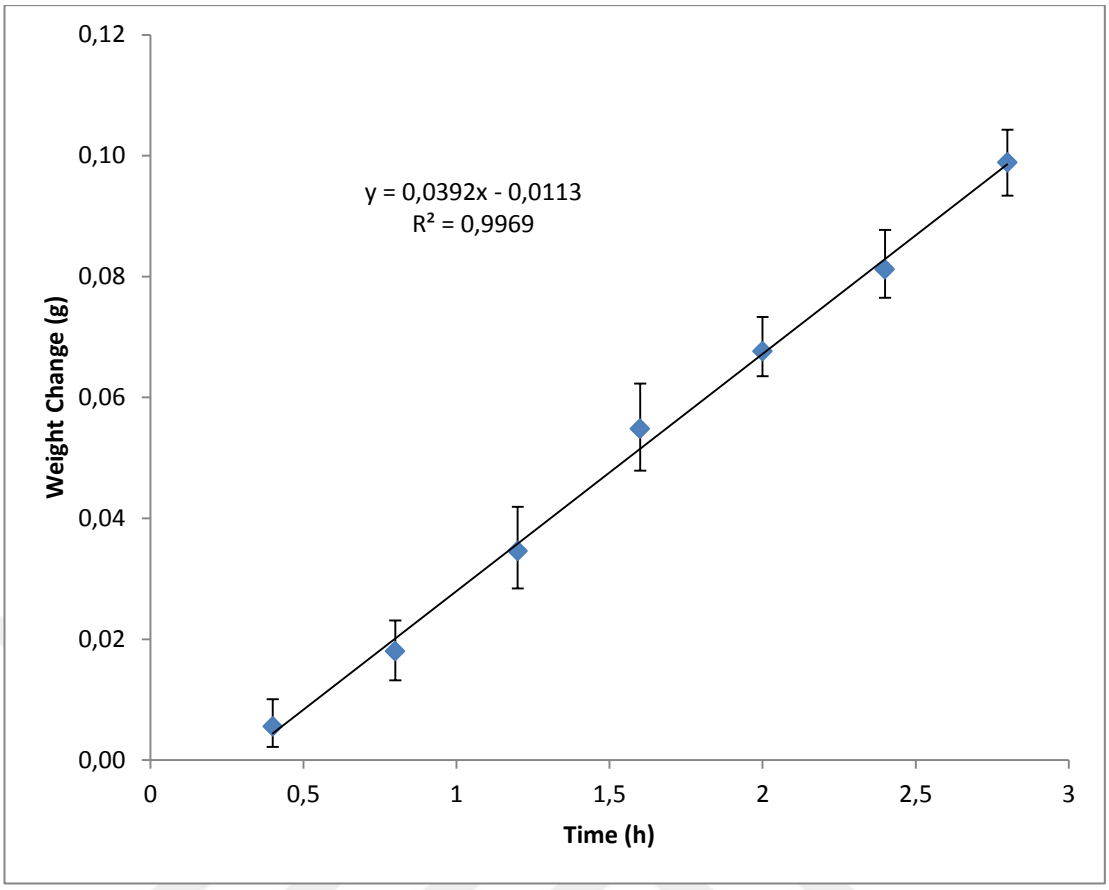

Figure 4.5: Water vapor permeability plot for HPMC-3 cps.

According to the plots, water vapor permeability results for the HPMC-3 coating was calculated with the slope of the lines and cup mouth area and given in Table 4.9.

Table 4.9: Permeability results of HPMC-3 cps.

HPMC-3 cps Trials	Slope	Permeability (g/m^2h^{-1})
Trial 1	0.0389	7.74
Trial 2	0.0396	7.88
Trial 3	0.0393	7.82
Average		7.81

For hydroxyl propyl methyl cellulose 3 cps (HPMC-3 cps) based film coating, the average water vapor permeability result was found to be 7.81 g/m^2h^{-1}. The viscosity values of polymeric film coatings were given in Table 4.3. It was determined that when the viscosity of solutions increased then the permeability

values were also increased. This result indicates that permeability of filter papers which were swollen with the polymeric film coating solutions was proportional with the viscosity of the polymer solutions.

Next trials were conducted for hydroxyl propyl methyl cellulose based polymeric solutions. HPMC-5 polymer was used for preparing the film coating solution and applied on to the filter papers. Three filter paper tests were used for calculating water vapor permeability and plot was given in Figure 4.6.

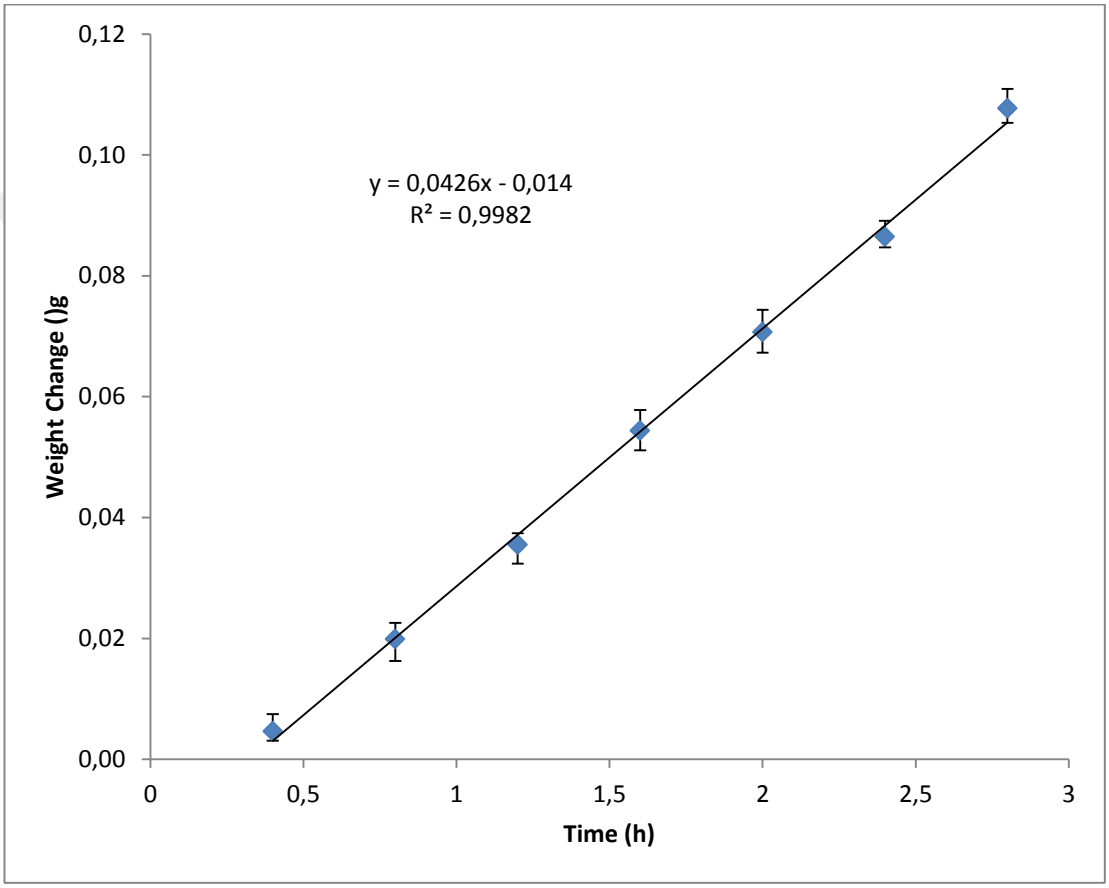

Figure 4.6: Water vapor permeability plot for HPMC-5 cps.

According to the plots, the water vapor permeability results for HPMC-5 coatings were calculated with the slope of the lines and cup mouth area and given in Table 4.10.

Table 4.10: Permeability results of HPMC-5 cps.

HPMC-3 cps Trials	Slope	Permeability (g/m^2h^{-1})
Trial 1	0.0427	8.49
Trial 2	0.0429	8.53
Trial 3	0.0423	8.42
Average		8.48

For HPMC-5 cps based film coating solution, the average water vapor permeability result was found to be 8.48 g/m^2h^{-1}. Permeability value for HPMC-5 is higher than HPMC-3 cps as expected, because viscosity of this solution is higher than original Opadry-200 and HPMC-3 cps solution.

