BOLU ABANT IZZET BAYSAL UNIVERSITY

THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

UV SPECTROPHOTOMETRIC STUDIES ON DRUG REMOVAL BY*P*-ALKYL/ALKOXY SUBSTITUTED BIS- CARBAMATE GELS

MASTER OF SCIENCE

MAHMUT KEPÜR

BOLU, AUGUST 2019

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APPROVAL OF THE THESIS

UV SPECTROPHOTOMETRIC STUDIES ON DRUG REMOVAL BY P-ALKYL/ALKOXY SUBSTITUTED BIS-CARBAMATE GELS submitted by **MAHMUT KEPÜR** and defended before the below named jury in partial fulfillment of the requirements for the degree of **Master of Science** in **Department of Chemistry, The Graduate School of Natural and Applied Sciences of Bolu Abant Izzet Baysal University in 21.08.2019** by

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Director of Graduate School of Natural and Applied Sciences

To my family

DECLARATION

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Mahmut KEPÜR

ABSTRACT

UV SPECTROPHOTOMETRIC STUDIES ON DRUG REMOVAL BY *P*-ALKYL/ALKOXY SUBSTITUTED BIS- CARBAMATE GELS
MSC THESIS
MAHMUT KEPÜR
BOLU ABANT IZZET BAYSAL UNIVERSITY GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
DEPARTMENT OF CHEMISTRY
(SUPERVISOR:ASSOC. PROF. DR. ÖZNUR DEMIR ORDU)

BOLU, AUGUST 2019

Low molecular weight organogelators are a family of organic molecules capable of gelling organic solvents. Organogelators form a three-dimensional network through non-covalent interactions such as hydrogen bonding, van der Waals interaction, π-π stacking or dipole-dipole interaction.

In recent years, significant progress has been made in the design of new gelling agents. Gels of low molecular weight organic compounds have important applications as new organic soft materials. Examples of these areas are drug delivery, cosmetics, sensor systems, phase selective cleaners. Especially phase selective organogelators are of great interest in water treatment and oil spill removal. These organogelators are preferred because they are cheaper and simpler than the methods currently used.

In the pharmaceutical sector, gels are used especially in relation to the delivery of drugs. For this purpose, various methods and models have been developed and their application areas have been examined.

In this study, *p*-alkyl/alkoxyl substituted bis-carbamate derivatives were synthesized to utilize their organogels for drug removal properties. Dry (xerogels) and wet gels were used for this purpose and their drug removal abilities were followed by UV spectroscopy. As a result, it was found that *p*-hexyloxy derivative with three methylene spacer was the best having a capacity for the removal of dexketoprofen trometamol.

KEYWORDS: Drug removal, low molecular weight organogelators, organogels, bis-carbamates, dexketoprofen trometamol

ÖZET

UV SPECTROPHOTOMETRIC STUDIES ON DRUG REMOVAL BY *P*-ALKYL/ALKOXY SUBSTITUTED BIS- CARBAMATE GELS
YÜKSEK LISANS TEZI
MAHMUTKEPÜR
BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ
FEN BİLİMLERİ ENSTİTÜSÜ
KIMYA ANABILIM DALI
(TEZ DANIŞMANI:DOÇ. DR. ÖZNUR DEMIR-ORDU)

BOLU, AĞUSTOS - 2019

Düşük molekül ağırlıklı organojelleştiriciler, düşük derişimlerde organic çözücüleri jelleştirebilen organik moleküllerin bir ailesidir. Organojelleştiriciler hidrojen bağı, van Der Waals etkileşimi, π-π istifleme veya dipol-dipol etkileşimi gibi kovalent olmayan etkileşimler yoluyla üç boyutlu bir ağ oluştururlar.

Son yıllarda, yeni jelleştirici ajanların tasarımında önemli ilerlemeler kaydedilmiştir. Düşük molekül ağırlıklı organik bileşiklerin jelleri, yeni organik yumuşak malzemeler olarak önemli uygulamalara sahiptir. Bu alanların örnekleri ilaç taşınımı, kozmetik, sensör sistemleri, faz seçici temizleyicilerdir. Özellikle faz seçici organojelleştiricilersu arıtma ve petrol sızıntısı temizlemede büyük ilgi çekmiştir. Bu organojelleştiriciler, günümüzde kullanılan yöntemlerden daha ucuz ve daha basit oldukları için tercih edilir.

İlaç sektöründe özellikle ilaçların taşınması ile alakalı olarak jeller kullanılmaktadır. Bu amaçla çeşitli metod ve modeller geliştirilmiş ve uygulama alanları incelenmiştir. Bu çalışmada, *p*-alkil/alkoksi sübstitüye biskarbamat türevleri, organojellerinin ilaç uzaklaştırma özelliklerinden yararlanmak üzere sentezlenmiştir. Bu amaçla kuru ve yaş jeller kullanılmış ve ilaç uzaklaştırma özellikleri UV spektroskopisi ile izlenmiştir. Sonuç olarak üç metilen zincirli *p*-hekziloksi türevinin, deksketoprofen trometamolü iyi kapasite ile uzaklaştırdığı bulunmuştur.

ANAHTAR KELİMELER:İlaç uzaklaştırma, düşük molekül ağırlıklı organogelators, organogels, bis-karbamatlar, deksketoprofen trometamol.

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LIST OF ABBREVIATIONS ANDSYMBOLS

3D	**:**Three dimensional
CAB	**:** 3-β-cholesteryl-4-(2-anthryloxy)butanoate
$CDCl_3$	**:**Deuterated chloroform
DNA	**:** Deoxyribonucleic acid
DSC	**:** Differential scanning calorimetry
E-L	**:** Ethyl Laurate
FT-IR	**:** Fourier Transform Infrared Spectroscopy
Hz	**:** Hertz
IPM	**:** Isopropyl myristate
LMOGs	**:** Low molecular-mass organic gelators
mgc	**:** Minimum gelation concentration
NBP	**:** n-Butyl Palmitate
NMR	**:** Nuclear magnetic resonance
p	**:** Para
PBA	**:** Phenylboronic acid
RT	**:**Room temperature
SEM	**:** Scanning electron microscope
TEM	**:**Transmission electron microscopy
USP	**:** The United State Pharmacopoeia
UV-Visible	**:** Ultraviolet–Visible spectroscopy
cps	**:** cycles per second
CW	**:**continuous-wave
MS	**:**mass spectroscopy
NSAID	**:**non-steroidal anti-inflammatory drug

ACKNOWLEDGEMENTS

The author wishes to express his deepest gratitude to his supervisor Assoc.Prof.Dr. Öznur DEMİR-ORDU for their guidance, advice, criticism, encouragements and insight throughout the research.

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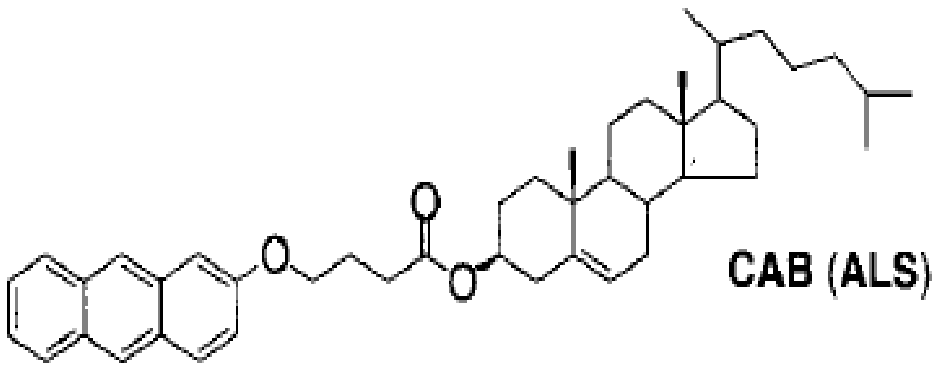
1. INTRODUCTION

1.1 Development of low molecular weight organogelators

Many low-molecular-weight organic molecule structureshaving molecular weight≤3000 have beenproved to be organogelators (LMOG, Low Molecular Weight Organogelators)that can cause gel formation indifferent organic solvents with low concentrations (≤5 wt %). These molecules form a three dimensional network structure by intermolecular forces like hydrogen bonding, dipole-dipole, van der Waals interactions etc. During its formation the solvent molecules are entrapped into this network and gel formation occurs.

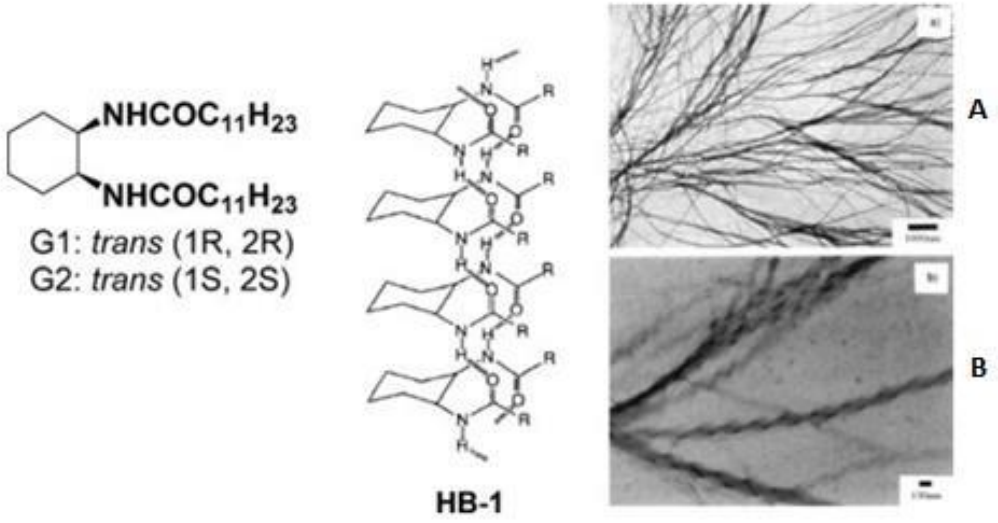
In 1987, Y. C. Lin and his coworker realized for the first time that low concentrations (generally<2 wt %) of 3-β-cholesteryl-4-(2-anthryloxy) butanoate (CAB, Scheme 1.1) produced a gelly material in organic liquids.



Scheme1.1. The structure of CAB (3-β-cholesteryl-4-(2-anthryloxy) butanoate) (Y. C. Lin et al., 1987).

After the first observation of gel formation by low molecular weight organogelators, many organic molecules with different functional groups have been found to form gel structures either by accident or by rational design. For example, in 1996 Hanabusa et al. found a few interesting gelling agents based on amide

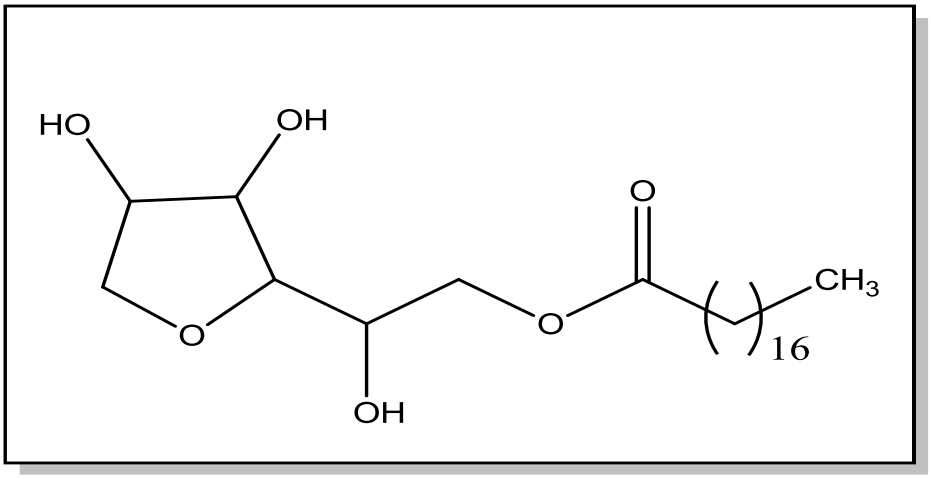
functionalities. They synthesizedbis-amide molecules starting with the chiral diamine molecules (trans-1,2-cyclohexyldiamine) (Scheme 1.2, G1 and G2 derivatives) and realized the formation of gel structure in organic solvents. They showed that gel structure was established by intermolecular H-bonding between amide groups and hydrophobic interactions between long alkyl chains.



Scheme 1.2. Amide based gelators (G1 and G2) and their H-bonding group HB-1 and TEM images of G1-acetonitrile gel (1 mM G1), magnification: (A) 7000; (B) 30000 (Dastidar et al., 2008).

In 1997, P. Terech and his coworker published a review including different types of molecules like fatty acid, anthryl group containing, aminoacid and steroid typemolecules of LMOGsand the properties of gels formed by them. They expected that there will be a dramatical increase in the interest towards the design of organogel forming structures in the future.

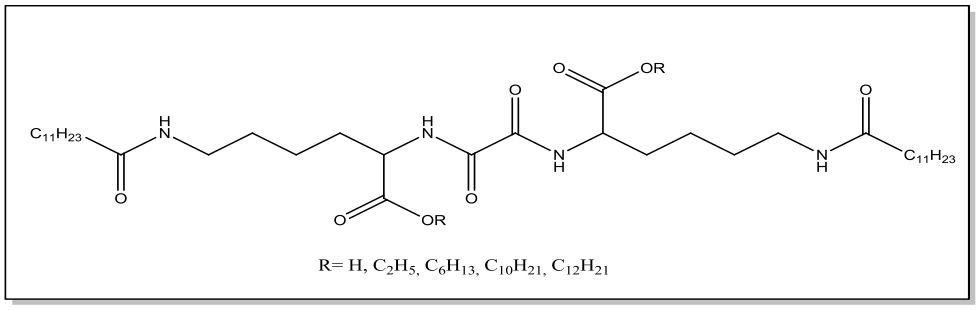
S. Murdan and his coworkers synthesized sorbitan monostearate molecule (Scheme 1.3) as a gelatorin 1999. They obtained opaque, semi-solid and thermally reversible gel structure in solvents like hexadecane isopropyl mistrat and corn oil. They reported their usage for the purpose of the application in drug (antigen) delivery systems.



Scheme 1.3. The structure of sorbitan monostearate (Murdan, 1999).

Tomioka and his coworkers (2001) studied self-assembly into microscopic aggregates through specific hydrogen bonding and Van der Waals interactions of synthesized didodecanoylamides and α, *ω*-alkylidenediamines. They reported that these interactions were responsible for the gel formation of organic solvents andthe diamine group chain length was effective on the gel formation.

Suzuki and his coworkers examined a new type of Gemini organogelatorsin 2003. Thisstructure connected by an oxalyl amide (Scheme 1.4) was synthesized easily, effectively, and cheaply. They also found that the compounds are good at organogelation.Their cyclohexane gels showed superior thermal stabilities. Their proved the presence of hydrogen bonding in gel formation by NMR and FT-IR spectroscopy.



Scheme 1.4. Chemical structure of series of oxalyl amide derivatives (Suzuki et al., 2003).

Brosse and his coworkers (2004) obtained a new family of aminoacid-type organogelators through an easy and inexpensive way. They presented that structural changes on the side-chains of the aminoacid derivatives permitted to modulate the gelation properties. In this study, the organogelators with the inclusion of a benzyl or an isopropyl group were found to enable gelation of nonpolar solvents at very low concentration (<2wt %) and the formation of thermostable gels.

Leroux and his coworkersin 2005 synthesized compounds based on L-alanine and they observed their ability of gelation in herbal oils that are mostly used in pharmaceutical industry and drug delivery systems.

Lu and his coworkers in 2006 synthesized benzoic acid hydrazine-based novel organogelators. They examined the interactions taking place in gel formation by usingUV-Visible, IR and 3D-gel structure by SEM analysis to explain the formation of the structures.

Smith and his coworkers (2007) synthesized new low molecular mass organic gelators (LMOGs) containing carbamate and urea groups to examine gelation in organic solvents like toluene and cyclohexane. They used SEM analysis for understanding thefibrous structure of these organogels. Moreover, they studied the gelation abilities in vegetable oils like olive oil, sunflower oil and esters (isopropyl myristate, ethyl laurate, isopropyl palmitate) used in pharmaceutical industry and reported the possibility of their usage in controlled drug releasing systems.

Chow and his coworkers (2007) synthesized the molecules with 3.5-diaminebenzoate linked esters containing α- or β-aminoacid and aromatic groups and examined gel properties in aromatic solvents. They examined the gelation mechanism by infrared spectroscopy and circular dichroism spectroscopy, revealing both H-bonding and π–π aromatic stacking interactions which are the main driving forces for gelation.They also observed thatthe additional aromatic rings in the Cbz-andaromatic-containing ester units significantly boosted the gelation abilities.

Sanders and his coworker (2007) synthesized chiral *N,N'*dimethylnapthalinediimide based aminoacid derivatives and examined their gelation abilities in organic solvents.In their study, they observed creativing helix

structure in nonpolar solvents formed by hydrogen bonding and concluded that the chirality of the helix structure is governed by the aminoacid functionality.

In 2008 Lim and his coworkers obtained gelation ofterpenes in propylene glycol and dibutyllauroylglutamide. They examined physicochemical properties of the terpene gels and used them in drug carrier systems and displayed the gelation of these terpenes as shown in Figure 1.1.