Next trials were conducted using hydroxyl propyl methyl cellulose based polymeric solutions. HPMC-6 polymer was used for preparing the film coating solution and coated onto the filter papers. Three filter paper tests were used for calculating water vapor permeability and plot was given in Figure 4.7.

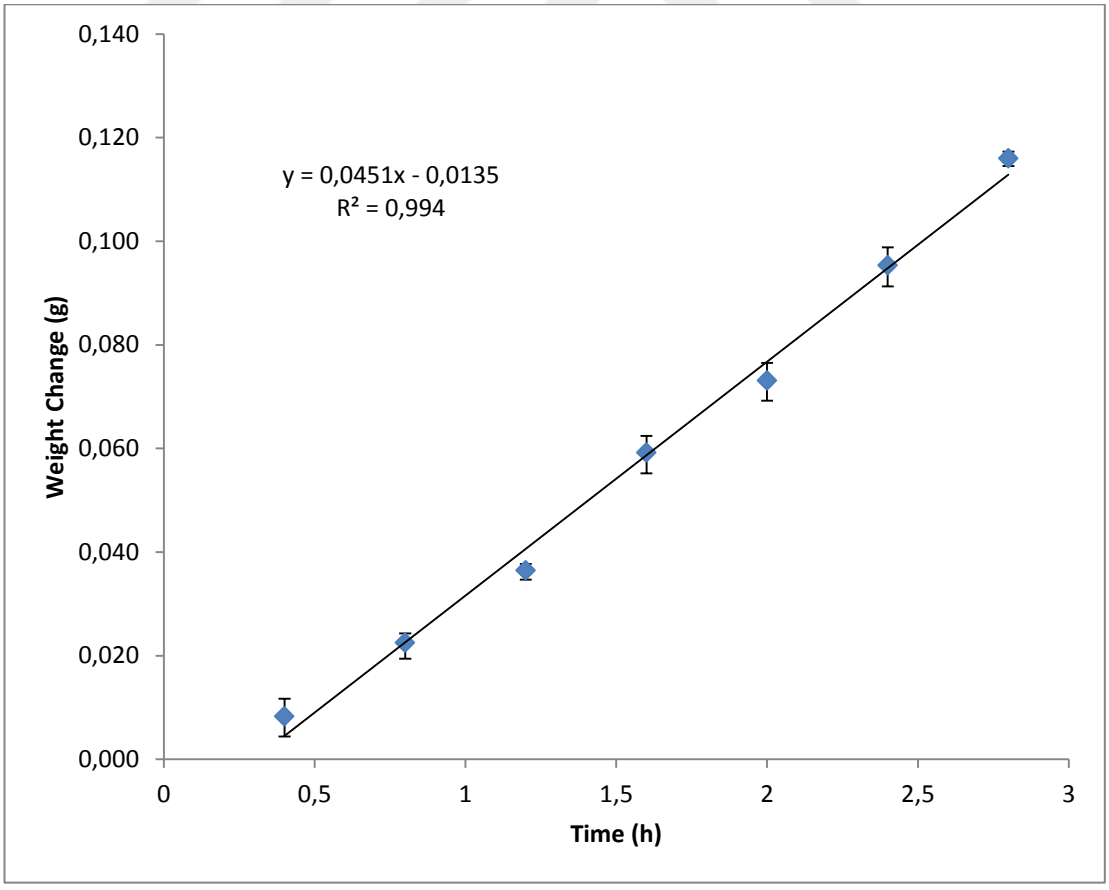

Figure 4.7: Water vapor permeability plot for HPMC-6 cps.

Water vapor permeability results for HPMC-6 calculated according to the slope of the lines and cup mouth area and given in Table 4.11.

Table 4.11: Permeability results of HPMC-6 cps.

HPMC-3 cps Trials	Slope	Permeability (g/m^2h^{-1})
Trial 1	0.0449	8.93
Trial 2	0.0454	9.03
Trial 3	0.0451	8.97
Average		8.98

Average water vapor permeability result was found to be 8.98 g/m^2h^{-1} for the HPMC-6 cps based film coating solution. This result was the highest value in all permeability trials except the uncoated filter paper. Viscosity of the polymer solution and type of the polymer directly affect the permeability characteristics of the coated filter paper and it can be said that HPMC-6 was the most permeable film coating solution in this study.

Afterwards, trials were conducted for hydroxyl propyl cellulose based polymeric solutions. HPC was used as polymer and film coating solutions were prepared. Three filter paper tests were used to calculate the water vapor permeability as given in Figure 4.8.

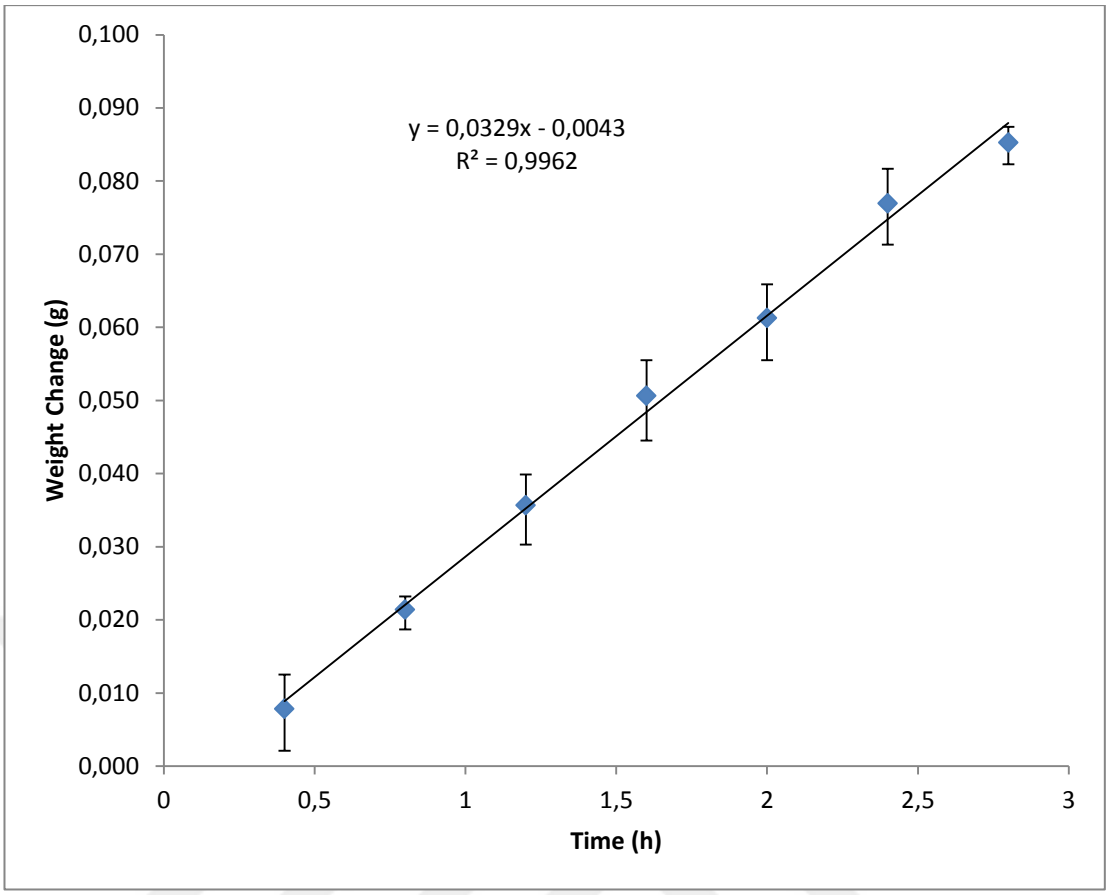

Figure 4.8: Water vapor permeability plot for HPC.

Water vapor permeability results for HPC calculated according to the slope of the lines and cup mouth area and given in Table 4.12.

Table 4.12: Permeability Results of HPC.

HPMC-3 cps Trials	Slope	Permeability (g/m^2h^{-1})
Trial 1	0.0329	6.55
Trial 2	0.0328	6.53
Trial 3	0.0331	6.59
Average		6.55

Average water vapor permeability result was found as 6.55 g/m^2h^{-1} for hydroxyl propyl cellulose based film coating solution. After polyvinyl alcohol based solution permeability results, these results were the closer values to original Opadry-200 solution. Viscosity value of the HPC solution was adjusted to 110 mPas and related situation directly affect the permeability results of filter papers.

All the average results of permeability values for the polymer coated filter papers were given in Figure 4.9.

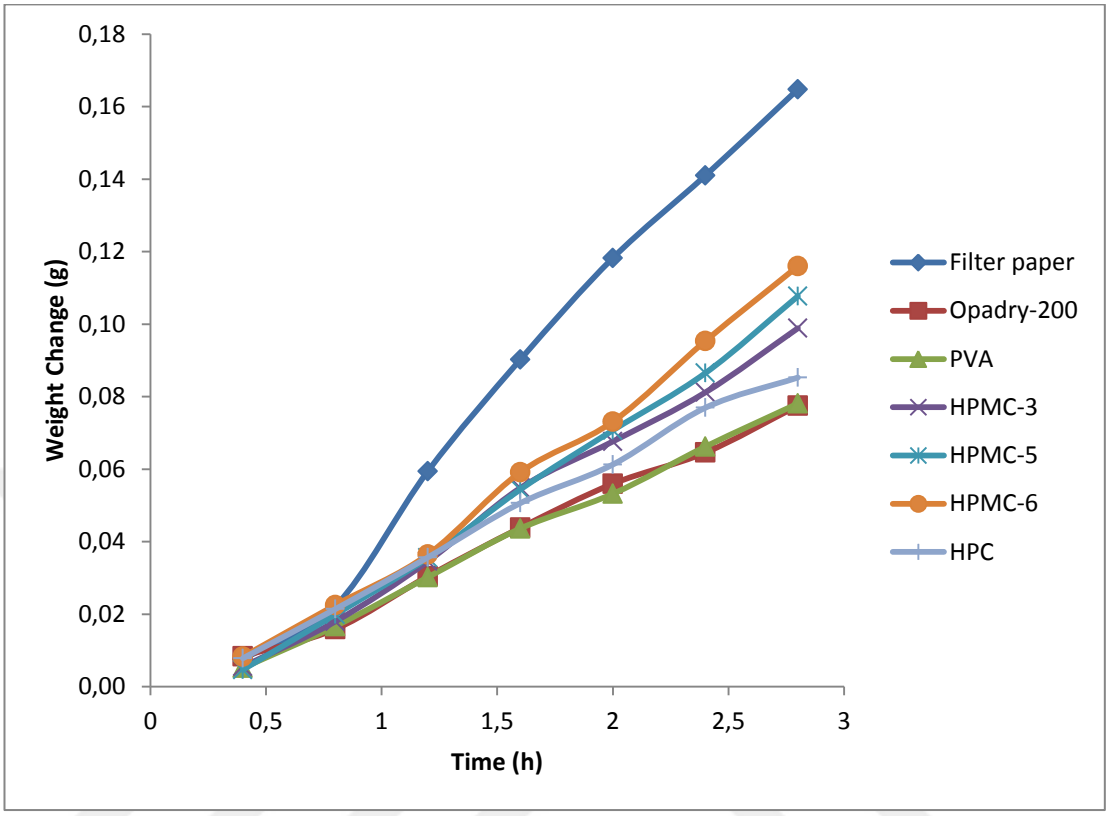

Figure 4.9: Water vapor permeability results for polymer coated filter papers.

According to the Figure 4.9, the original solution Opadry-200 has the smallest slope similar to the PVA based film coating solution. Solution viscosities were the key parameters in the permeability results. The higher the solution viscosity, the larger permeability values were obtained. The viscosities of polymeric solutions varied between 110-130 mPas as shown in Table 4.3. After permeability studies were performed; it was determined that viscosity and permeability results were proportional to each other.

4.3.2. Water Vapor Permeability of Film Coated Tablets

In order to measure of water vapor permeability of polymer film coated tablets, 5 film coated tablets were used in each trial. Film coating of these tablets were performed using different polymer film coating solutions. Original Opadry-200, PVA, HPMC-3, HPMC-5, HPMC-6 and HPC were used as the polymers of these solutions. 5 film coated tablets were dried in 105^{o}C in an oven then kept in a

desiccator for 5 minutes and the first average weight of film coated tablets were measured. Then these tablets were kept at 23-25^{o}C and 65 % relative humidity conditions in a closed desiccator. The weight of the film coated tablets were measured till the weights remain constant value (around 1-1.5 hours).

The total surface area of a standard tablet was calculated as given in section 3.2.8 and found to be 0.000155 m^2. The slope of the straight line given on the graphs was used for the calculation of water vapor transmission through film coated tablets which was performed according to the formula 4.1 and results were given below. Slope of the straight line (G\t) over film coated tablet area (A) gave the permeability results.

Initially, Opadry-200 polymeric solution coated tablets were used as the original (reference) film coating solution of the multivitamin tablets. The plot of the Opadry-200 coated tablets was given in Figure 4.10.

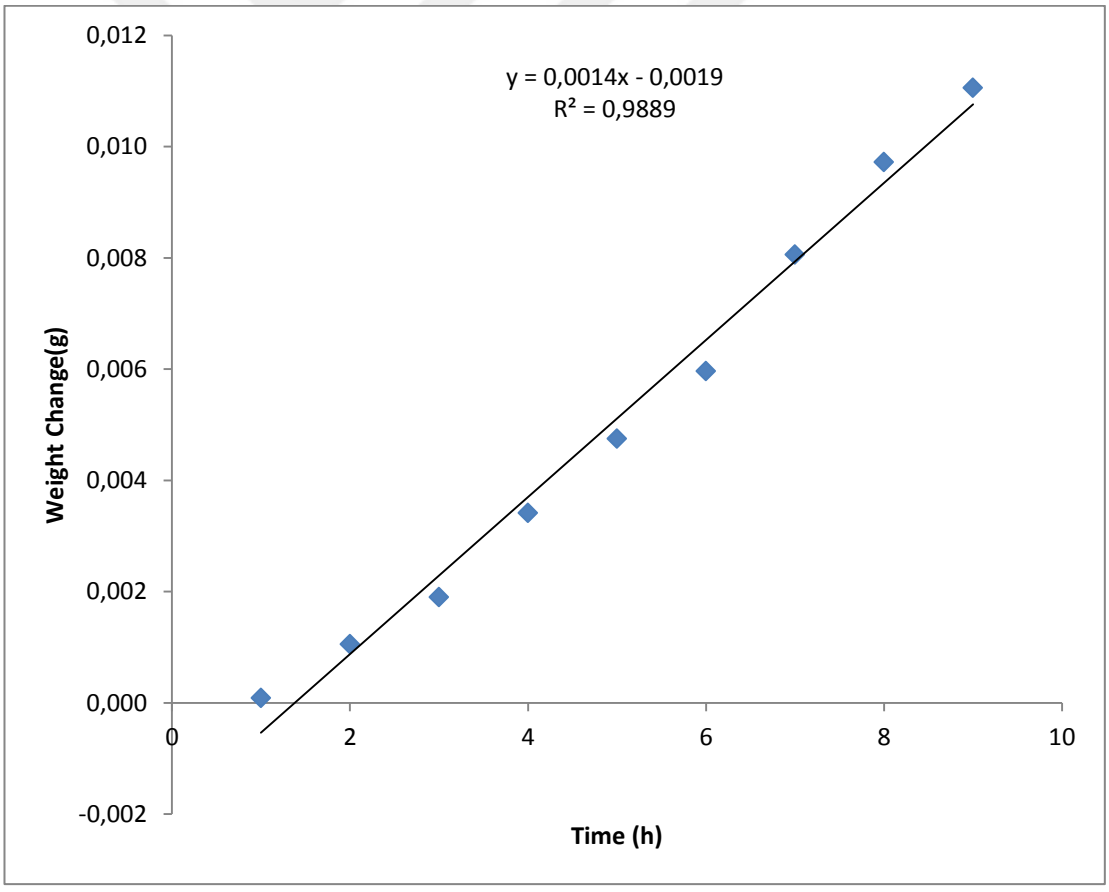

Figure 4.10: Water vapor permeability plot for Opadry-200 coated tablets.