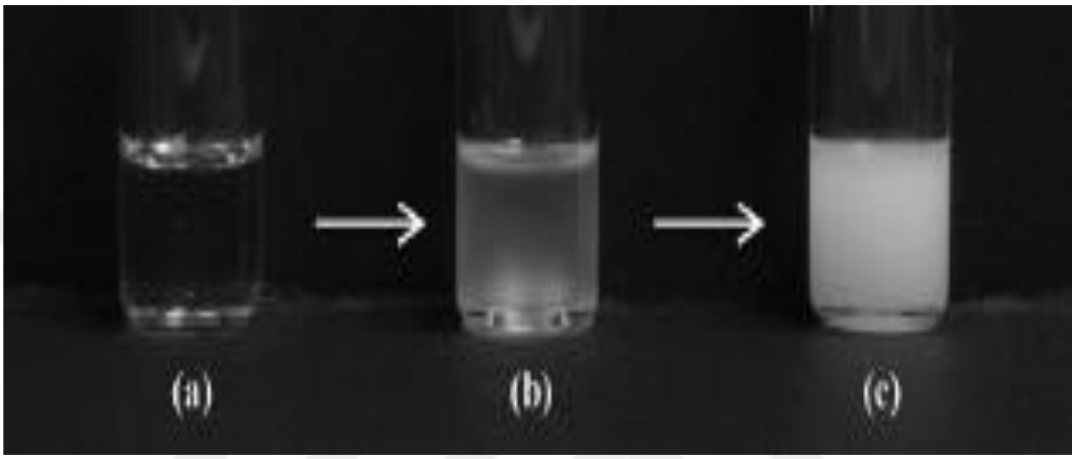
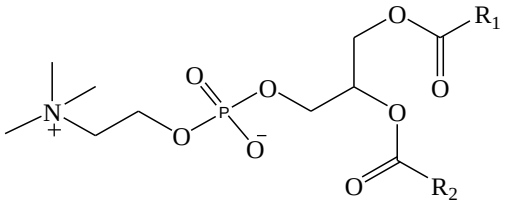
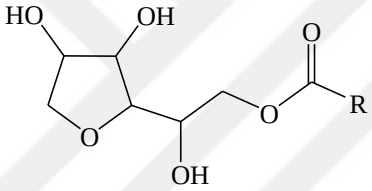
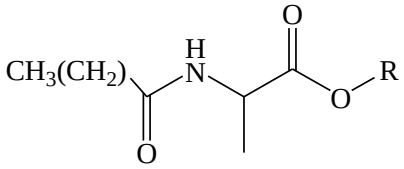
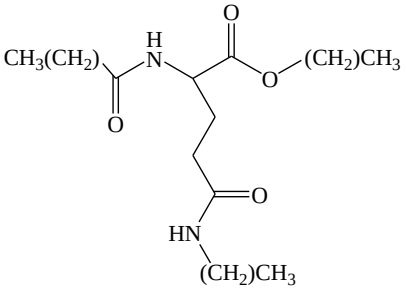


Figure 1.1. Gelation process (a) after heating clear solution; (b) uniform, cloudy suspension upon cooling and standing; (c) white gel upon further standing (Lim et al., 2008).

Leroux and Vintiloiu in 2008 published an article about the use of different types of organogelling molecules as drug delivery systems shown in Table 1.1

Luo and his coworkers (2009) studied on low molecular weight organogelators (LMOGs) based on monochain derivatives of ethylenediamine (Figure 1.2). They synthesized derivatives of succinic acid and gelled them in organic solvents such as benzene, toluene, *o*-xylene, carbontetrachloride and isopropyl alcohol. They used SEM analysis in order to examined the gel network structure in nonvolatile toluene and carbontetrachloride and FT-IR spectroscopy to prove the presence of H bonding (Figure 1.2).

Table1.1. Drug delivery systems using organogels (Leroux et al., 2008).

Organogelators	Aplication Area	Applied Drugs
 R_1 ve R_2 = Fatty Acids [Linoleic acid(55%) and Palmitic Acid (13%)] Lesitin	Skin and Body Application	Diclofenac Piroxicam Tetrabenzamidine Scopolamine and boxaterol Propranolol Nicardipine Aceclofenac İndomethanic and diclofenac
 R = $(CH_2)_{16}CH_3$ or $(CH_2)_{10}CH_3$ Sorbitan monosterit or molauret	Nose Mouth Subcutaneous İntramuscular	Propranolol Cyclosporin A
 R = CH_3 or CH_2CH_3 *N*-steroil-1-alanin methyl or ethyl ester	Subcutaneous	Rivastigmine Leuprolide
 *N*-lauril-1-glutamic acid di-n-butilamide	Application to the body use skin path	Haloperidol

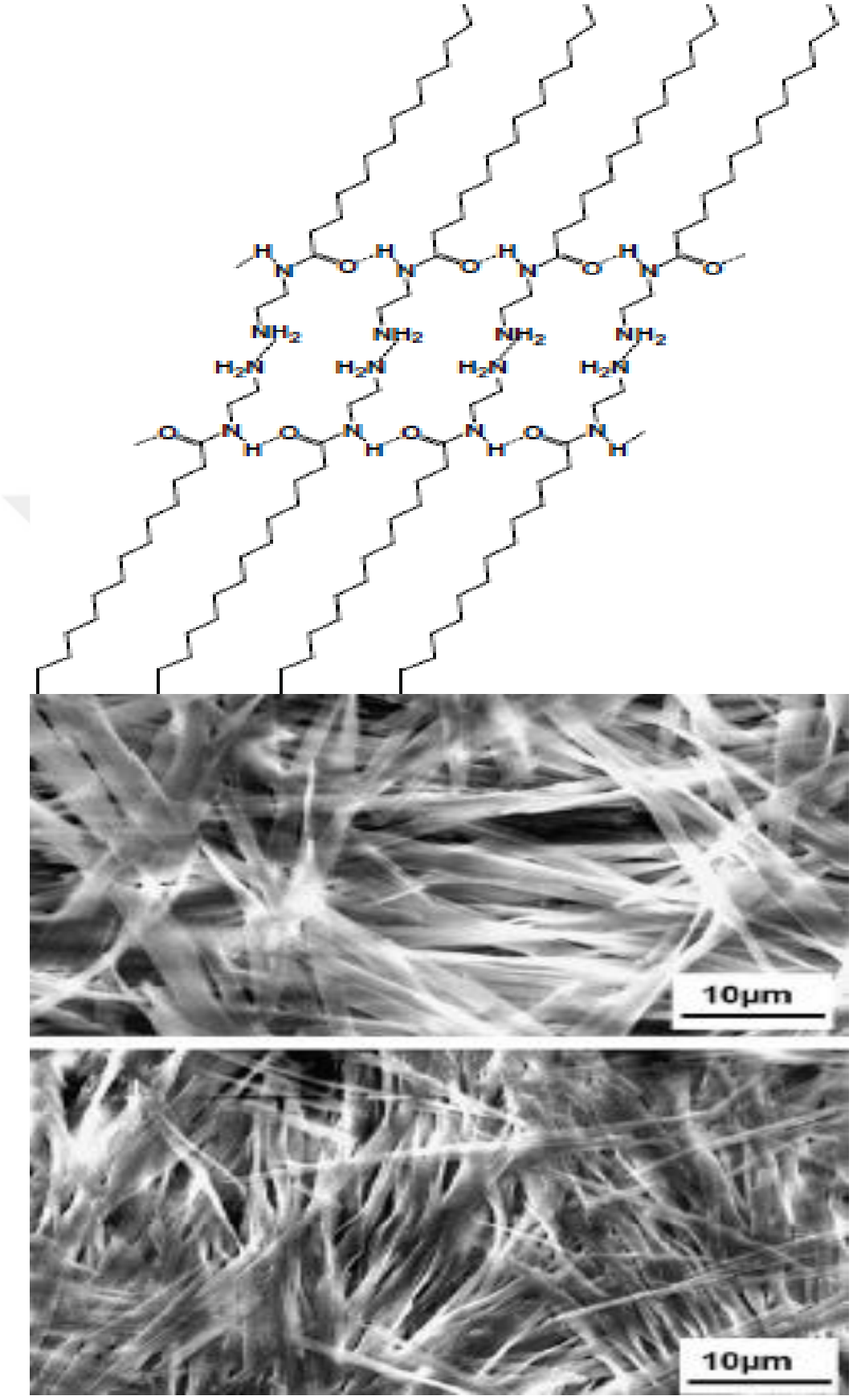


Figure 1.2. The structure of aggregates in organogel formation andSEM images of xerogels (Luo et al., 2009).

Lin and his coworkers (2010) synthesized a chiral peptide organogelator that can be self-assembled in nonpolar solvents. They observed hydrogen bonding interactions between the neighbouring organogelator molecules and the peptide head groups.

Sundararajan and his coworker in 2011 synthesized biscarbamate-based as organogelators and gelled themin benzonitrilein the form of nanotube shape and fiber structure. They discovered incarceration of silver nanoparticles, phthalocyanine and pryline dyes in these nanotubes (Figure 1.3).

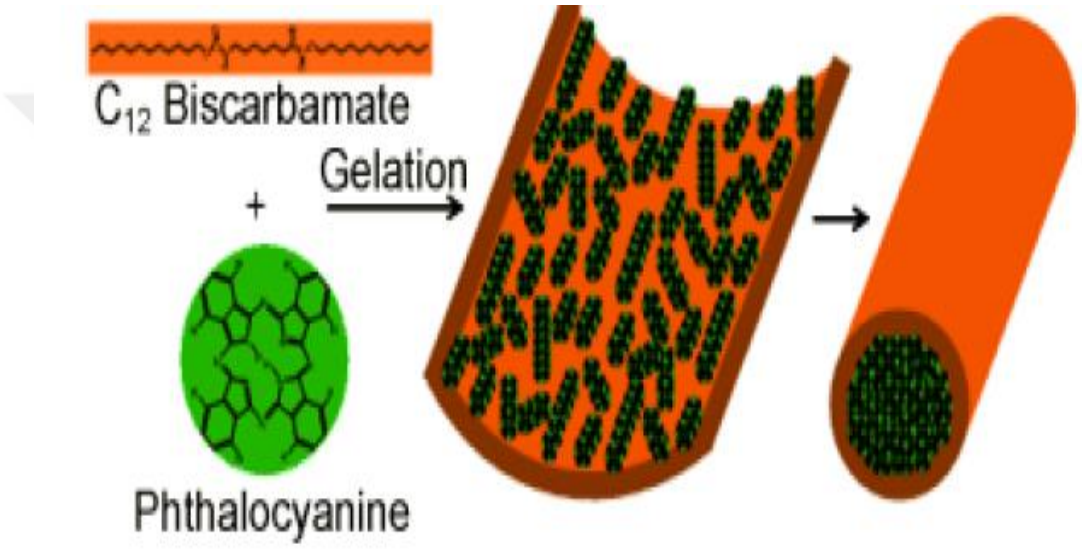


Figure 1.3. Nanotube shape of biscarbamates in benzonitrile (Sundararajan et al., 2011).

Chung and his coworkers (2013) displayed gelation properties of biscalix[4]arene derivatives for alcohols andreported phase selective cleaning properties of gels for sea water contaminated by diesel (Figure 1.4).

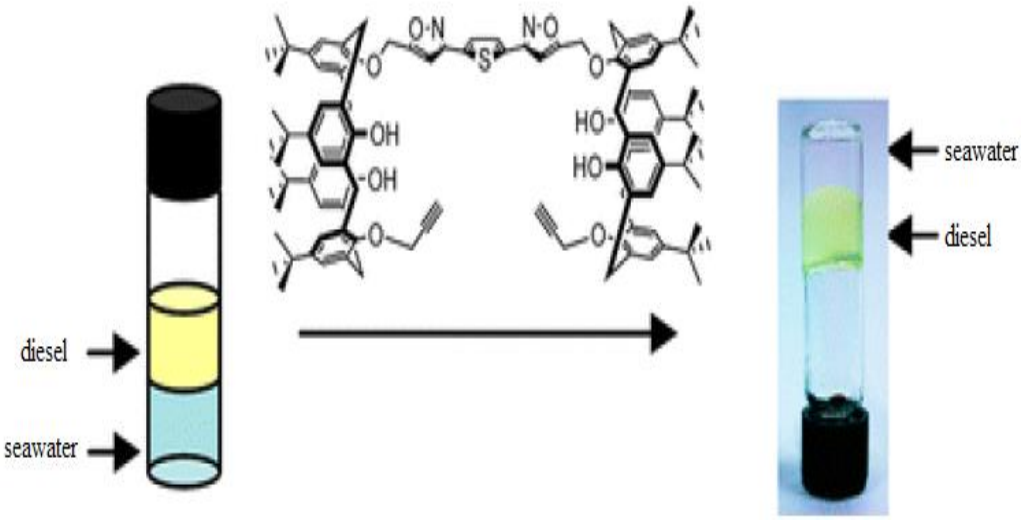
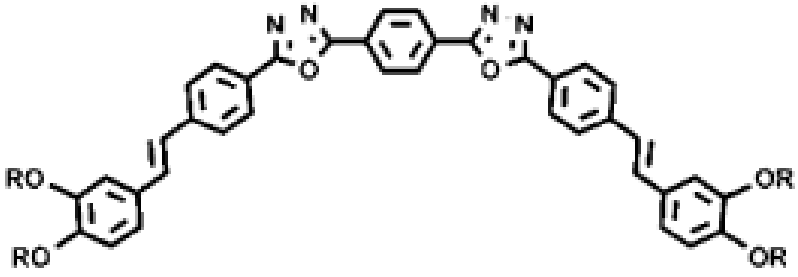


Figure 1.4. Phase selective gelation of biscalix[4]arene (Chung et al., 2013).

Aneesh and his coworkers (2014) published that luminescent oxadiazole-based stilbene molecules such as OXD8, OXD10, etc. (Scheme 1.5) had remarkable gelation characteristics and were able to behave as supergelators in nonpolar solvents producing self-standing gels with very high thermal and mechanical stability. Particularly these self-assembled molecules do not have any hydrogen-bonding interactions. It was observed supergelation is driven solely by π-π aromatic stacking interactions of the molecules.



OXD1: R = CH_3 OXD4: R = C_4H_9

OXD6: R = C_6H_{13} OXD8: R = C_8H_{17}

OXD10: R = $C_{10}H_{21}$ OXD12: R = $C_{12}H_{25}$

Scheme 1.5. Oxadiazole-based stilbene molecules chemical structures (Aneesh et al., 2014).

Pang and his coworkers (2015) characterized and designed a naphthalimide based fluorescent gelatorcontaining an alkenyl group. The naphthalimide based

fluorescent gel has been formed by instant precipitate gel formation triggered by ultrasound at room temperature. They characterized gelation process in n-propanol by absorption spectroscopy, fluorescence spectroscopy, IR spectroscopy and scanning electron microscopy (SEM) (Figure 1.5).

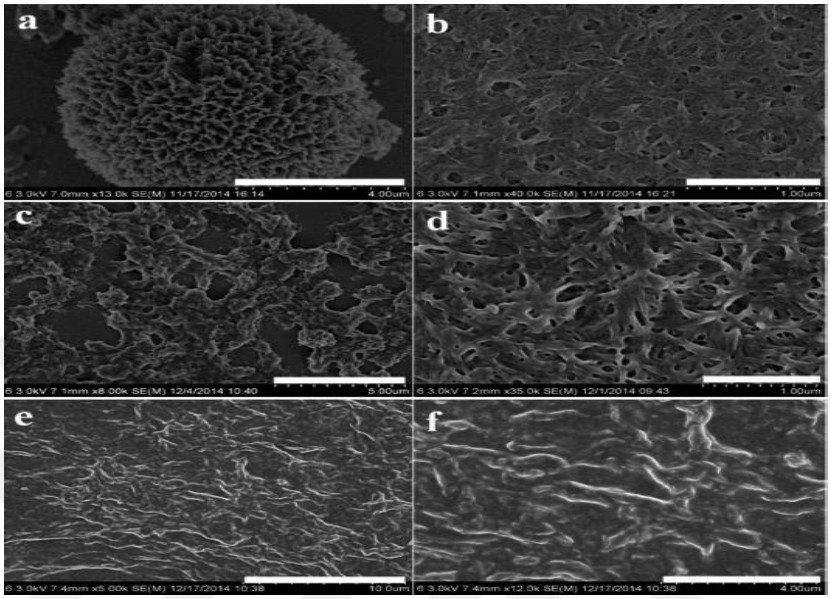


Figure 1.5. SEM images of naphthaline based xerogels (Pang et al., 2015).

Xu and his coworkers (2015) designed and synthesized low molecular weight gelators with different hydrocarbon chain lengths (Figure 1.6.) based on phenylboronic acid (PBA). They observed efficient gelationat relatively low concentrations with interested aggregates of nanofibersand microspheres piled with nanofibers,thin films and spherical thin shells. They showed the gelation ability of the gelators increased with the increase of alkyl chain length and concluded that the molecular interactions were reliable for gelation, proved by FT-IR spectroscopy and ^{1}H NMR spectroscopy measurements.