The slope of the line was calculated to be 0.0014 g/h. When this value was divided to the surface area of the tablets, it gives the result of water vapor transmission through the Opadry-200 film coated tablets to be 9.03 g/m^2h^{-1}.

Then polyvinyl alcohol (PVA) based film coating solution was used for the film coating of tablets. The plot of the PVA coated tablets was given in Figure 4.11.

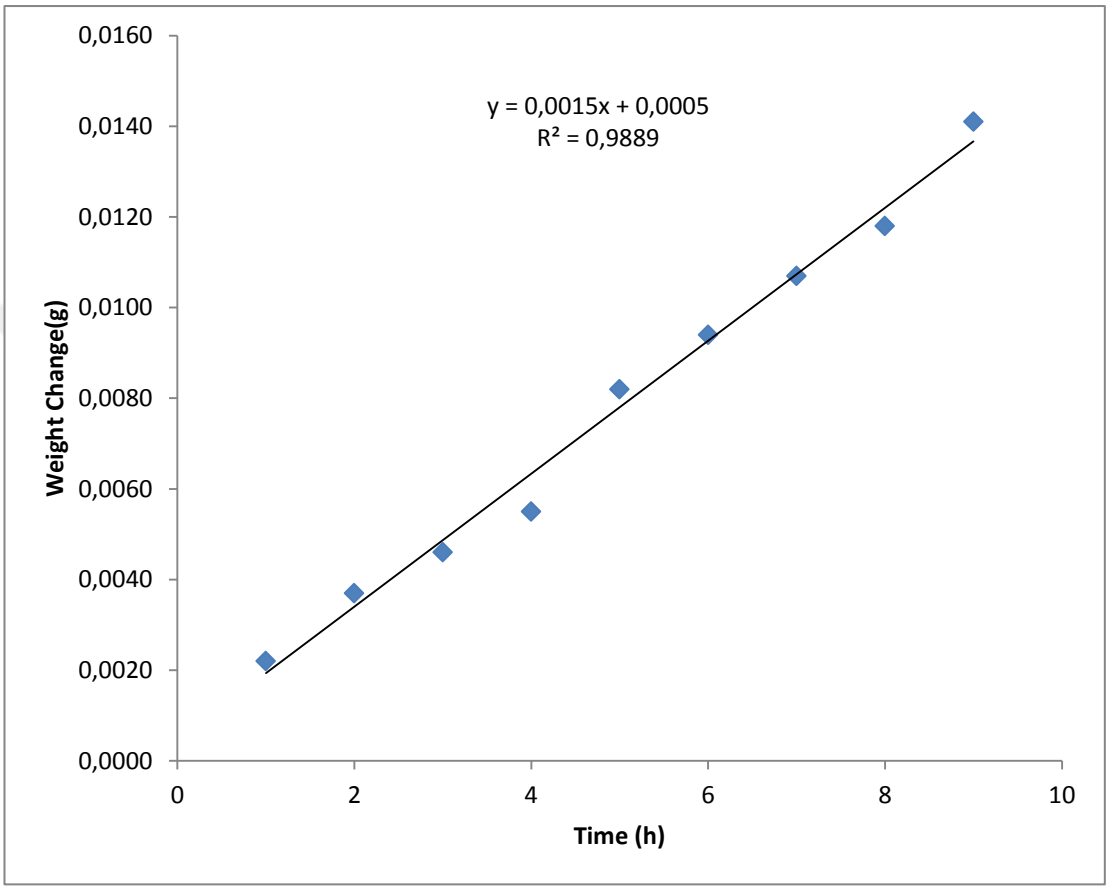

Figure 4.11: Water vapor permeability plot for PVA coated tablets.

The slope of the line was calculated to be 0.0015 g/h. When this value was divided to the surface area of the tablets, it gives the result of water vapor transmission through PVA film coated tablets to be 9.68 g/m^2h^{-1}.

Between Figures 4.12 – 4.14 plots of the hydroxy propyl methly cellulose (HPMC) 3, 5 and 6 cps based film coating solutions used for tablets were given.

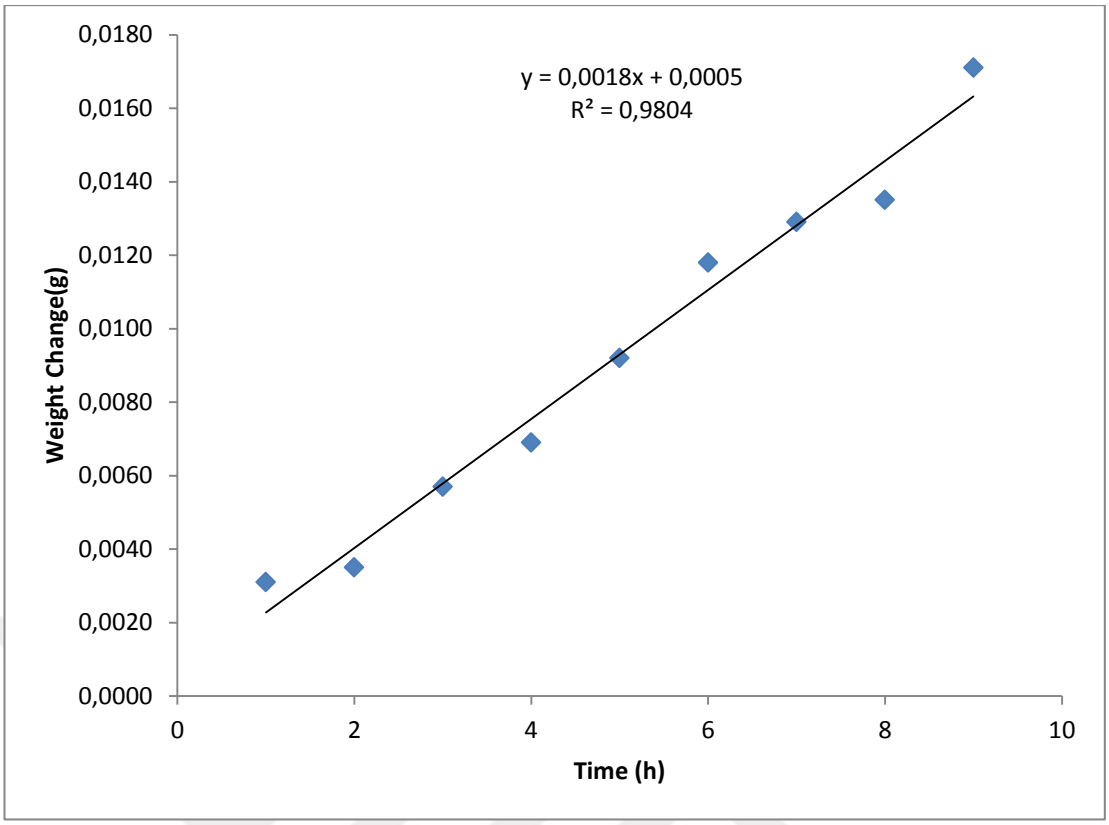

Figure 4.12: Water vapor permeability plot for HPMC-3 cps coated tablets.

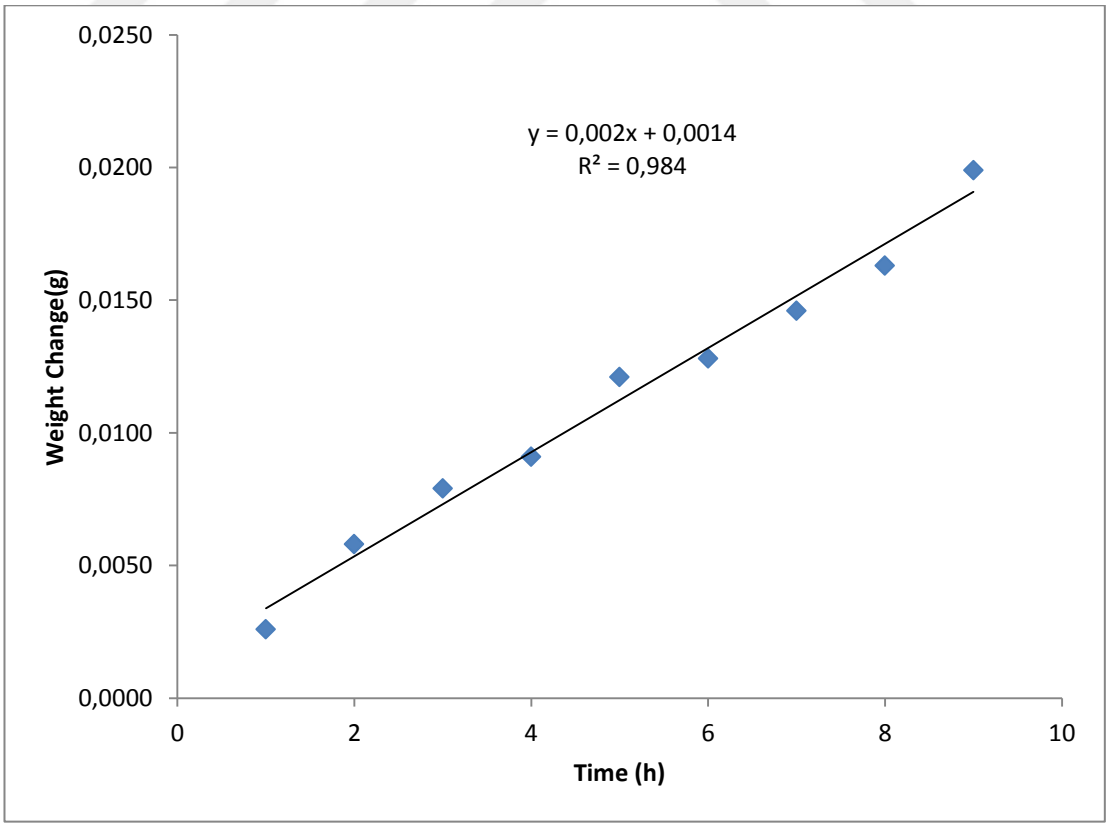

Figure 4.13: Water vapor permeability plot for HPMC-5 cps coated tablets.

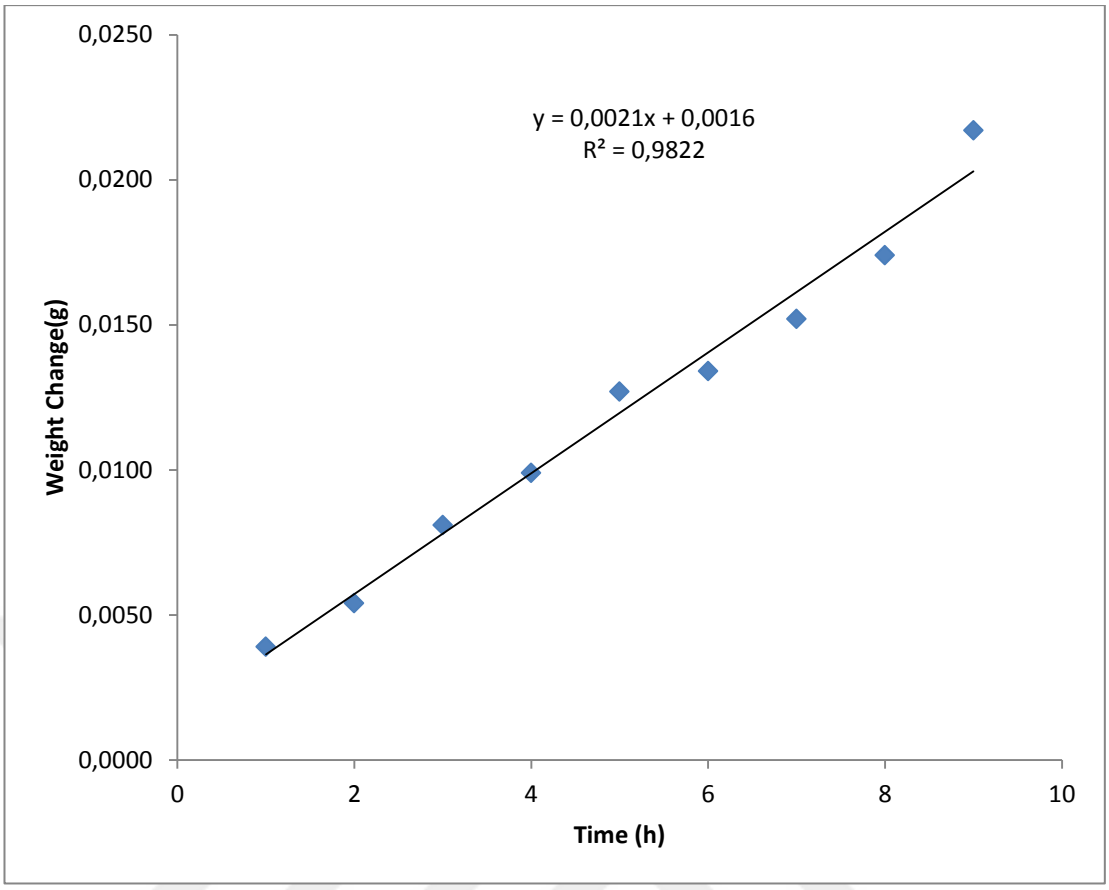

Figure 4.14: Water vapor permeability plot for HPMC-6 cps coated tablets.

For HPMC-3 cps coated tablets slope of the line was calculated as 0.0018 g/h, for HPMC-5 cps slope was 0.0020 g/h and for HPMC-6 cps calculated as 0.0021 g/h. Surface area of the tablets was 0.000155 m^2. According to these values, the permeability result for HPMC-3 cps was calculated as 11.61 g/m^2h^{-1}, for HPMC-5 cps 12.90 g/m^2h^{-1} and for HPMC-6 cps 13.55 g/m^2h^{-1} respectively. According to these results it was seen that when the viscosity of the solution increased, then the water vapor permeability results also increased proportionally.

Next trial was performed for the hydroxyl propyl cellulose (HPC) based film coated multivitamin tablets as seen in Figure 4.15.

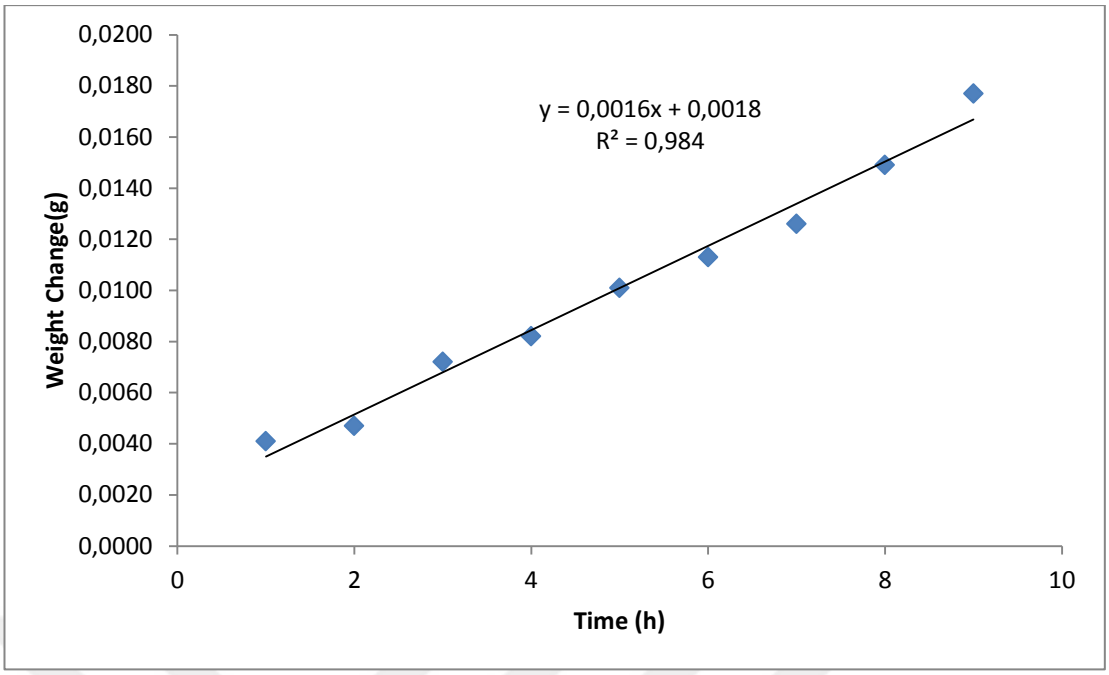

Figure 4.15: Water vapor permeability plot for HPC cps coated tablets.