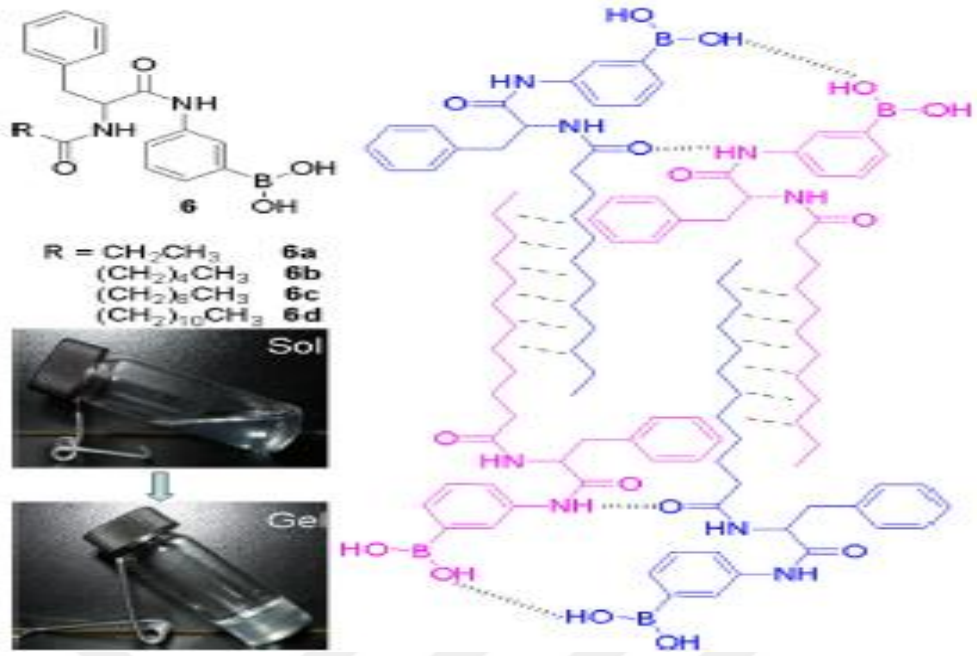
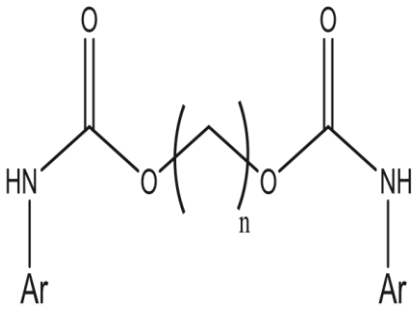


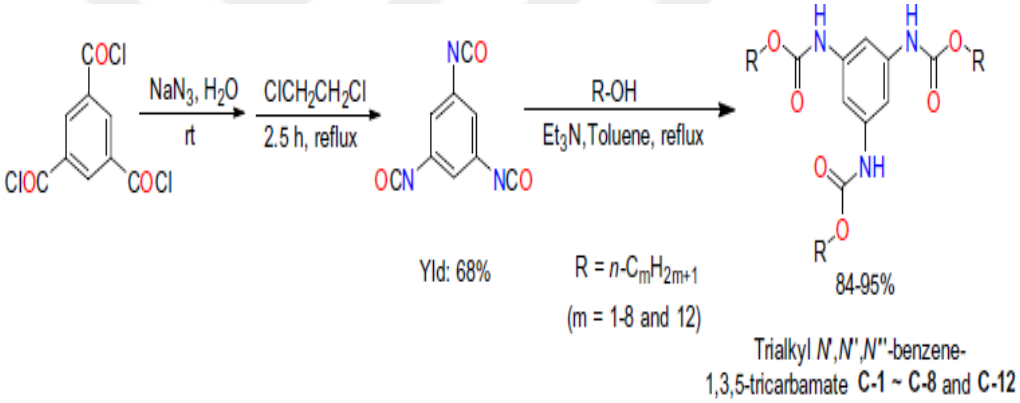
Figure 1.6. The chemical structure of gelators; interactions between gelator molecules and sol-gel transition of organogels (Xu et al., 2015).

Demir-Ordu and her coworkers (2015) synthesized low molecular weight organogelatorswith bis-carbamate functional groups (Scheme 1.6.). They studied structure possessionrelationshipaccording to the gelling properties in organic solvents. These organogels offered self-rallying behavior that could be turned back by heat. They investigated the organogel formation by FT-IR, temperature dependent NMR, and SEM studies. The results showed the most effective interactions in the self-assembly resulting in fibrillar structures werehydrogen bonding, π-π stacking, and van der Waals interactions. The methylene group number between two carbamate groups had also animportant effect on organogelation properties. In this study, theeffectof temperature on the gelation was also enquiredfor totally compounds. The *p*-hexyl derivativeformed a gelly structureonly at -18 ^{0}C temperature. No gel formation was observed for this derivetive atroom temperature. Thermal effects on the gels werealso examined by the methods of dropping-ball experiments and DSC.*para*-Alkoxyphenyl derivatives were found to be better organogelators inisopropyl myristate, *n*-butyl palmitate,oil derivatives and ethyl laurate compared to alkyl ones.



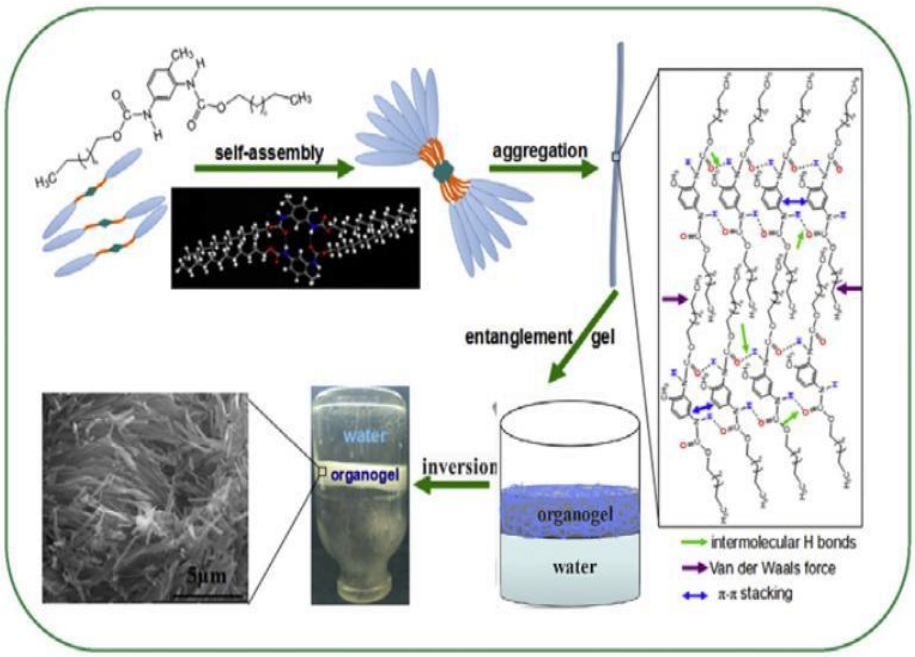
Scheme 1.6. The chemical structure of bis-carbamate compounds (Demir-Ordu et al., 2015).

Chu and his coworkers (2016) synthesized and characterized molecules based on threefold symmetric tricarbamate group as imaginative low molecular weight organogelators (Scheme 1.7). They have observed their gelation properties in polar and nonpolar organic solvents and they used NMR, UV spectroscopy and TEM to investigate gelation mechanism.



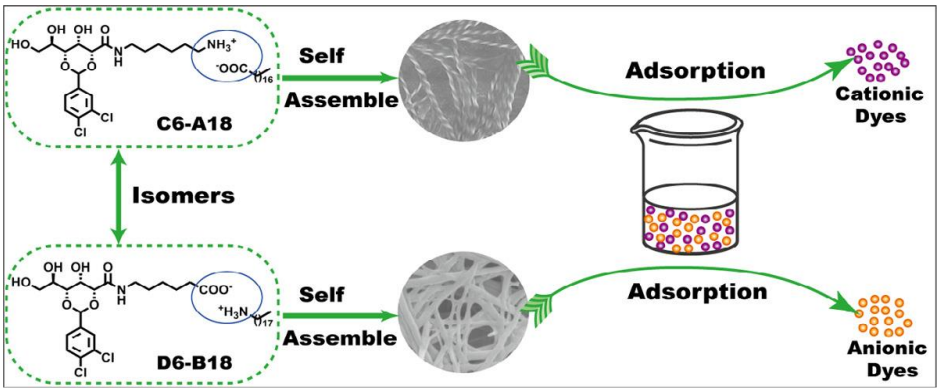
Scheme 1.7. Synthesis of the tricarbamates (Chu et al., 2016).

Wang and his coworker (2017) synthesizedbicarbamates supramolecular organogelator series with different shape and size of alkyl chains(Scheme 1.8).They found that intermolecular forces in self-assembly formation were double hydrogen bonding, π-π stacking and van der Waals interactions, etc. Furthermore, they reported the phase selective organogel formationfor organic solvents and oils. These phase-selective organogels have spontaneously 3D network structures in several types the organic solvents and oils in oil/water combination. For example; petroleum products (crude oil, diesel, gasoline), cyclohexane, hexane.



Scheme 1.8. Schematic notation of self-organization in gel networks (Wang et al., 2017).

Han and his coworkers (2018) investigated different amine-carboxylic acid interactions in hydrogels. They studiedon dissimilarself-assembly properties of gelatorsin water and characterizedthe resulted distinguishable morphologies by SEM andatomic force microscopy. They workedalso onxerogels obtained from the isomeric two component hydrogel-sand exhibited opposite surface charges. They found that these xerogels providedefficient and selective anionic-cationic dyes adsorption. Based on these opposite surface charges, resultingxerogels indicated dye adsorption capabilitieshaving different selectivities (Scheme 1.9.). In this study, they reported that this material can be used for efficient and selective phase seperation of toxic dyes from contaminated water.



Scheme 1.9. Schematicnotation ofselective adsorption of anionic-cationic dyes (Han et al., 2018).

1.2 Theory

1.2.1 Definition of Gels

There are a few gel definitions in literature. The gel is easier to recognize than to define by Dr. Dorothy Jordon Lloyd in 1926 and this definition still holds (Lloyd 1926).

Aneasily understood definition of gel is a soft, solid-like material or solid material, which consist of solid and liquid components. During the gel formation the solid component (fiber network) immobilizes the liquid component and avoidsthe liquid from flowing by surface tension (Savale, 2016).

Another approach by The United States Pharmacopoeia (USP) definition is, gels are semisolids and either suspensions of large or small inorganic/organic molecules or small inorganic particles interpenetrating with liquid (Bhardwaj et al., 2012).

1.2.2 Types of Gels

Gels are usually classified into two types:

a) Chemical Gels

b) Physical Gels

In chemical gels the network is completely covalent in nature, and as a result process for the formation of such gels is irreversible.

The fibers in the gel are composed of gelator molecules interact to form a 3D network that holds the solvent, and at the macroscopic level, this formation results in gel formation (Chen et al., 2018).

In physical gels, between fibers there are physical linkages like dipole-dipole interactions, van der Waals, etc. Physical gels are thermo-reversible because of this the physical bonds between fibers break over the sol-gel transition temperature and a solution forms. In the other case, if the gel is cooled under the sol-gel transition temperature, it can be converting back into the gel. Low molecular weight organogels are special class of physical gels. These organogelator molecules form a three-dimensional network by self-assembly through non-covalent interactions for example π-π stacking, H-bonding, van der Waals interactions (Sperling, 2006). The fibers in the gel physically interact to form a 3D network to hold the solvent and to result in gel formation (Chen et al., 2018).

Classification of the gels according to the solvent used in gelation is given as organogels and hydrogels (Sri, et al., 2012).

1.2.2.1 Hydrogels

Hydrogels have three dimensional of water soluble polymers are cross-linked networks. The water-soluble polymer made by hydrogels. (Bindu Sri M., Ashok V. and Arkendu chatterjee)

Hydrogels are rarely found as a colloidal gel in water dispersion medium. Hydrogels are physical or chemical crosslinked polymer networks. Hydrogels can

absorb important amounts of aqueous solution. Hydrogels containing hydrophobic groups swell has a small quantity than containing hydrophilic groups. Hydrophobic groups collapse in the presence of water so water molecule exposure is minimizing (Sri et al., 2012).

Structure of hydrogels classified as three classes (Sri et al., 2012).

- Hydrogen bonded hydrogels
- Amorphous hydrogels
- Semi-crystalline hydrogels

1.2.2.2 Organogels

Organogels defined semi-solid systems and the system is the organic liquid phase. Organogels are immobilized by a 3D network composed of self assembled; interlace gelator fibers (Vintiloiu and Leroux, 2008).

Another approach organogels include gelator substance and a non-polar or polar solvent. Organogels formation of the 3D network structure occurs by noncovalent interactions for example π-π stacking, van der Waals interactions, coordination etc. each other gelator molecules. The organogels compact inside a three-dimensional network. The organogelators converted the reversible process by the action of heat (Gupta et al., 2014).

Thermodynamically stable semi-solid system affected of encapsulated the organogels which is usually viscoelastic (Sahoo et al., 2011).

The organogelators same to be regarded as bicontinuous system which gelator and organic solvent molecules (Esch et al., 2015).

Organogels, dependent on weight of gelator molecule are divided by two parts (Figure 1.7.);

- Low molecular weight organogelators (LMOGs)
- Polymeric gelators (Vintiloiu and Leroux, 2008)

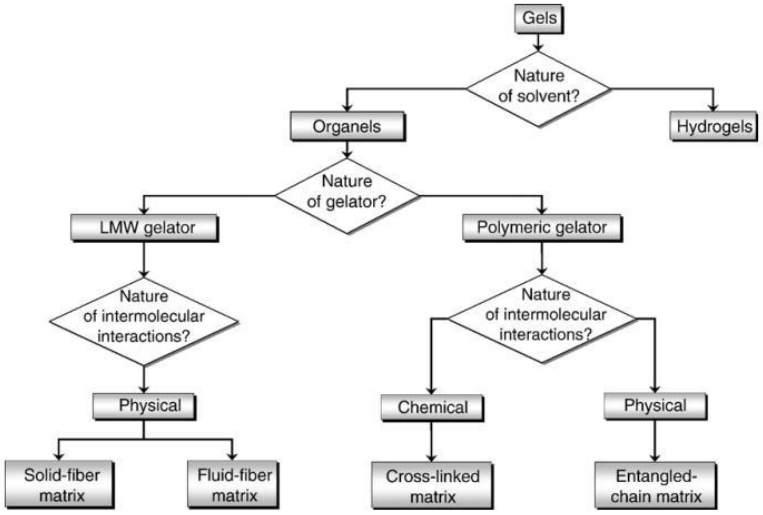


Figure 1.7. Schematic representation of organogels classification (Vintiloiu and Leroux, 2008).

1.2.2.2.1 Low molecular weight organogelators (LMOGs)

Low-molecular weight organic compounds, having a molecular weight less than 3000 have been found to be organogelators (LMOGs) that can form gel structurein several organic solvents at relatively low concentrations (≤5 wt %)(Demir-Ordu et al., 2015).

Low molecular weight organic gels (LMOGs) have become one of the most active circumference and they can occur into regular nano-architectures and nano-design throught specific noncovalent interactions including hydrophobic interaction, hydrogen bonds, π-π interactions and other forces. Thelow molecular mass organic gels (LMOGs) which are physical gelation of organic solvents have many potential applications in biomedical field, including multifunctional textile materials, drug release, and implants (Youbo Di, Wei Hong, and Jinming Dai, 2013).

The formation of low molecular weight organogels is affected by the following factors (Hoare and Kohane, 2008);

- Prevention of crystallization
- Intertwining of the aggregates in a 3D network
- An anisotropic growth process control for fiber formation

1.2.2.2.2 Polymeric organogelators

Polymeric organogelators possess organogelation properties even at low concentrations. Polymeric organogelators obtain gel properties by modifying the chemical structure of the chemical backbone (Pawar et al., 2014).

Polymeric gelators use the physical or chemical crosslinks and solidify the organic solvents. Polymeric gels perform the hyperbranched and star-shaped polymers (Vintiloiu and Leroux, 2008).

1.2.3 Conditions required for gelation

Gelations have three important criteria required:

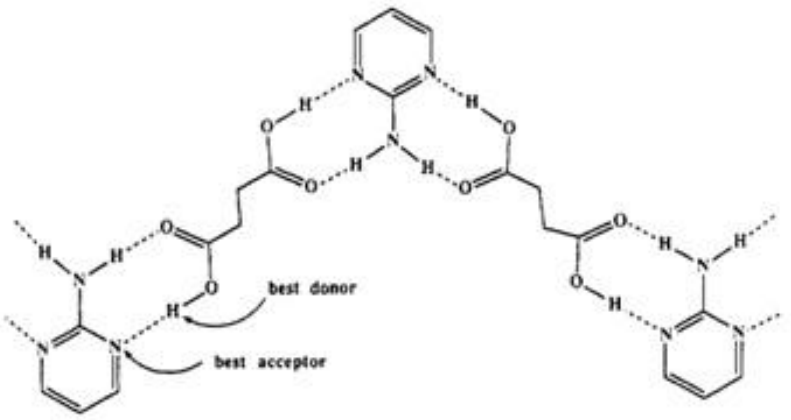
1. Molecule must be partially soluble in the solvent. Thus, it dissolves when the heat is applied and it gels when it is cooled.
2. Molecule must be partially insoluble in the solvent. If the solubility is very low, when heat is given, dissolving is not completed and gelation is not observed.
3. Molecule self-assembly can interact with noncovalent interaction (H-bond, π-π interaction and hydrophobic interaction). H-bonding is the most important factor for gel structure constituent (Smith, 2007).