Slope of the line was calculated to be 0.0016 g/h, when this value was divided to the surface area of the tablets, it gives the result of water vapor transmission through HPC film coated tablets to be 9.03 g/m^2h^{-1}.This result is closer to original Opadry-200 solution results when compared with the hydroxyl propyl methyl cellulose (HPMC) result. The average results of film coated tablet permeability results were given in Figure 4.16.

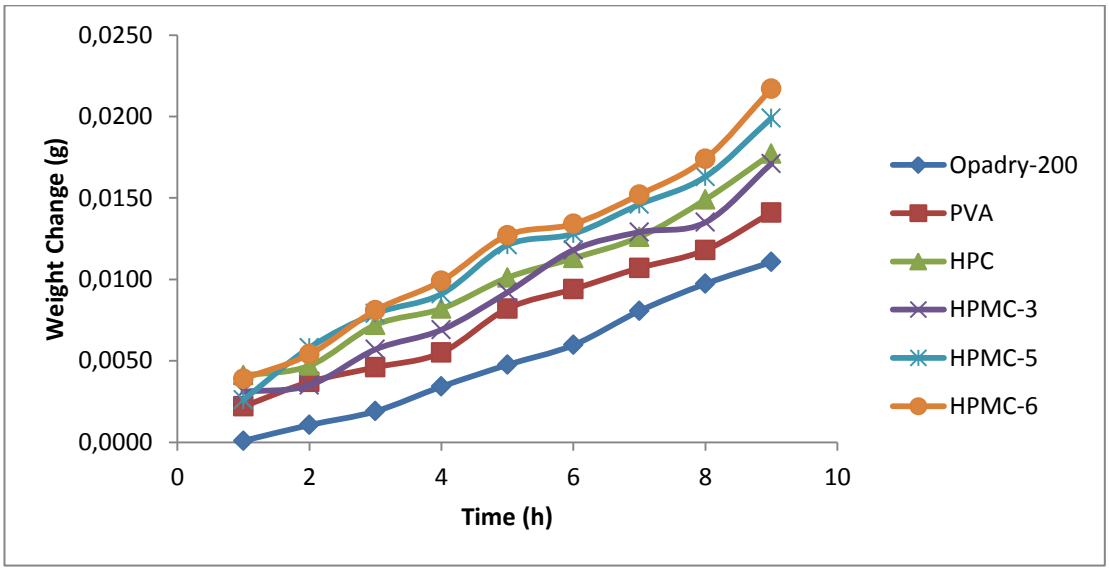

Figure 4.16: Water vapor permeability results for tablet used trials.

4.4. Moisture Content Results of Film Coated Tablets

The moisture contents of the film coated tablets were determined with a Karl-Fischer titration equipment. Film coated tablets were transformed into powder form in mortars and 0.5 g of tablet powder was used in all studies. Opadry-200, PVA, HPMC-3 cps, HPMC-5 cps, HPMC-6 cps and HPC used film coated tablets were examined initially after kept in 105^{o}C chamber for 1 hour. After that, the moisture content (% of water inside the film coated tablet) of multivitamin tablets were determined for 6, 24 and 48 hours and results were given in Table 4.13.

Table 4.13: Moisture Content of Film Coated Tablets.

Time (h)	Opadry-200	PVA	HPC	HPMC-3cps	HPMC-5 cps	HPMC-6 cps
0	0.40	0.45	0.40	0.40	0.40	0.45
6	2.82	2.93	3.14	3.35	3.42	3.57
24	4.16	4.25	4.38	4.49	4.55	4.62
48	5.13	5.20	5.31	5.39	5.48	5.56

According to the results, the water percentage in the tablets increases up to 6 % in 48 hours. Maximum limit of this value in tablet specifications in the literature was given to be 6 % and it can be said that our results were consistent with literature values. HPMC-6 cps used film coating has the largest value as 5.56 % after 48 hours and smallest value was 5.13 % with Opadry-200 coating.

In order to compare the analytical results; firstly the viscosity of polymeric solutions versus the water vapor permeability of filter papers was plotted as given in Figure 4.17.

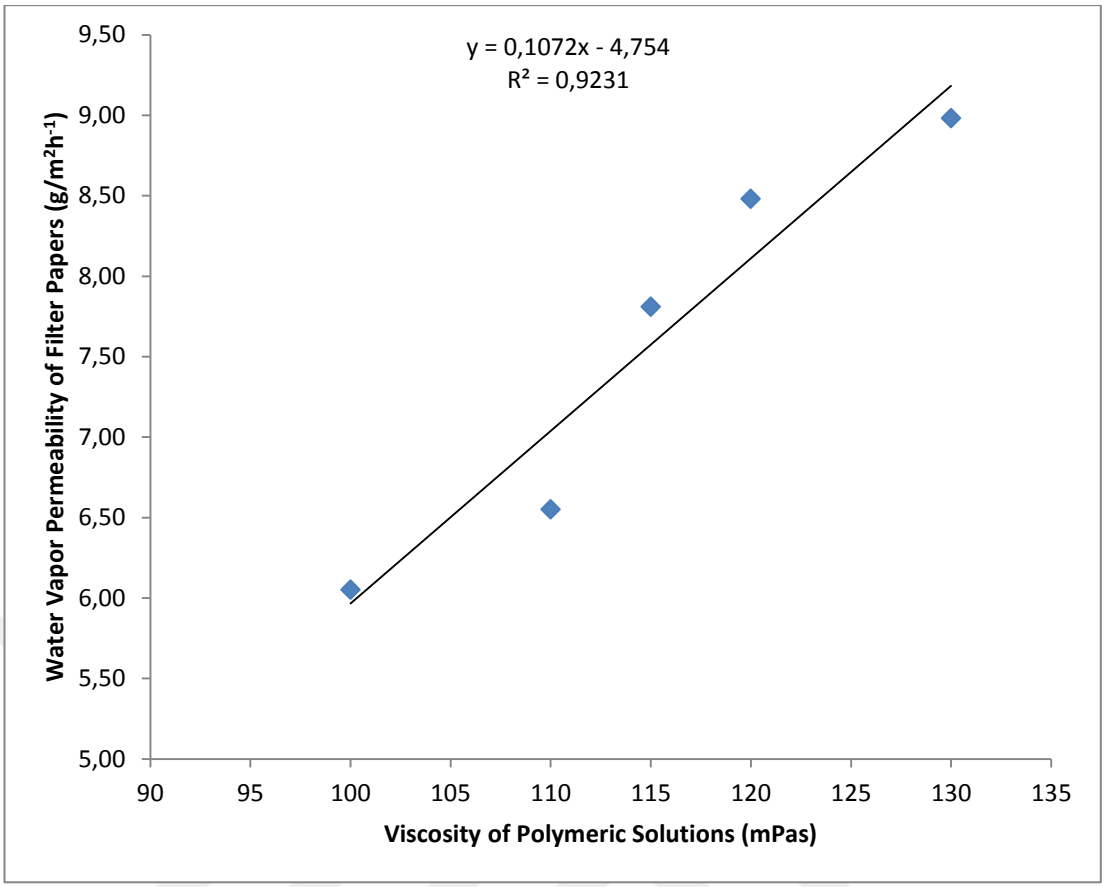

Figure 4.17: Viscosity of polymeric solutions versus water vapor permeability of filter papers.

It was seen that when the viscosity of the coating solutions was increased, then the permeability values of filter papers and film coated tablets were also increased. It was concluded that the viscosity of the polymeric solution is an important parameter, since this parameter directly affects the performance of the film coating. High viscosity solutions could not be sprayed from the nozzle to the uncoated tablets and elapsed time will be extended. Additionally, water vapor permeability indicates the resistance of film coating to the moisture. Water vapor permeability values demonstrates the stability and performance of the film coating.

In Figure 4.18, the plot of water vapor permeability of filter papers versus film coated tablets was given.

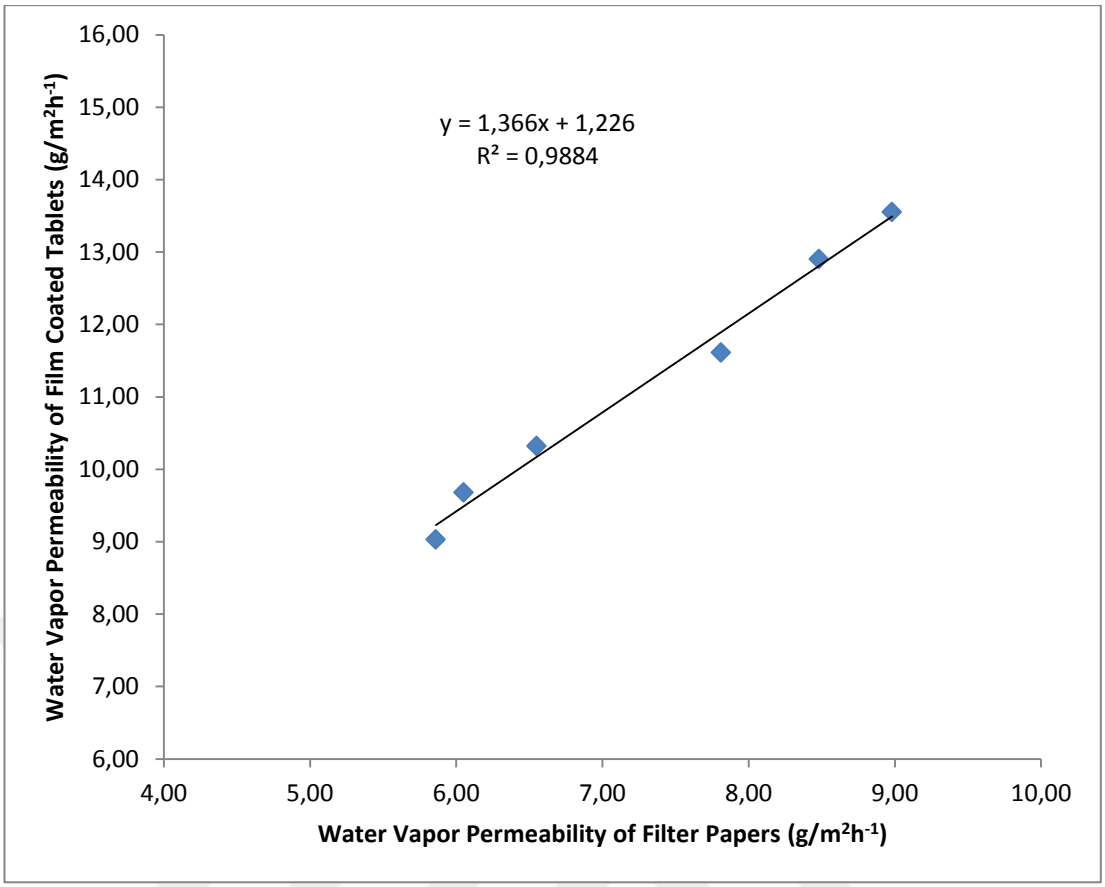

Figure 4.18: Water vapor permeability of filter papers and film coated tablets.

According to the Figure 4.18, a linear relation can be seen between the water vapor permeability results of filter papers and the film coated tablets as expected. When the main polymer of film coating solution was changed, the water vapor permeability value of related solution was also changed proportionally. The minimum permeable solution was found to be Opadry-200 and the highest permeable polymeric solution was HPMC-6 cps respectively.

Similar relation between water vapor permeability and moisture content of film coated tablets can be seen in Figure 4.19.

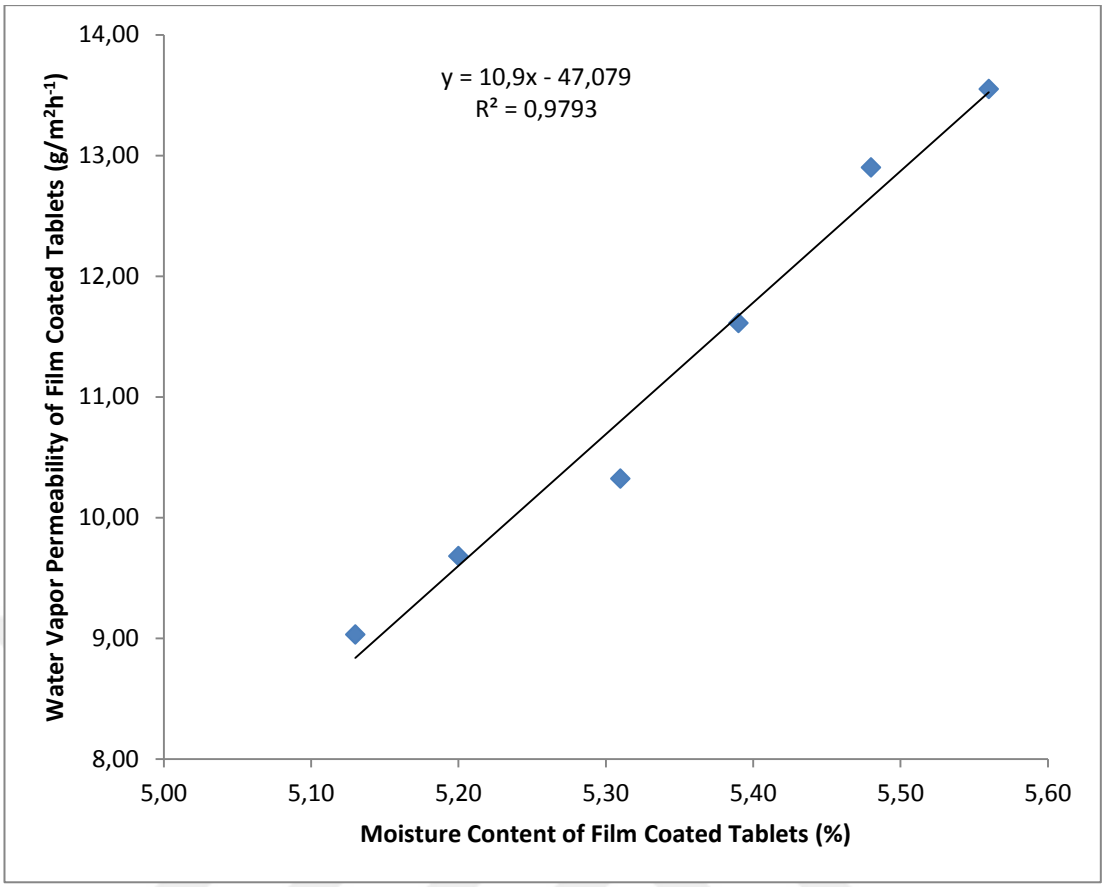

Figure 4.19: Water vapor permeability versus moisture content of film coated tablets.

There is a linear relation between moisture content and water vapor permeability of film coated tablets as seen in Fig. 4.19 indicating that when the water vapor permeability of film coated tablets increases, the moisture content of the tablets also increases.

4.5. Weight and Length Measurement Results of Film Coated Tablets

The weights and lengths of the film coated multivitamin tablets were measured in order to compare the thickness of the coatings. 10 tablets were used for each study and average weights and lengths were reported. Automatic balance equipment Mettler Toledo ML model was used for weight measurements. An electronic compass was used for length measurements. In Table 4.14 weight of the film coated tablets were given.

Table 4.14: Weight of the film coated tablets.