1.2.4 Types of intermolecular interactions

Gelator molecules eachother include intermolecular interactions for instance London dispersion forces, hydrogen bonding, ionic-ionic, dipole-dipole, van der Waals and π-π stacking interactions. There is a relationship between gelator structure, intermolecular interactions and gelation properties. The molecular structure of the gelator has a minor change and is able to change the molecule from a gelator into a non-gelator (Vintiloiu and Leroux, 2008).

1.2.4.1 Hydrogen bonding

According the IUPAC, between the hydrogen and more electronegative than hydrogen atom has attractive interaction and called the hydrogen bond. (Scheme 1.10.)(Arunan et al., 2004).



Scheme 1.10. Hydrogen bond formation (Etter, 1990)

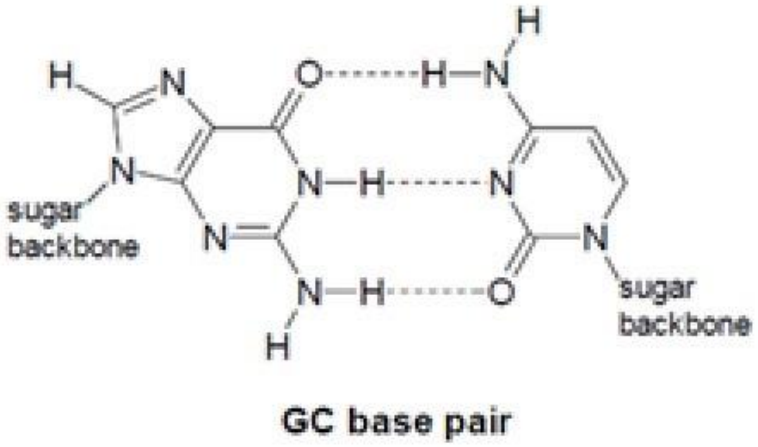
Another approach the valence bond theory a hydrogen atom does only one chemical bond. However, hydrogen is formally divalent and the additional bond is called hydrogen bond. There are two kind of hydrogen bonding (Kollman and Allen, 1971):

1. Hydrogen bonds connecting atoms of electronegativity higher than hydrogen.
2. Hydrogen bonds connecting atoms of lower electronegativity.

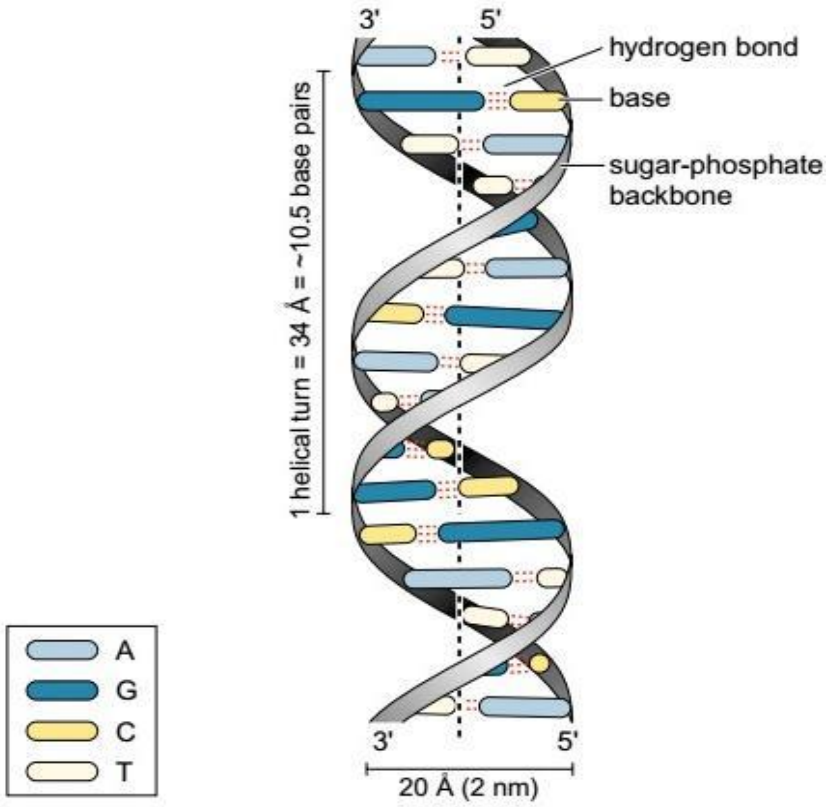
Hydrogen bonding occurs between a proton donor (A-H) acceptor group (M), where proton donor group has an electronegative atom like O, N, S, P, Se, X (F, Br, I, Cl). The acceptor group has a lone electron pair of an electronegative atom, or a π-electron orbital of a multiple bond (unsaturated) system. In the M–H···H–A system (M = metal such as Ir or Re, A = O, N, etc.), H···H contact is between 1.75–1.90 A° (Alkorta et al., 1998).

Mostly, a hydrogen bond has proton shared by two lone electron pairs. Increase the dipole moment between donor and the electron pair acceptor group cause the increasing strength of the hydrogen bond (Lucas, 2001).

The helix of DNA is the example of a self-assembled hydrogen bonded array (Scheme 1.11), which is formed by complementary hydrogen bonding between guanine and cytosine, adenine and thymine base pairs (Lucas, 2001).



Scheme 1.11. Hydrogen bonding in DNA (Lucas, 2001)



Scheme 1.12. Schematic model of the DNA structure (Dickerson, 1983)

1.2.4.2 π – π Interaction

π-π interaction is a noncovalent interaction and it has a small but important role in the formation of organic molecules. π-π interaction consist between functional group and an aromatic ring or two aromatic rings. The functional group has a lone pair electron which the electron pair affect electron donor, meanwhile the aromatic rings affect an electron acceptor (Hitomi et al., 2007).

According to Hunter interactions that consist of the parallel face to face orientation termed aromatic π-π stacking interaction. This interaction takes an important role for supramolecular chemistry (Figure 1.8) (Waller et al., 2006).

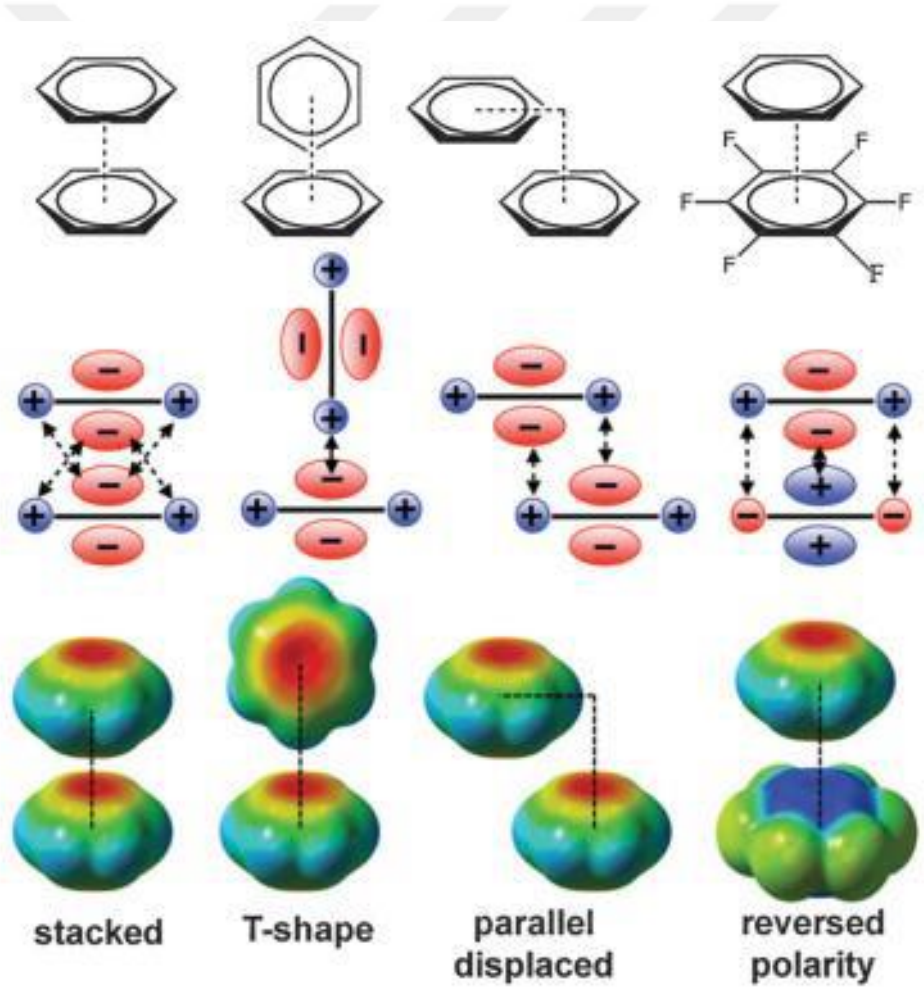


Figure 1.8. Geometries, quadrupole moments and ESPs (blue is (+) and red is (-) of typical π-π aromatic interactions (Matthews, Welton and Hunt, 2014).

1.2.4.3 Van der Waals interactions

Van der Waals forces define a combination of the attractive and repulsive electrical forces between atom and molecules and it is example for weak intermolecular forces (Helmenstine, 2015).

Intermolecular forces illustrate melting-boling point, solubility, heat conductivity, electrical conductivity, crystal structure, and hardness of substansces. All of the intermolecular forces are electrostatic and this force occur attraction between opposite charges. The electrostatic interactions for non-charge molecules (with no formal charges) are often classified as (Ebbing and Gammon, 2009);

A) Dipole dipole interactions

B) London forces

A) Dipole – Dipole Interactions

Polar molecules can attract another use the dipole–dipole forces. The dipole–dipole force is an attractive intermolecular forceand cause the tendency of polar molecules to align themselves, in other words the positive end of one molecule is near the negative endof another molecule. Recall that a polar molecule has a dipole moment as aresult of the electrostatic structure of the molecule (Ebbing and Gammon, 2009).

B) London forces

London forces on the other word dispersion forces are the weak attractive forces between molecules. The varying positions of the electrons during their motion about nuclei because resulting from the small, instantaneous dipoles that appear. London forces become strongeras the increasing molecular weight. This is due to the increased polarizability and greater surface area (Ebbing and Gammon, 2009).

1.2.5 Gelation process

Low molecular weight organogelators can be gelated at a concenration of less then 2% in organic solvents (Demir-Ordu et al., 2015).

The self-assembly process is driven by a variety of different forces, depending on the use of solvents. Hydrogen bonding is generally to the highest degreethe important force for aprotic, organic solvents, directing by itself process. Though the other significant role can also play π-π stacking interactions of aromatic rings, metal coordination, and electrostatic interactions. The important role forwater and to a lesser extent, polar protic organic solvents, hydrogen bonding and electrostatic interactions are not as important, because of ability for the solvent to participate in these types of interactions. Hydrophobic forces for instance the other Van der Waals forces and π stacking are the major contributors by itself of LMOGs in water. In any case nature of the solvent must be maintained for gelation to ocur for the gelator molecules and the sensitive balance between hydrophobicity and hydrophilicity. The gelator molecule is very soluble and complete thawing will take place on its own. Lead leads to extreme solvophobicity, exclusion of solvent, and precipitation or recrystallization (Lucas, 2001).

In general, a gel formation occurs by the following steps (Figure 1.9). At elevated temperature, the gelator molecules are needed to destroy strong intermolecular interactions responsible for self-assembley. Upon cooling of the solution these intermolecular interactions became stronger resulting in gelation (Lucas, 2001):

1. These interactions by itself occurs in 1D and results in the formation of thin fibers bacause of an anisotropy. Along the fibers new fibers can form or entangle, therefore creating bundles including several thin fibers which minimizes the large surface free energy of the single fibers.

2. As a result of an increase in the number of entanglement, a 3D-network forms over time.

3. The formation of a gel is recognised at the macroscopic level.

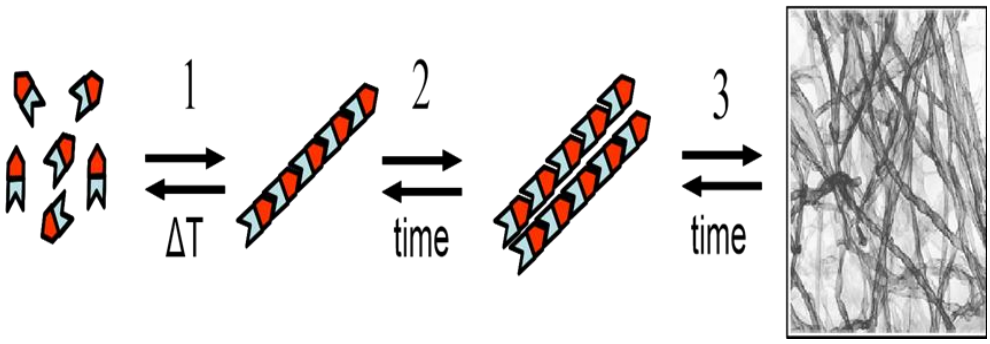


Figure 1.9. Schematic representation of the formation of a three dimension network starting form dissolved gelator molecules (Lucas, 2001).

As shown in Figure 1.10, The molecules start to condense and three situations are possible when the hot solution is cooled:

- a highly ordered grouping giving rise to crystals,
- a random grouping resulting in an amorphous precipitate
- an aggregation process intermediate between these two gives rise to a gel (Maity, 2007).

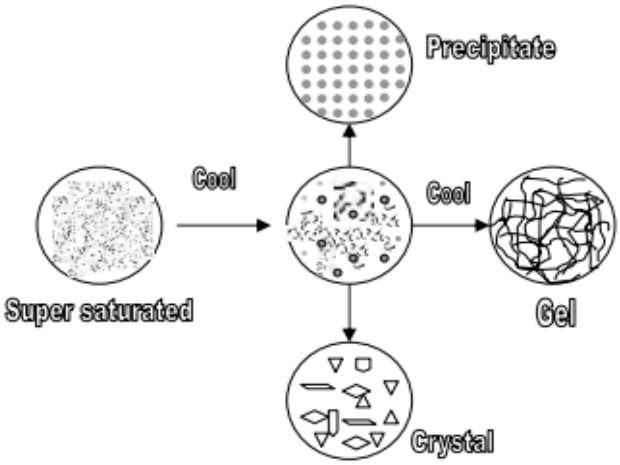


Figure 1.10. Schematic representation of aggregation modes (Maity, 2007)

1.2.6 Adsorption

Adsorption; generally known the surface retention of molecules, atoms, or ions. The other identification opposed to absorption. In other words the particles are adsorbed on a solid surface in the adsorption system.

The adsorption process always involves multiple interactions. Adsorption interaction is categorized the physical and chemical adsorption (Adamson, A.W., Gast, A.P., 1967, Physical Chemistry of Surfaces).

Electrostatic interactions consist of hydrogen bonding and hydrophobic attraction. Thats are responsible for weak and reversible involving small energy changes for the physical adsorption, on the other side covalent bonding cause the chemical adsorption which is irreversible and strong involving great energy changes. The physical and chemical adsorption is spontaneously. The intermediate character may be seen. Usually the chemical bonds are occuring solid surfaces depending on ionic surfactants. That can adsorb on solids either through physical adsorption or chemical adsorption during the non-ionic surfactants generally adsorb on solids through physical adsorption.

Adsorption is used to remove individual component which is physically or chemically bonded to a surface.

The attraction forces happen between molecules. That is an illustration the force of attraction between neutral, chemically saturated molecules. The van der Waals define non ideal gas behavior

Adsorption isotherms are often used to determine properties of porous adsorbents, zeolites, activated carbons, silica gels, etc.

1.2.7 Spectroscopy

Spectroscopy is a technique they absorb electromagnetic radiation based on differences for analyzing the structure of molecules. Although there are many types of spectroscopy so organic chemistry used mostly four:

- NMR spectroscopy;
- IR spectroscopy;
- UV spectroscopy (depending on a different principle)
- MS (mass spectroscopy).

Firstly, NMR spectroscopy caused the most detailed information regarding the atomic connectivity from the molecule. That could information for particularly hydrogens and carbons from the structure in the vicinity of individual nuclei. The basic information of spectroscopy relevant to NMR, IR, UV spectroscopy and describe how a spectrometer works.

Electromagnetic radiation can be specificated the waves or particles. A wave is defined a wavelength (λ) and frequency (ν). The wavelength (λ) and frequency (ν) are related by the expressions;

$$c = \lambda \nu$$

The c is the speed of lighton the other word the speed of the radiation, $3x10^{10}$ cm s^{-1}. Frequency is reported in cycles per second (cps) or hertz (Hz). Spectroscopy works discrete "packets" of energy and quanta absorb electromagnetic radiation. Absorption occurs only when radiation supplying exactly the right packet reaches the compound under investigation. If the frequency of the incident radiation is ν, the packet has energy $\Delta E = h \nu$ (Figure 1.11.).

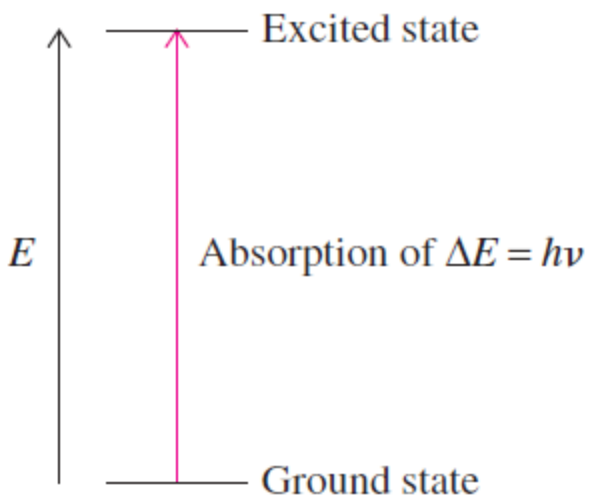


Figure 1.11. Absorption of energy occurs when incident radiation has exactly the right frequency ν so that its energy h ν equals the energy difference ΔE between the ground state and the excited state of a molecule [ν, frequency of absorbed radiation; h (Planck's constant) =6,626x10^{-34} J s].