Tablet	Opadry-200	PVA	HPC	HPMC-3cps	HPMC-5 cps	HPMC-6 cps
1	188.4	190.9	191.2	193.4	188.2	191.2
2	189.3	191.4	188.3	192.7	193.1	191.7
3	191.2	188.7	191.2	190.0	188.9	189.4
4	191.6	189.5	190.7	188.3	190.4	188.1
5	188.7	190.1	191.2	191.3	191.4	188.0
6	192.5	192.7	189.8	189.8	189.7	190.7
7	191.5	191.5	191.6	192.0	193.4	192.5
8	189.4	188.3	190.1	191.5	188.3	188.9
9	189.9	192.5	192.5	192.6	189.0	189.3
10	191.2	191.8	191.9	191.7	191.5	192.8
Average	190.4	190.7	190.9	191.3	190.4	190.3

Average weights of the uncoated tablets were 180 ± 5 % mg, and after coating operation, average film coated tablets must be 189 ± 5 % mg. In each trial, the weight range for the film coated multivitamin tablet were between 179.6 – 198.5 mg. Over or below of these values are not accepted according to the specification limits of the drug. Average result of the Opadry-200 was found 190.4, PVA was found 190.7, HPC was found 190.9, HPMC-3 Cps was found 191.3, HPMC-5 Cps was found 190.4 and HPMC-6 Cps was found 190.3 respectively. All average weight results were found to be within limits.

Afterwards the length measurements for film coated tablets were performed. The length range should be between 3.80 – 4.00 mm according to the specification of the multivitamin tablets. The results of the length measurements can be seen in Table 4.15. Again all results fits well with the specifications given in the literature.

Table 4.15: Length of the film coated tablets.

Tablet	Opadry-200	PVA	HPC	HPMC-3cps	HPMC-5 cps	HPMC-6 cps
1	3.91	3.92	3.93	3.94	3.89	3.94
2	3.94	3.91	3.88	3.90	3.91	3.94
3	3.88	3.89	3.87	3.89	3.92	3.87
4	3.92	3.88	3.90	3.92	3.88	3.88
5	3.91	3.94	3.88	3.88	3.89	3.89
6	3.92	3.87	3.88	3.91	3.87	3.90
7	3.89	3.89	3.91	3.90	3.94	3.91
8	3.88	3.92	3.90	3.87	3.89	3.87
9	3.92	3.91	3.92	3.89	3.87	3.88
10	3.89	3.88	3.87	3.93	3.88	3.89
Average	3.91	3.90	3.89	3.90	3.89	3.90

4.6. Solubility Results of Film Coated Tablets

The dissolved amount of riboflavine and folic acid vitamins was determined with the solubility analysis. The weighed tablets were placed into glass bechers and were dissolved in water. After 1 hour, the samples were collected into vials and these vials entered to HPLC equipment in order to measure the dissolved amount of the vitamins. Solubility tests were performed for 6 different film coated tablets. The averages of the results was given as % dissolved riboflavine and % dissolved folic acid in Table 4.16.

Table 4.16: Dissolution results of multivitamin film coated tablets.

Film Coating Material	Riboflavine Dissolution %	Folic Acid Dissolution %
Opadry-200	96.7	95.8
PVA	94.9	95.0
HPC	95.2	95.3
HPMC-3	95.1	94.7
HPMC-5	94.1	94.3
HPMC-6	94.3	94.5

Solubility results of the film coated tablets shows the amount of dissolved active pharmaceutical ingredient inside equipment vessel. In here, the equipment vessel simulates the human body, which active ingredient of multivitamin tablet (riboflavin and folic acid) will be dissolved. According to the specification of film coated multivitamin tablets, the limit of dissolution defined to be not less than % 80. The results of dissolution analysis for riboflavine and folic acid showed the conformity to the specification of the drug.

5. CONCLUSION

The objective of this thesis study is to maintain the stability of multivitamin tablets against moisture by applying some novel polymeric coatings onto the tablets. The original coating solution of multivitamin tablets was the Opadry-200 solution, which contains PVA as the main polymer. The content of the multivitamin tablets was not changed during the experiments and the amounts of riboflavin and folic acid inside the tablets were remained same. In order to observe the performance of film coating materials, six different film coating polymers such as hydroxyl propyl cellulose (HPC), hydroxyl propyl methylcellulose (HPMC) and polyvinyl alcohol (PVA) were applied onto the multivitamin tablets. Only the main polymer was changed in the film coating solutions and other ingredients such as magnesium silicate, titanium dioxide, polyethylene glycol, methacrylic acid copolymer, quinoline yellow and sodium bicarbonate were kept constant in all studies.

All the moisture content (% water) results of film coating ingredients were found to be below 5.0%, and the highest value was found for quinolone yellow (4.24%) and the lowest for macrogol/PEG (0.21%). The viscosities of polymeric coating solutions were found to be close to each other for the same solid contents. For example, the viscosity of the original Opadry-200 solution was found to be 110 mPas and HPMC-6 cps solution was found to be 130 mPas respectively. Other film coating solutions viscosity values were found between these values.

Water vapor permeability tests were performed through the polymer coated filter paper samples. Water vapor permeability result for the uncoated filter paper was found to be 13.64 g/m^2h^{-1} and for the reference PP sheet, 0.67 g/m^2h^{-1} similar to literature reports. Afterwards, the permeability tests of the filter papers coated with the polymeric solutions were performed and the results were found between 5.86 g/m^2h^{-1} to 8.98 g/m^2h^{-1} respectively. Later, the water gain of the film coated tablets were measured. The total surface area of a standard tablet was calculated to be 0.000155 m^2. The water vapor permeability results of the film coated tablets were found to be between 9.03 g/m^2h^{-1} to 13.55 g/m^2h^{-1} respectively. It was determined that the water vapor permeability results of the film coated tablets increased proportionally with the water vapor transmission results through the coated filter paper.

Afterwards, the moisture contents of film coated tablets were determined with a Karl-Fischer titration equipment. The water contents of the tablets coated with HPMC-6 has the largest value as 5.56 % and smallest value was obtained as 5.13 % with Opadry-200 coating in 48 hours test time. The maximum limit of this value in the tablet specifications was given as 6 % so our results are below this limit.

The weights and lengths of the film coated multivitamin tablets were measured in order to calculate and compare the thickness of the coatings. 10 tablets were used for each study and the average weights and lengths were reported. Average weight result of the Opadry-200 was found 190.4 mg, and other coatings varied between 190.3 and 191.3 mg. Average length result of the Opadry-200 was found 3.91 mm, and other coatings varied between 3.89-390 mm. Lastly, solubility analysis of the active ingredients in the film coated multivitamin tablets were performed. The dissolved amount of active pharmaceutical ingredients; riboflavin and folic acid were measured in this test. The highest riboflavine and folic acid dissolution results were reached with Opadry-200 as 96.7 % and 95.8 % respectively. According to the specification of film coated multivitamin tablets, the limit of dissolution should be not less than % 80 and we achieved larger dissolution of active ingredients than the specification.

According to this thesis study, PVA was found to be the most suitable polymer to coat onto multivitamin tablets because of the lowest water vapor permeability of this polymer film. In addition, PVA is the cheapest one among these film coating polymers. The second most successful polymer was found to be the HPC polymer which has low permeability and viscosity; however the disadvantage of HPC is its high viscosity in normal concentrations, which directly affect the film coating operation.

For the future work, different drug tablets can be investigated besides multivitamin tablets. Different aqueous polymeric film coating polymers can be investigated other than PVA, HPC and HPMC. Additionally analysed properties of film coating solutions and film coated tablets can be increased.

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BIOGRAPHY

I was born in Lüleburgaz, Kırklareli in 2nd of June, 1984. My bachelor's degree in İzmir Institute of Technology, Department of Chemical Engineering, was completed in 2009. My master degree in Graduate School of Natural and Applied Sciences, Department of Chemical Engineering in Gebze Technical University completed in 2016. I started working in a pharmaceutical company, Zentiva Health Products in 2010 as an Analytical Method Development Specialist and still working in the same company as an Quality Assurance Specialist as of 2014. My foreign language is English, and I'm married with one child.