Transfer ground state to excited states is role the absorption of quanta and radiation by a molecule brings about transitions. These absorptions can be mapped by instruments use the spectrometers so it called spectroscopy. The visible, infrared or radio region contains a source of electromagnetic radiation with a frequency. The apparatus which NMR, IR, UV etc. are designed so that radiation of a specific wavelength range and passes through the sample. In the traditional continuous-wave (CW) spectrometer has changed continuously radiation frequency and its intensity is measured use detector. That intensity recorded on calibrated paper in the traditional continuous-wave (CW) spectrometer. The sweep of radiation appears as a straight line called baseline because of the absence of absorption. Whenever the sample absorbs electromagnetic radiation the base line is change on the other word detector registers as a peak, or deviation from the baseline. These absorptions can be mapped by instruments called the spectrum of the sample. New-generation spectrometers are very effective and that use a different and much faster recording technique. That pulse of electromagnetic radiation covers the entire frequency range examination (NMR, IR and UV) is used to obtain the whole spectrum instantly. Moreover, rather than simple absorption, as in traditional CW instruments, the decay of the absorption event with time is recorded, a procedure that requires a more elaborate computer analysis, called Fourier Transform (FT), after the French mathematician Joseph

Fourier (1768 – 1830). This technique great value when only small amounts of sample. Technique available and multiple pulse accumulation of the same spectrum allow for much higher sensitivity. The organic molecules may absorb radiation at various wavelengths. Spectroscopy is possible because absorption is restricted to quanta of defined energies, hν, to effect specific excitations with energy change ΔE.

$$\Delta E = h\nu = \frac{hc}{\lambda} \qquad (c = \text{velocity of light})$$

Organic compounds color is quantify from 400 to 800 nm wavelength range in the spectroscopy and called visible spectroscopy. Besides also examine the called ultraviolet spectroscopy and range between 200 to 400 nm, (Figure 1.12.). The two range are very near so same spectrometer can use.

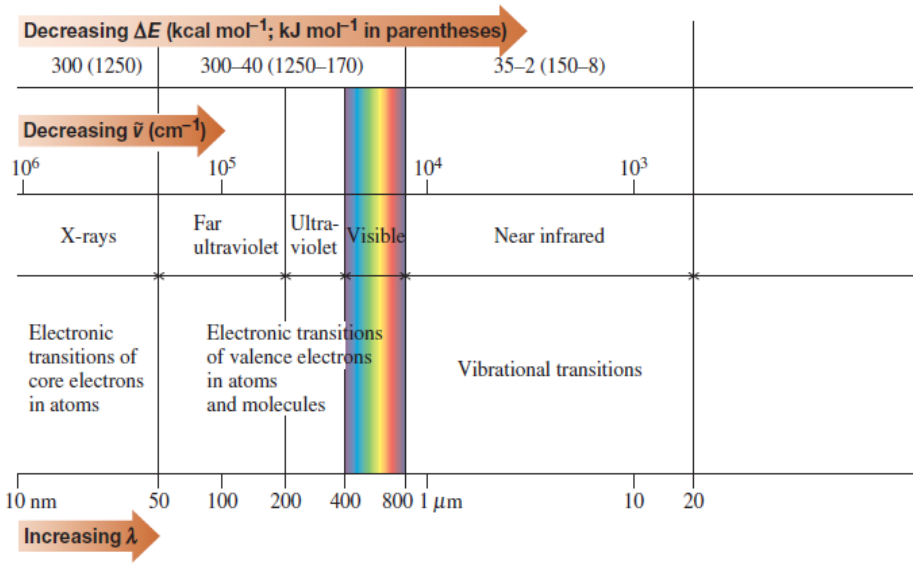


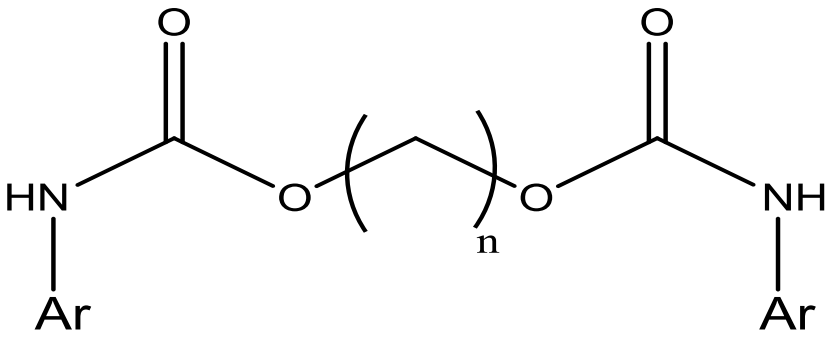
Figure1.12. The spectrum of electromagnetic radiation.

2. AIM AND SCOPE OF THE STUDY

Thermoreversible supramolecular organogels are the forms of soft matter containing low molecular weight organogelators (LMWOs). These organogels have found many applications in different areas such as drug delivery, water purification etc. Molecules of LMWOs give rise to 3D entangled supramolecular networks through non-covalent intermolecular interactions such as hydrogen bonding, π-π stacking, van der Waals interactions and other weak interactions. These non-covalent interactions create aggregates of gelators in the form of fibrillar, tubular or helical structures, which subsequently results in the immobilization of the solvent molecules.

Aromatic/hydrogen bonding groups and aliphatic chains are known to be responsible for gel formation by self-assembly. Generally, LMWOs that are capable of forming double hydrogen bonding sites (like in bis-ureas, bis-amides) are known to have intermolecular hydrogen bonds with two neigboring molecules. Some bis-carbamate derivatives also produced self-assembled aggregates through hydrogen bonds between carbamate functionality. Recently, it was reported (Demir-Ordu et al., 2015) that hydrogen bonding, π-π stacking and van der Waals interactions were found to be the driving forces for the self-assembled gel formation in bis[N-(*p*-aryl)-carbamoyloxy]alkanes (Scheme 2.1). The results also showed that the organogelation abilities are affected by *p*-alkyl or *p*-alkoxy chain-length and the number of methylene units between two carbamate units.

The odd-even effect observed in methylene spacer groups between two hydrogen bonding sites is a well-known and an extensively studied phenomenon. In a previous study (Demir-Ordu et al., 2015), the compounds possessing an odd number of methylene units (n: 3,5, Scheme 2.1) in the spacer exhibited an improved gelation ability. For *p*-alkyl-substituted derivatives, decreasing this number improved the gelation capability because of the important role of solubility effect on gelation.



Compound No	n	Ar	Compound No	n	Ar
3-Naph	3	α-naphthyl	**3-Pr**	3	*p*-propylphenyl
4-Naph	4	α -naphthyl	**4-Pr**	4	*p*-propylphenyl
5-Naph	5	α -naphthyl	**5-Pr**	5	*p*-propylphenyl
6-Naph	6	α -naphthyl	**6-Pr**	6	*p*-propylphenyl
3-Me	3	*p*-tolyl	**3-Bu**	3	*p*-Butylphenyl
4-Me	4	*p*-tolyl	**4-Bu**	4	*p*-Butylphenyl
5-Me	5	*p*-tolyl	**5-Bu**	5	*p*-Butylphenyl
6-Me	6	*p*-tolyl	**6-Bu**	6	*p*-Butylphenyl
3-OMe	3	*p*-methoxyphenyl	**3-OBu**	3	*p*-Butoxyphenyl
4-OMe	4	*p*-methoxyphenyl	**4-OBu**	4	*p*-Butoxyphenyl
5-OMe	5	*p*-methoxyphenyl	**5-OBu**	5	*p*-Butoxyphenyl
6-OMe	6	*p*-methoxyphenyl	**6-OBu**	6	*p*-Butoxyphenyl
3-Et	3	*p*-ethylphenyl	**3-Hex**	3	*p*-Hexylphenyl
4-Et	4	*p*-ethylphenyl	**4-Hex**	4	*p*-Hexylphenyl
5-Et	5	*p*-ethylphenyl	**5-Hex**	5	*p*-Hexylphenyl
6-Et	6	*p*-ethylphenyl	**6-Hex**	6	*p*-Hexylphenyl
3-OEt	3	*p*-ethoxyphenyl	**3-OHex**	3	*p*-Hexyloxyphenyl
4-OEt	4	*p*-ethoxyphenyl	**4-OHex**	4	*p*-Hexyloxyphenyl
5-OEt	5	*p*-ethoxyphenyl	**5-OHex**	5	*p*-Hexyloxyphenyl
6-OEt	6	*p*-ethoxyphenyl	**6-OHex**	6	*p*-Hexyloxyphenyl

Scheme 2.1. Chemical structures of the compounds (Demir-Ordu et al., 2015)

It was also found that *p*-alkoxy derivatives formed a 3D network structure via fiber formation while *p*-alkyl derivatives had porous structures. After evaporation of the gelation solvent the resulting dry gels (xerogels) were analyzed by scanning electron microscopy (SEM). SEM images for *p*-hexyl, *p*-butoxy and *p*-hexyloxy bis-carbamate derivatives were shown in Figures 2.1-2.6.

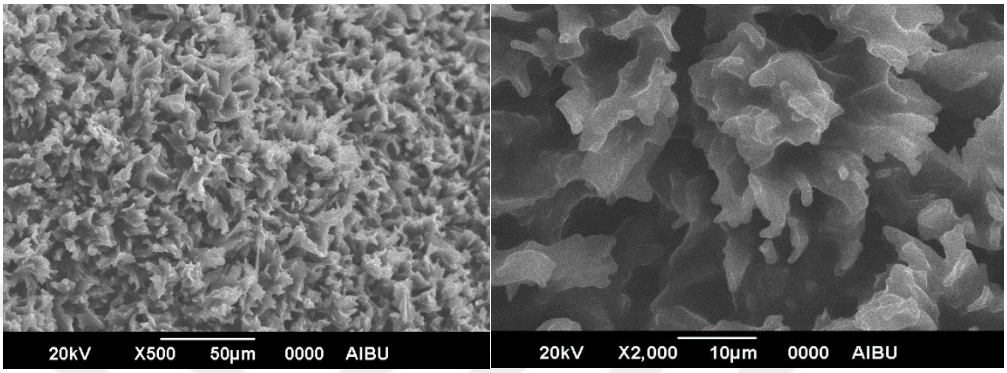


Figure 2.1. SEM images of 3-Hex obtained from the vacuum-dried toluene gels (Demir-Ordu et al., 2015).

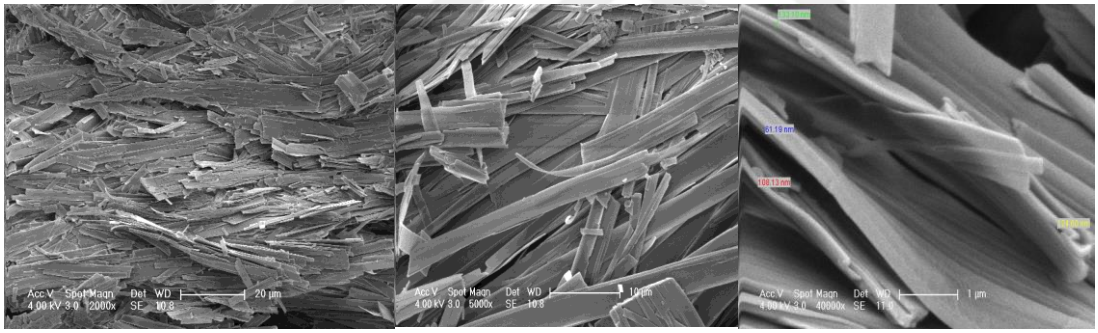


Figure 2.2. SEM images of 5-OBu obtained from the air-dried toluene gels (Demir-Ordu et al., 2015).

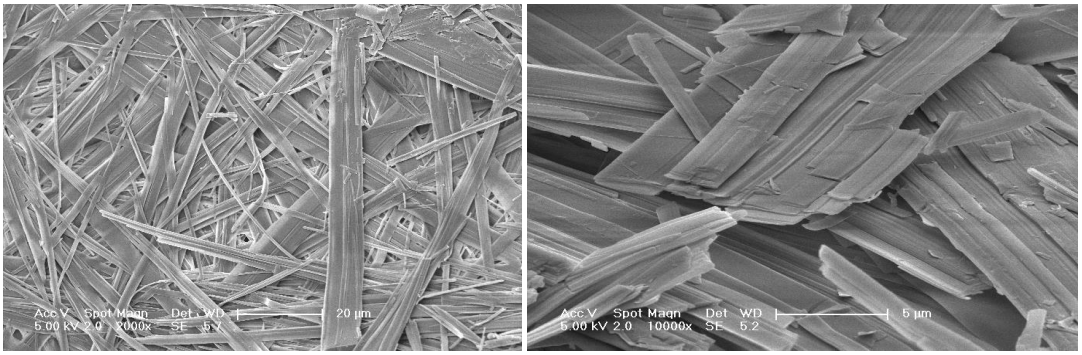


Figure 2.3. SEM images of 3-OBu obtained from the air-dried xylene gels (Demir-Ordu et al., 2015).

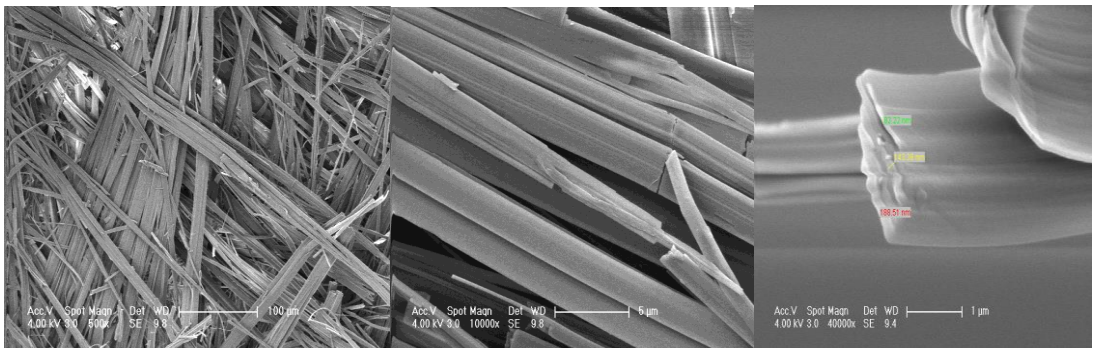


Figure 2.4. SEM images of **3-OBu** obtained from the air-dried toluene gels (Demir-Ordu et al., 2015).

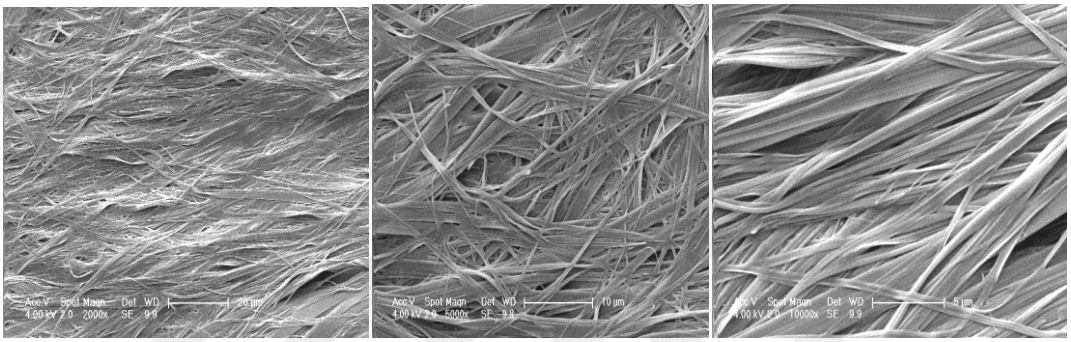


Figure 2.5. SEM images of **5-OHex** obtained from the air-dried toluene gels (Demir-Ordu et al., 2015).

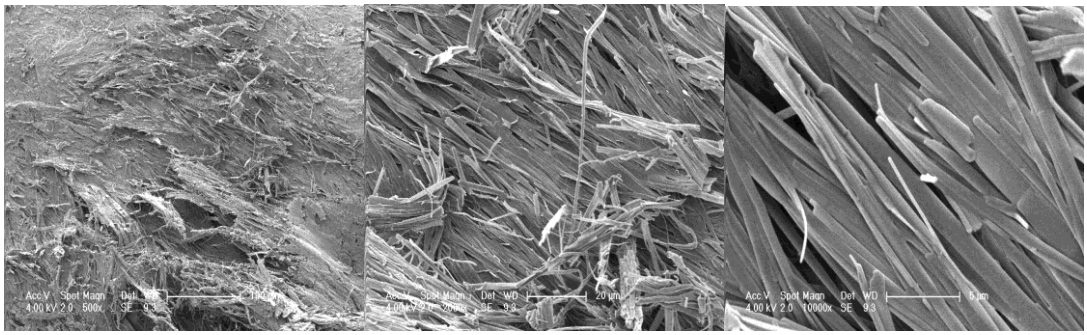


Figure 2.6. SEM images of **3-OHex** obtained from the air-dried toluene gels (Demir-Ordu et al., 2015).

In literature, there are many applications for the usage of dry (xerogels) and wet organogels in removal purposes especially in water purification. For example, Das et al. (2008) synthesized dipeptide-based low molecular weight organogelators and prepared wet and dry gels to remove toxic dyes such as cystal violet, rhodamine 6G from water (Figure 2.7.).

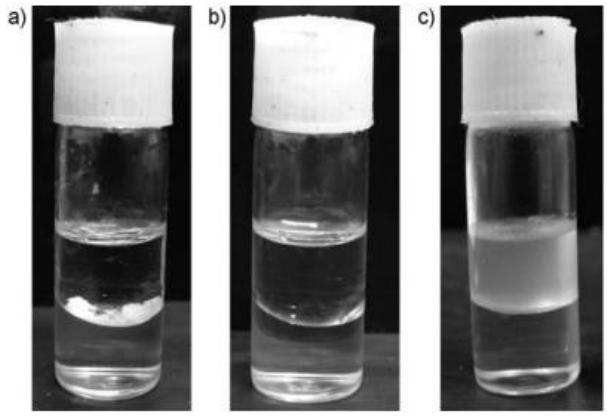


Figure 2.7. a) 1 mL toluene together with 1 mL water mixture including 10 mg of gelator. b) solution preparation upon heating. c) Phase-selective gel formation of toluene layer at RT (Das et al., 2008).

John and coworkers (2010) synthesized sugar-based gelators for oil spill remediation. They studied the recovery of oil and reuse of the gelator for the first time for cleaning purposes. In their study, gelators efficiently and selectively removed the oil part from oil–water mixtures (Figure 2.8.).

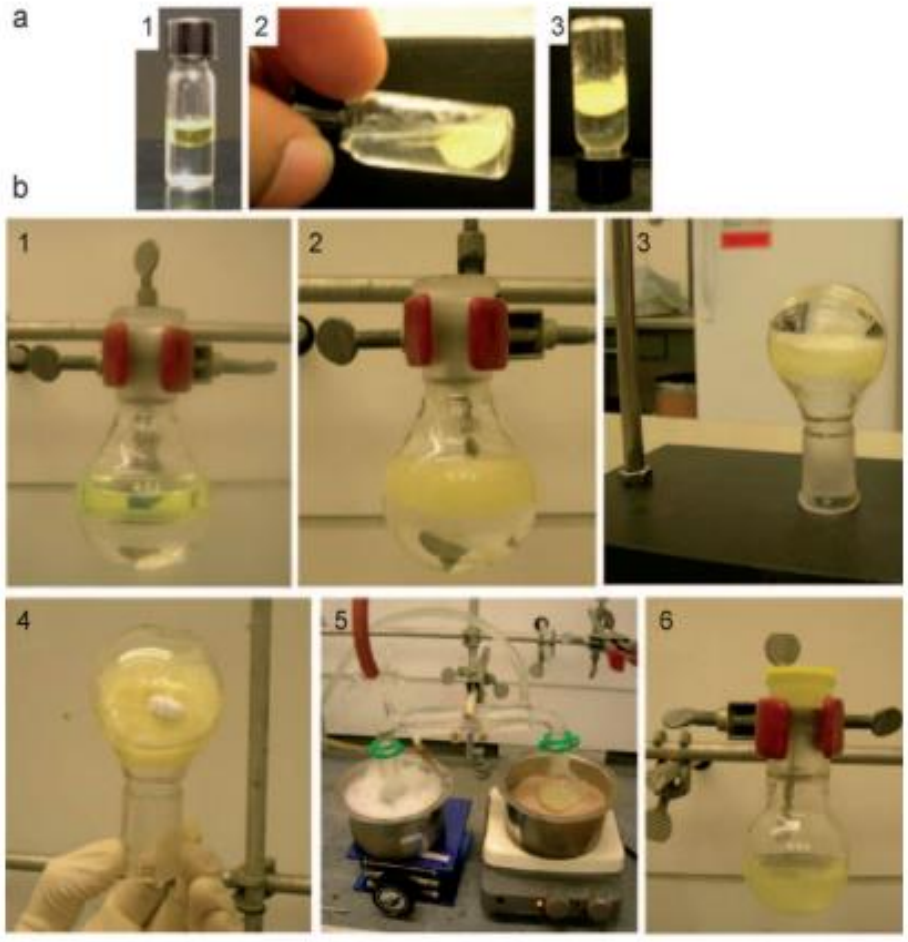


Figure 2.8. Phase-selective gelation and recovery of diesel from a two-phase system (John et al., 2010).

Chen et al. (2011) achieved the synthesis of LMWOGs bearing 2-substituted antraquinine and a hydrazine subunit. They also found that the hydrazide-based organogelators showed phase-selective gelation in aromatic solvent-water mixtures (Figure 2.9.).

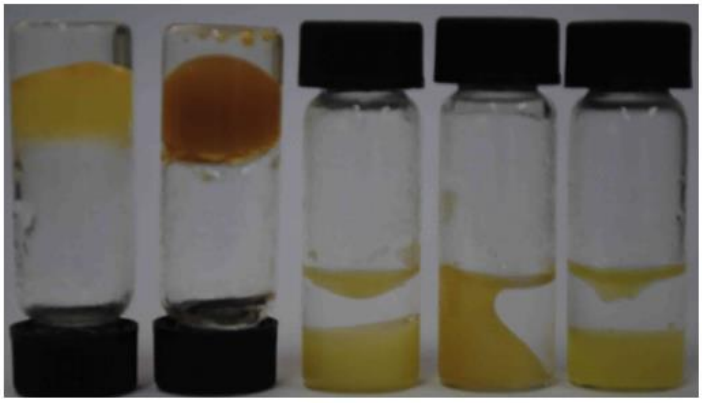


Figure 2.9. Phase selective gelation in presence of water (1/1 vol %) and sequential: toluene, aniline, 1,2-dichlorobenzene, chlorobenzene, chloroform (Chen et al., 2011).

Chung and his coworkers (2013) reported that biscalixarene framework with short alkyl chains was capable of producing organogels in several alcohols. They also indicated that the obtained gel exhibited phase selective gelation property that is promising for recovery of oil-spill (Figure 2.10.)

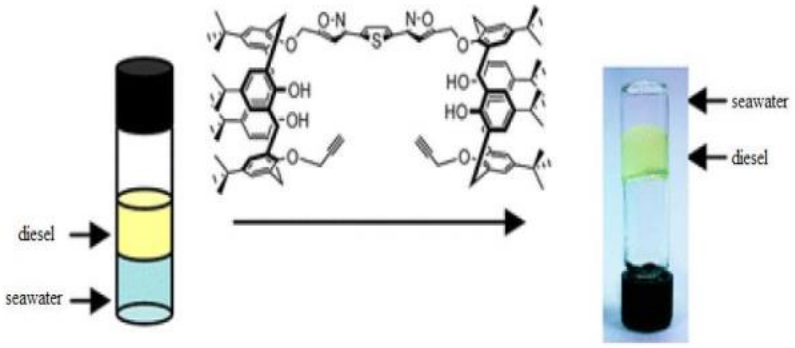


Figure 2.10. Phase selective gelation of biscalix[4]arene (Chung et al., 2013).

Feng et al. (2014) studied on the preparation of C_2-symmetrical-benzene compounds showing selective gelation against aromatic solvents and used phase selective gelation for water-oil mixtures (Figure 2.11.). They reported that phase selective gelation of this C_2 based organic gelator may have many applications for the removal of oil spill.

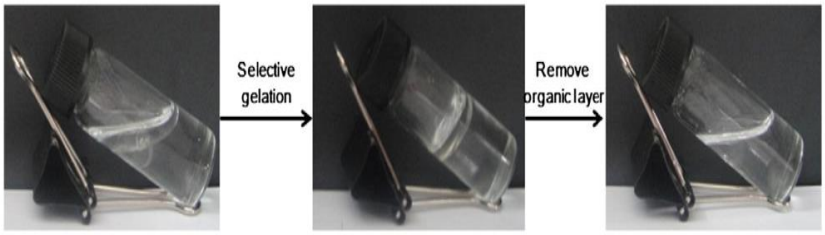


Figure2.11. Selective organogel formation from oil/water of C_2-symmetrical-benzene compounds (Feng et al., 2014).

Wang and his coworker (2017) have synthesized biscarbamate-based organogelators having different alkyl chain lengths. They reported that (Figure 2.12.) these phase-selective organogels have self-assembled 3D network structures in organic solvents and oils from oil/water mixtures, like petroleum products (crude oil, diesel, gasoline), cyclohexane, hexane and shows high oil removal and oil retention rates.

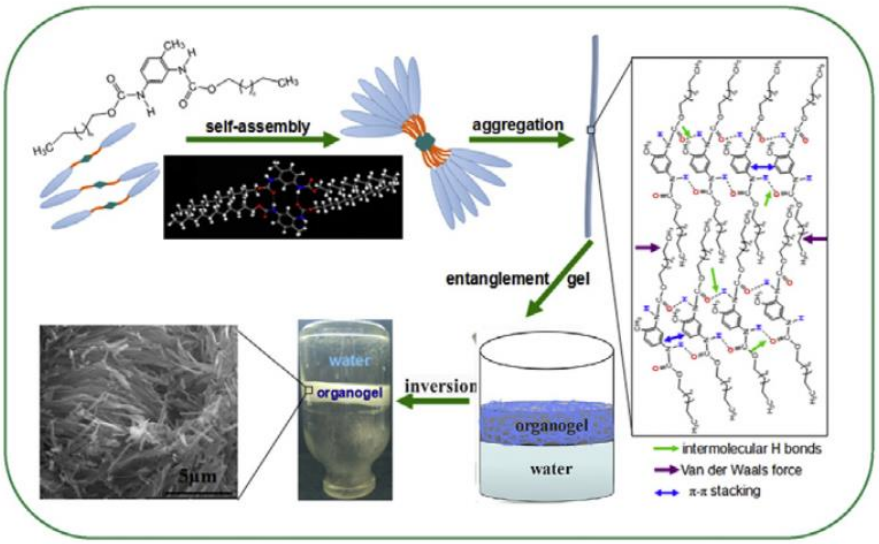
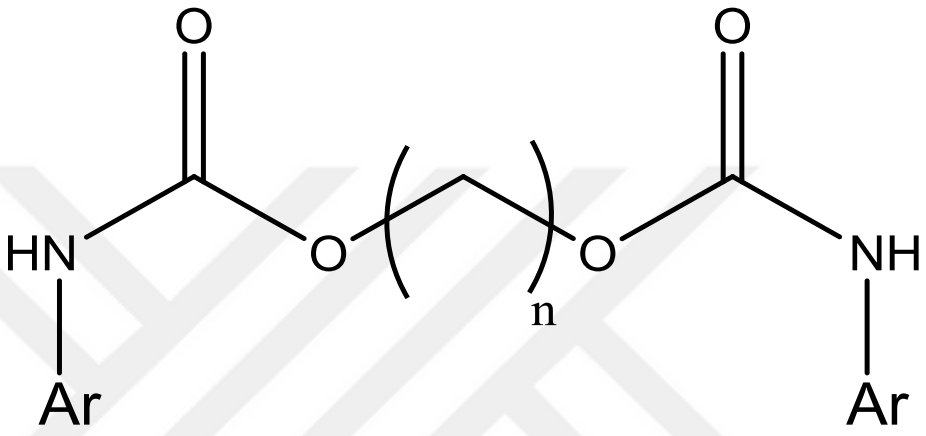


Figure 2.12. Schematic representation for the gel network formation and phase-selective gelation (Wang et al., 2017).

With these results in hand, the aim of the study is to synthesize bis-carbamate derivatives (Scheme 2.2.) to utilize their organogels for drug removal properties. Compounds shown in Scheme 2.2 were chosen due to the possible porous structure of **3-Oct** derivative similar to that of **3-Hex** (Figure 2.1) and the proved 3D fiber network structure for **3-OBu**, **5-OBu**, **3-OHex** and **5-OHex** (Figures 2.2-2.6) which is expected to be better for drug removal properties and hence for water purification.



Compound No	n	Ar
3-Oct	3	*p*-octylphenyl
3-OBu	3	*p*-Butoxyphenyl
5-OBu	5	*p*-Butoxyphenyl
3-OHex	3	*p*-Hexyloxyphenyl
5-OHex	5	*p*-Hexyloxyphenyl

Scheme 2.2. The chemical structure of the studied compounds (Demir-Ordu et al., 2015).

3. MATERIALS AND METHODS

NMR spectra which are ^{13}C-NMR and ^{1}H-NMR spectra were recorded at 400 MHz for proton and 100 MHz for carbon on JEOL NMR spectrometers, spectrometer at ambient temperature. All chemical shifts (δ) are reported in part per million (ppm) down field from TMS; *J* values are given in Hz. The abbreviations used for NMR signals are:

s=singlet,

d=doublet,

t=triplet,

q=quartet,

m=multiplet.

IR spectra were recorded on a SHIMADZU FTIR-8400S instrument (KBr pellet).

Melting point were determined on a MELTEMP apparatus and uncorrected.

3.1 Experimental

3.1.1 Absorption Spectrophotometry, Ultraviolet and Visible

Determination of absorbance; the absorbance (A) of a solution is defined as the logarithm to base 10 of the reciprocal of the transmittance (T) for monochromatic radiation:

$$A = \log_{10}(\frac{1}{T}) = \log_{10}(\frac{I_o}{I})$$

$T = I/I_o$;

I_o = intensity of incident monochromatic radiation;

I = intensity of transmitted monochromatic radiation.

In the absence of other physical-chemical factors, the absorbance (A) is proportional to the path length (b) through which the radiation passes and to the concentration (c) of the substance in solution in accordance with the equation:

$$A=\varepsilon cb$$

ε = molar absorptivity, if b is expressed in centimetres and

c= moles per litre.

Unless otherwise prescribed, the absorbance was measured at the precibed wavelength using a path length of 1 cm. Unless otherwise prescribed, the measuremets were carried out with reference to the same solvent or the same mixture of solvents.

3.1.1.1 Drug Removal Studies followed by UV Spectroscopy

A certain amount of adsorbent (in the form of dry or wet gel) was added into a solution with a certain concentration of drug. After the solution was kept at a certain temperatures for a certain time, the absorbance was measured at the maximum absorption wavelength of the drugs (Dexketoprofen trometamol, paracetamol, ibuprofen, ciprofloxacin HCl) by UV-Vis spectrophotometer, then according to the following formula respectively the removal rate φ of drugs were calculated.

$$Removal\ rate\ \varphi = \frac{C_o - C_e}{C_o} \times 100\%$$

3.1.2 Drugs and preparation methods

3.1.2.1 Paracetamol

Dissolve 150 mg paracetamol in 200 mL volumetric flask by adding 50 mL 0,1 N NaOH then dilute it with distilled water and shake. Take 2 mL of this solution and 5 mL 0,1 N NaOH then dilute it to 250 mL with distilled water and shake. Read the absorbance at (257±2 nm). (British Pharmacopeia)

3.1.2.2 Ibuprofen

Dissolve 111,1 mg ibuprofen in 250 mL volumetric flask by pH 7,2 phosphate buffer solution and shake. 2 mL of this solution is diluted to 100 mL with pH 7,2 phosphate buffer solution and shake. Read the absorbance at (221±2 nm).

Preparation of pH 7,2 Phosphate Buffer Solution = Mix 250 mL of 0,2 M monobasic potassium phosphate and 173,5 mL of 0,2 M sodium hydroxide and dilute the solution to the 1000 mL with distilled water.

Preparation of 0,2M Monobasic Potassium Phosphate = 27,22 g monobasic potassium phosphate is (KH_2PO_4) dissolved in the distilled water and diluted to 1000 mL with same solvent.

Preparation of 0,2M Sodium Hydroxide = 8 g sodium hydroxide is dissolved with distilled water and diluted to 1000 mL with water. (United State Pharmacopeia)

3.1.2.3 Ciprofloxacin HCl

Dissolve 64 mg of ciprofloxacin HCl in 100 mL volumetric flask with 0,1 N HCl and dilute it with 0,1 N HCl. Dilute 1 mL of solution to 100 mL with 0,1 N HCl. Read the absorbance at (276±2 nm).

3.1.2.4 Dexketoprofen Trometamol

Weigh 100 mg dexketoprofen trometamol in 100 mL volumetric flask and dilute it to 100 mL with distilled water and shake. Dilute 1 mL of this solution to 100 mL with distilled water and shake. Read the absorbance at (260±2 nm).

3.1.3 Drugs used in the study

3.1.3.1 Paracetamol (Acetaminophen)

Paracetamol (acetaminophen, *N*-acetyl-*p*-aminophenol, 4-acetamidophenol) is a widely used minor analgesic. The structure of paracetamol is shown in Figure3.1.(St. Louris, 2001)

Another name of Paracetamol is N-(4-Hydroxy phenyl) acetamide, and is one of the most popular over-the analgesic and antipyretic drugs.

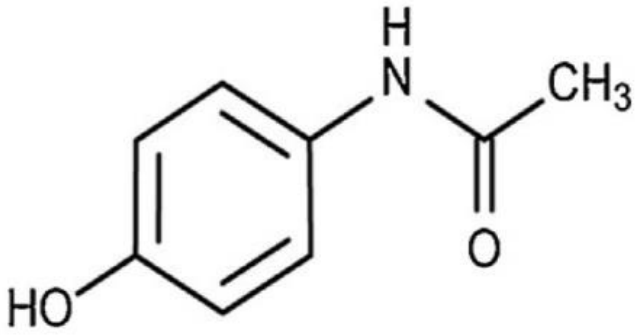


Figure3.1. The structure of paracetamol (B.D. Clayton et al., 2001).

Paracetamol is widely used in medical practice for analgesic and antipyretic drugs. However, for long term treatment with paracetamol plays an important role in relief of mild to moderate chronic pain associated with cancer and osteoarthritis.

3.1.3.2 Ibuprofen

Ibuprofen, also called 2-(isobutylphenyl)-propionic acid(Figure3.2.), thats belongs to the non-steroidal anti-inflammatory drug which is used to treat headaches andminor pains, fever, migraine, muscle pain, toothaches and arthritis all over the world.

Although it is known that S-ibuprofen is responsible for the anti-inflammatory effects while R-ibuprofen might cause some long-term side effects (Sheldon, 1993), ibuprofen is still sold as a racemic mixture in the market due to the complexity involved in the separation of enantiomers.

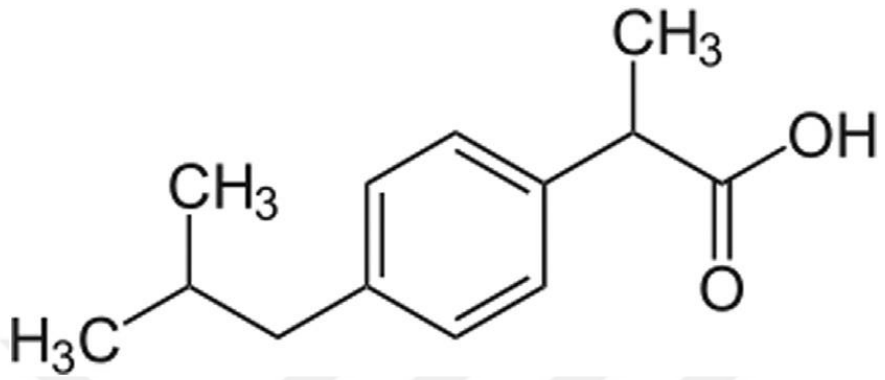


Figure 3.2. Chemical structure of ibuprofen

3.1.3.3 Ciprofloxacin HCl

Ciprofloxacin hydrochloride, namely 1-cyclopropyl- 6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid hydrochloride (Figure3.3.), is a second generation fluoroquinolone antimicrobial with a wide spectrum of activity against Gram-negative and Gram-positive bacteria, including Pseudomonas aeruginosa.

It is used for the treatment of various infectious diseases, including urinary tract the respiratory tract infections.

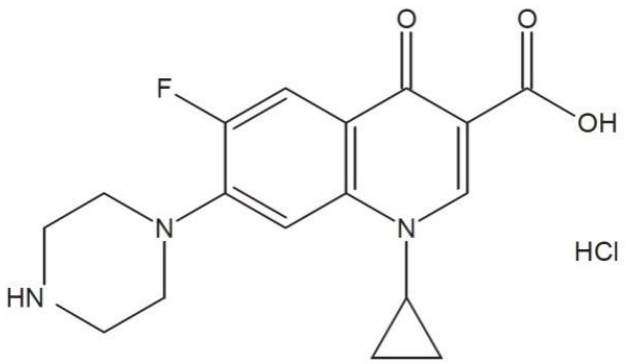


Figure 3.3. Chemical structure of ciprofloxacin hydrochloride

In situ spectrum ofCiprofloxacin HCl absorbance was measured from 200 to 400 nm (Figure 3.4.). The optimum wavelength for quantitative analysis is at 278 nm.

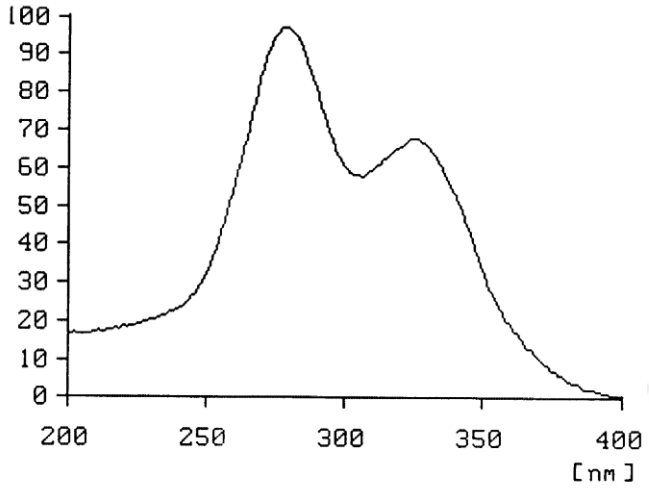


Figure 3.4. In situ spectrum of ciprofloxacin hydrochloride measured from 200 to 400 nm (Novakovic et al.,2001).

3.1.3.4 Dexketoprofen Trometamol

Dexketoprofen trometamol is an S-(+)-2-(3-benzoylphenyl) propionic acid tromethamine salt (Figure 3.5). Dexketoprofen is a non-steroidal anti-inflammatory drug (NSAID) and it is a quick onset of effect. Dexketoprofen trometamol is more influential and its gastrointestinal adverse effects is less than compared with ketoprofen caused. Dexketoprofen trometamol administration was found to be highly effective in the treatment of moderate to severe pain.

It has been used in dysmenorrhea, osteoarthritis, and dental or orthopedic surgery and found to be highly effective.

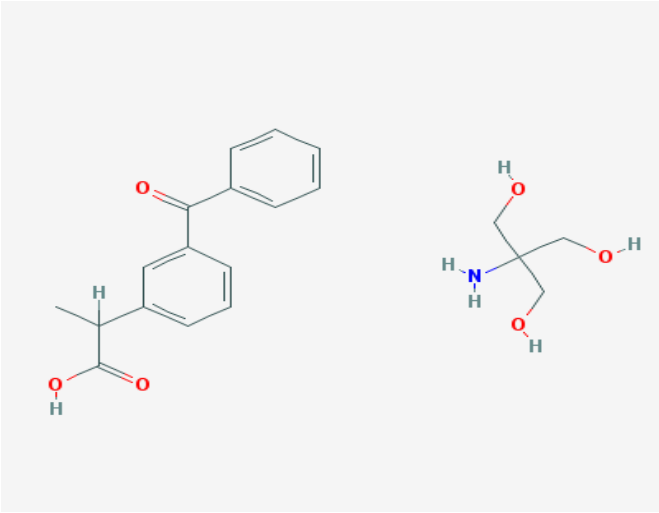
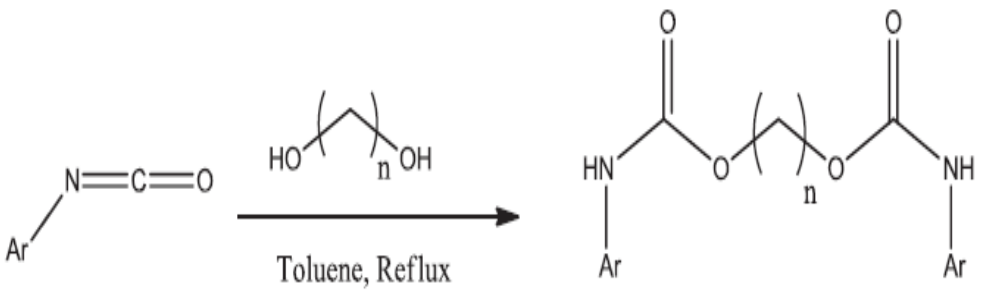


Figure 3.5. Dexketoprofen trometamol (Anıl et al., 2016).

3.2 The general procedure

3.2.1 The Synthesis of 1,3-bis[N-(*p*-aryl)-carbamoyloxy]propanes (3-Oct, 3-OBu, 5-OBu, 3-OHex, 5-OHex)

Bis-(*p*-aryl) carbamates **(3-Oct, 3-OBu, 5-OBu, 3-OHex, 5-OHex)** synthesized by the reaction of 1,3-propanediol or 1,5-pentanediol with suitable *p*-aryl isocyanates in 79-97% yields (Scheme 3.1).



Scheme 3.1. Synthesis of the compounds.

3.2.2 1,5-Bis[N-(*p*-butoxyphenyl)-carbamoyloxy]pentane (5-OBu)

1,5-Bis[N-(p-butoxyphenyl)-carbamoyloxy]pentane (5-OBu) was prepared according to the general procedure using 1.0 g (5.23 mmol) *p*-butoxyphenyl isocyanate, 0.23 g (2.18 mmol) 1,5-pentanediol.

White solid; yield (pure): 0.89 g (83%); mp 152-153 ºC.

^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 0.86 (t, J=7.2 Hz, 6H), 1.35- 1.49 (m, 6H), 1.61-1.70 (m, 8H), 3.89 (t, J=6 Hz, 4H), 4.06 (t, J=6.6 Hz, 4H), 6.83 (d, J=9.0 Hz, 4H), 7.32 (d, J=9.0 Hz, 4H), 9.36 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ, ppm: 154.6, 154.2, 132.6, 120.2, 114.96, 67.7, 64.3, 31.3, 28.7, 22.5, 19.2, 14.2. IR (neat): ν, cm^{-1}: 3335, 3081, 2956, 2941, 2869 and 1697. Anal. Calcd for $C_{27}H_{38}N_2O_6$: C, 66.64; H, 7.87; N, 5.76. Found: C, 66.34; H, 7.68; N, 5.87.

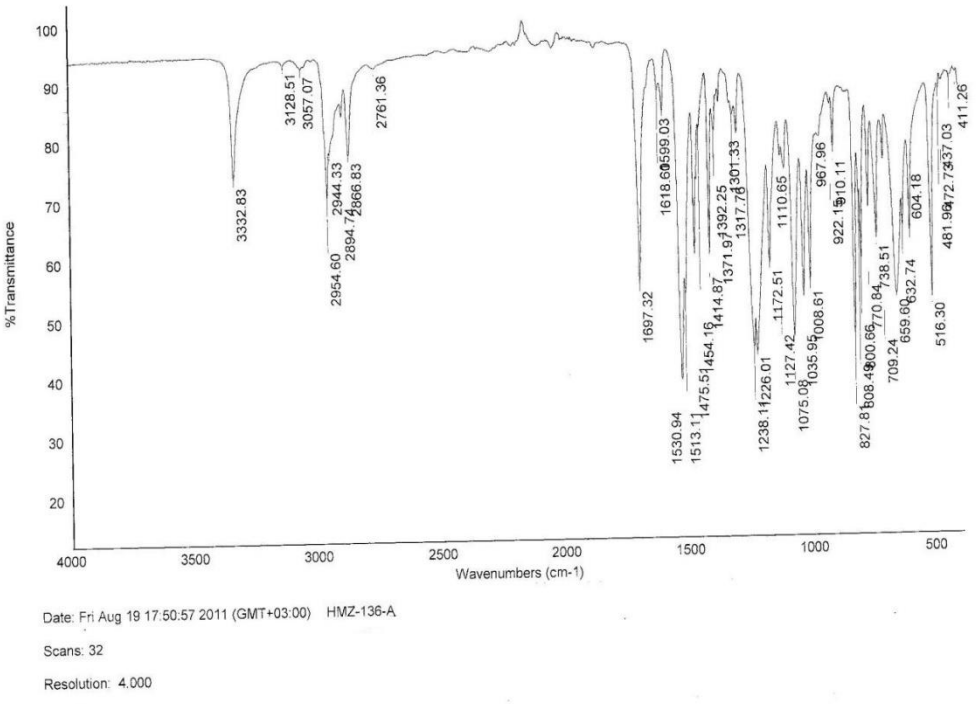


Figure 3.6. IR spectrum of **5-OBu** compound

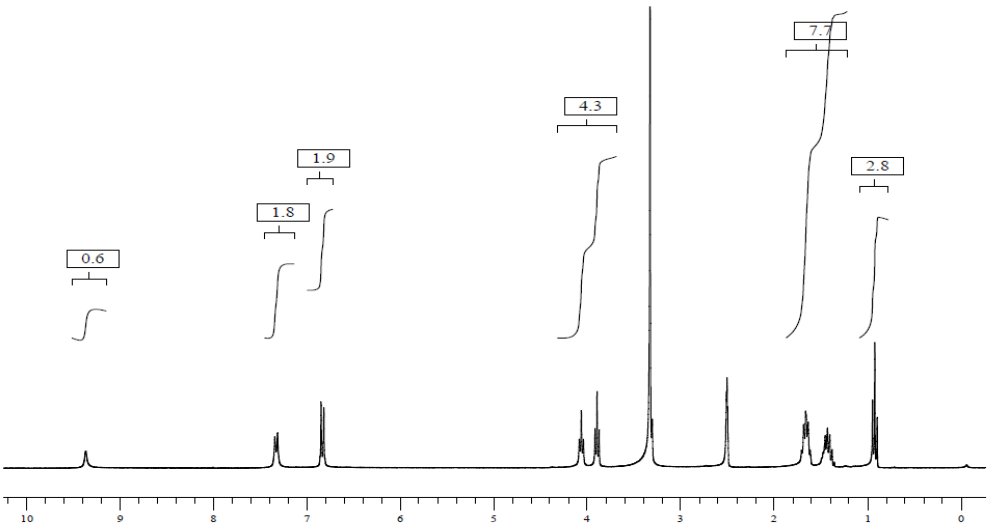


Figure 3.7. 300 MHz ^{1}H NMR spectrum of **5-OBu** compound (solvent= DMSO-d_6).

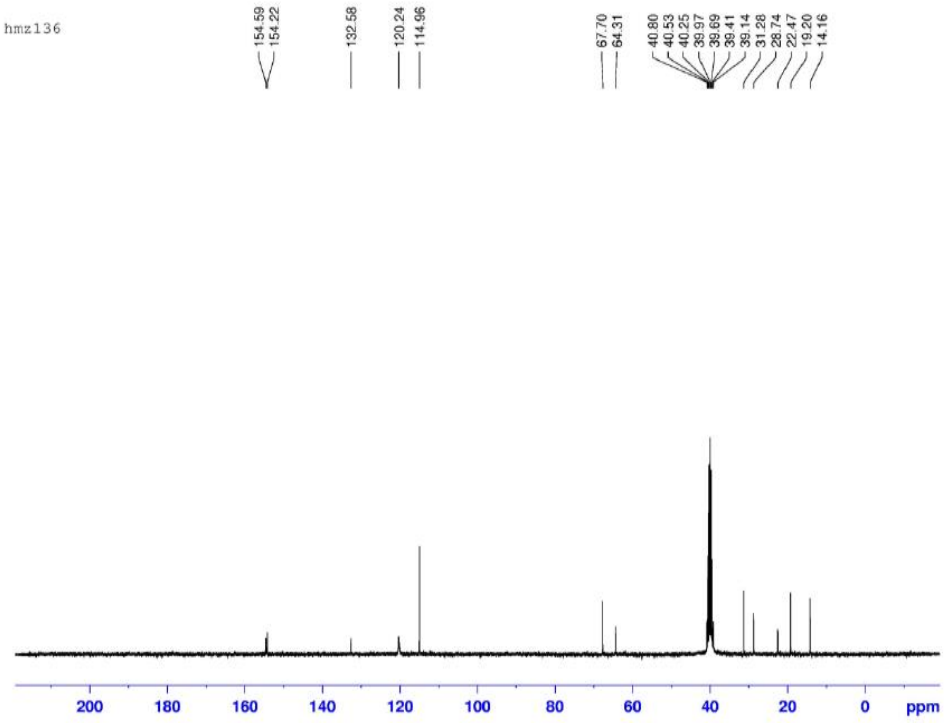


Figure 3.8. 75 MHz ^{13}C NMR spectrum of **5-OBu** compound (solvent= DMSO-d_6).

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3.2.3 1,3-Bis[N-(*p*-butoxyphenyl)-carbomoyloxy]propane (3-OBu)

1,3-Bis[N-(*p*-butoxyphenyl)-carbamoyloxy]propane (**3-OBu**) was prepared according to the general procedure using 1.0 g (5.23 mmol) *p*-butoxyphenyl isocyanate, 0.17 g (2.18 mmol) 1,3-propanediol.

White solid; yield (pure): 0.79 g (82%); mp 157-158 ºC.

^{1}H NMR (300 MHz, DMSO-d_6) δ, ppm: 0.92 (t, J=7.2 Hz, 6H),1.35-1.48 (m, 4H),1.61-1.71 (m, 4H),1.93-2.00 (m, 2H), 3.90 (t, J=6.3 Hz, 4H), 4.16 (t, J=6.0 Hz, 4H), 6.83 (d, J=9.0 Hz,4H), 7.33 (d, J=9.0 Hz, 4H), 9.42 (s, 2H). ^{13}C NMR (75 MHz, DMSOd_6) δ, ppm: 154.7, 154.1, 132.5, 120.3, 114.97, 67.7, 61.4, 31.3, 28.9, 19.2, 14.2. IR (neat): ν, cm^{-1}: 3320, 3056, 2958, 2932, 2873, 1698. Anal. Calcd for $C_{25}H_{34}N_2O_6$: C, 65.48; H, 7.47; N, 6.11. Found: C, 65.28; H, 7.39; N, 6.45.

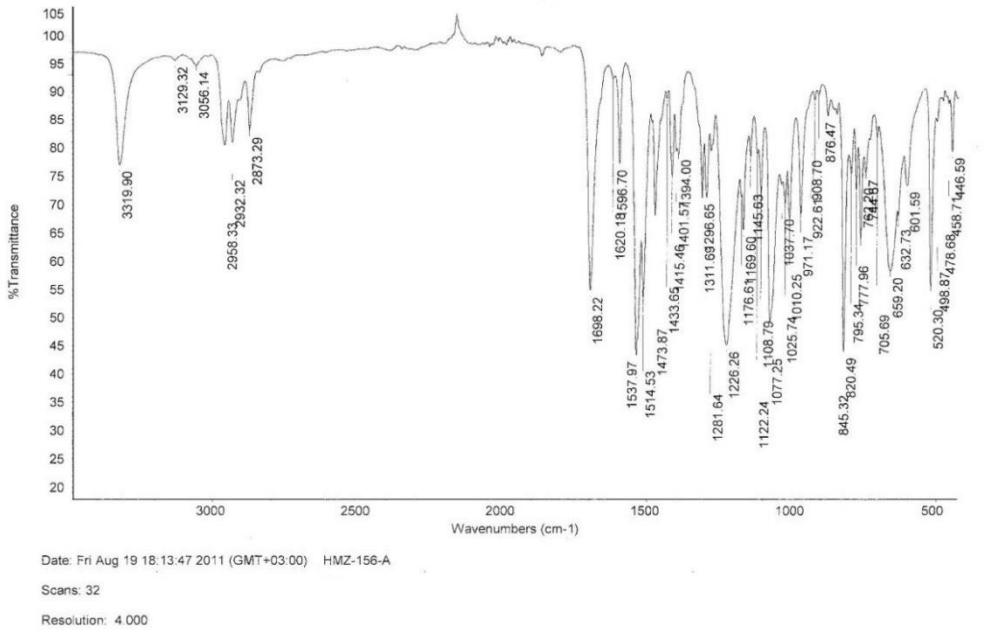

Figure 3.9. IR spectrum of **3-OBu** compound

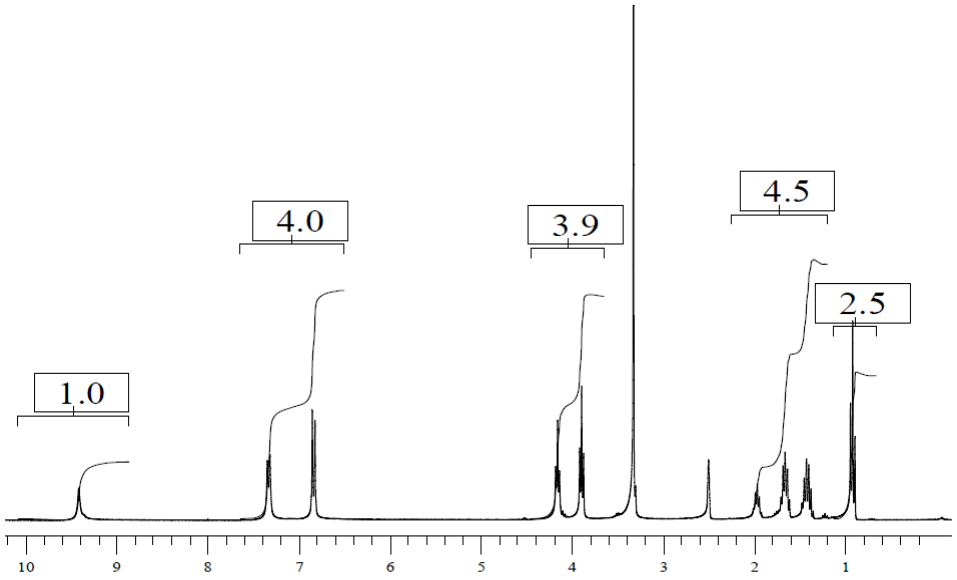

Figure 3.10. 300 MHz ^{1}H NMR spectrum of **3-OBu** compound (solvent= DMSO-d_6).

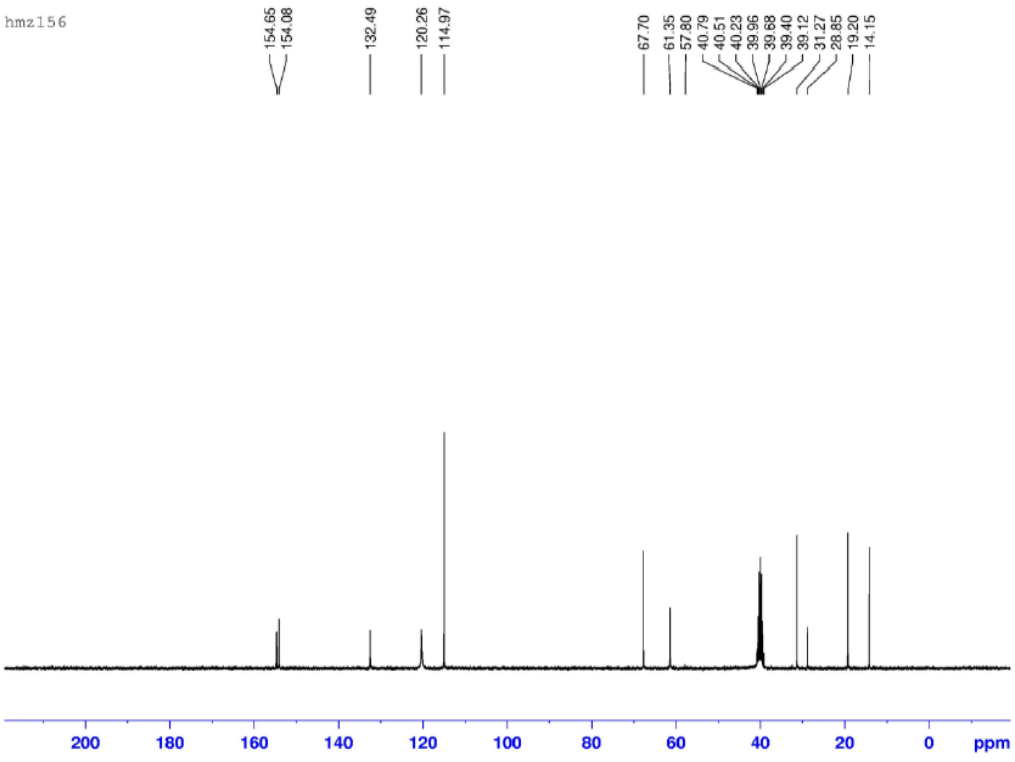

Figure 3.11. 75 MHz ^{13}C NMR spectrum of **3-OBu** compound (solvent= DMSO-d_6).

3.2.4 1,5-Bis[N-(*p*-hexyloxyphenyl)-carbamoyloxy]pentane (5-OHex)

Compound **5-OHex** was prepared according to the general procedure using 0.75 g (3.42 mmol) *p*-hexyloxyphenyl isocyanate, 0.15 g (1.43 mmol) 1,5-pentanediol.

White solid; yield (pure): 0.74 g (96%); Mp 150-151 ^{0}C.

^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 0.85 (t, *J*=7.2 Hz, 6H), 1.25-1.29 (br m, 6H),1.33-1.43 (m, 8H),1.59-1.68 (m, 8H), 3.86 (t, *J*=6.8 Hz, 4H), 4.04 (t, *J*=6.8 Hz, 4H), 6.81 (d, *J*= 8.8 Hz, 4H), 7.30 (d, *J*= 8.8 Hz, 4H), 9.36 (s, 2H).^{13}C NMR (100 MHz, DMSO-d_6) δ, ppm:154.5, 154.2, 132.6, 120.1, 114.9, 67.97, 64.3, 32.9, 31.5, 29.2, 28.7, 25.6, 22.5,14.4.IR (KBr pellet): ν, cm^{-1}: 3333, 3055, 2951, 2939, 2867, 1697.Anal. Calcd for $C_{31}H_{46}N_2O_6$: C, 68.61; H, 8.54; N, 5.16. Found: C, 68.44; H, 8.45; N, 5.32.

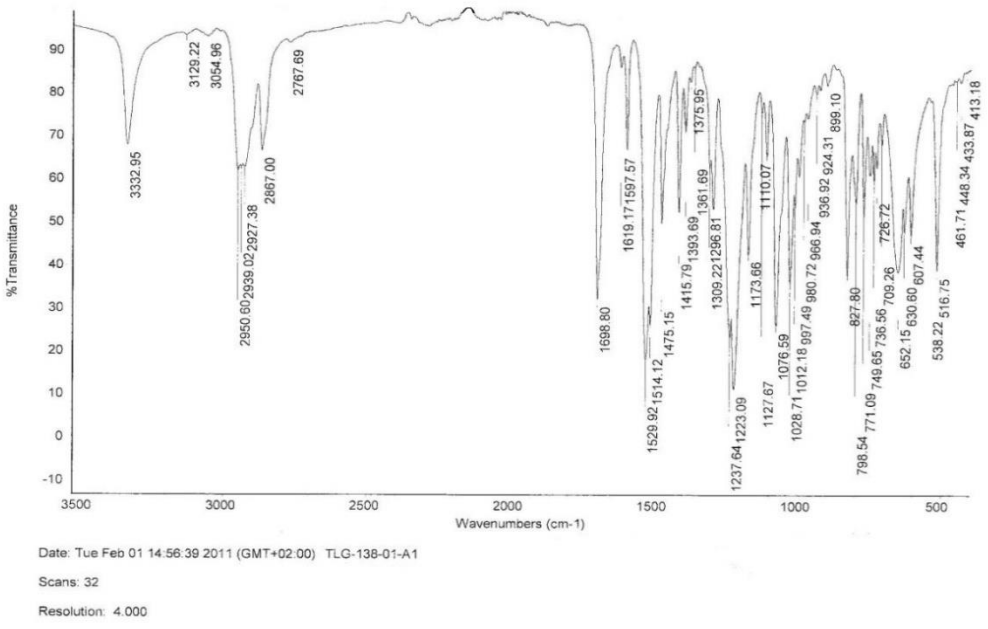

Figure 3.12. IR spectrum of **5-OHex**

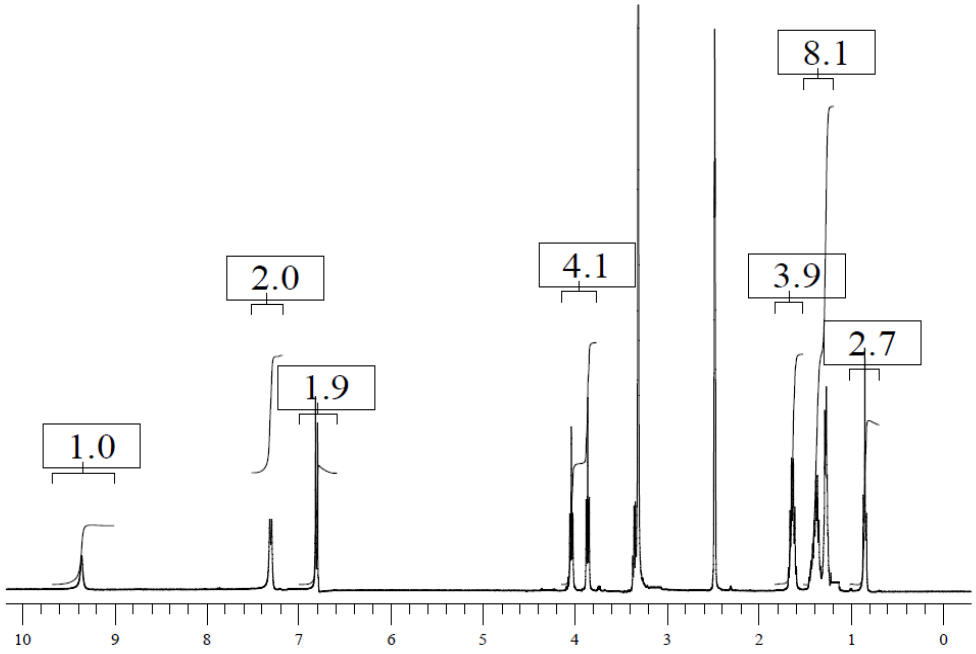

Figure 3.13. 400 MHz ^{1}H NMR spectrum of **5-OHex** (solvent= DMSO-d_6).

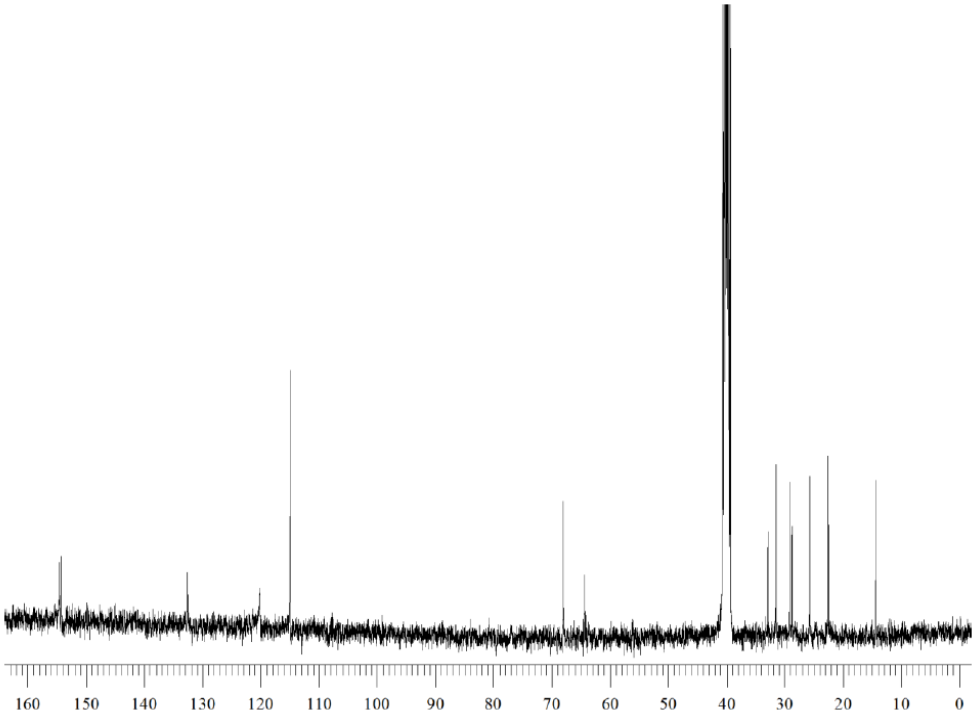

Figure 3.14. 100 MHz ^{13}C NMR spectrum of **5-OHex** (solvent= DMSO-d_6).

3.1.1. 1,3-Bis[N-(*p*-hexyloxyphenyl)-carbamoyloxy]propane (3-OHex)

Compound **3-OHex** was prepared according to the general procedure using 0.75 g (3.42 mmol) *p*-hexyloxyphenyl isocyanate, 0.11 g (1.43 mmol) 1,3-propanediol.

White solid; yield (pure): 0.71 g (97%); Mp 153-155 ^{0}C.

^{1}H NMR (400 MHz, DMSO-d_6) δ, ppm: 0.85 (t, *J*=6.0 Hz, 6H), 1.27 (br m, 8H),1.37 (br m, 4H),1.61-1.68 (m, 6H), 3.86 (t, *J*=6.4 Hz, 4H), 4.14 (t, *J*=6.0 Hz, 4H), 6.81 (d, *J*= 9.2 Hz, 4H), 7.31 (d, *J*= 5.6 Hz, 4H), 9.42 (s, 2H).^{13}C NMR (100 MHz, DMSO-d_6) δ, ppm: 154.6, 154.0, 132.5, 120.2, 114.9, 67.97, 61.3, 31.5, 29.2, 25.6, 22.5,14.4.IR (neat): ν, cm^{-1}: 3319, 3056, 2954, 2929, 2870, 1694.Anal. Calcd for $C_{29}H_{42}N_2O_6$: C, 67.68; H, 8.23; N, 5.44. Found: C, 67.28; H, 8.09; N, 5.51.

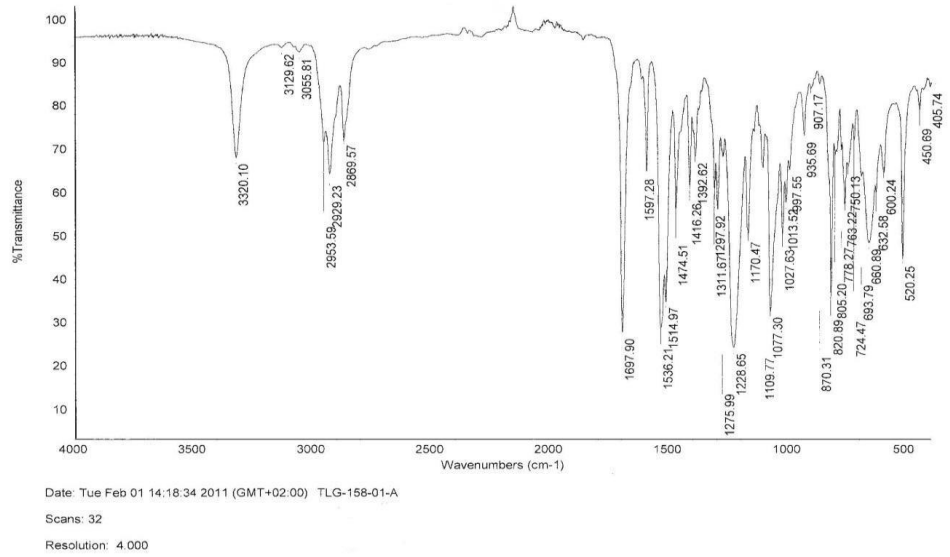

Figure 3.15. IR spectrum of **3-OHex**

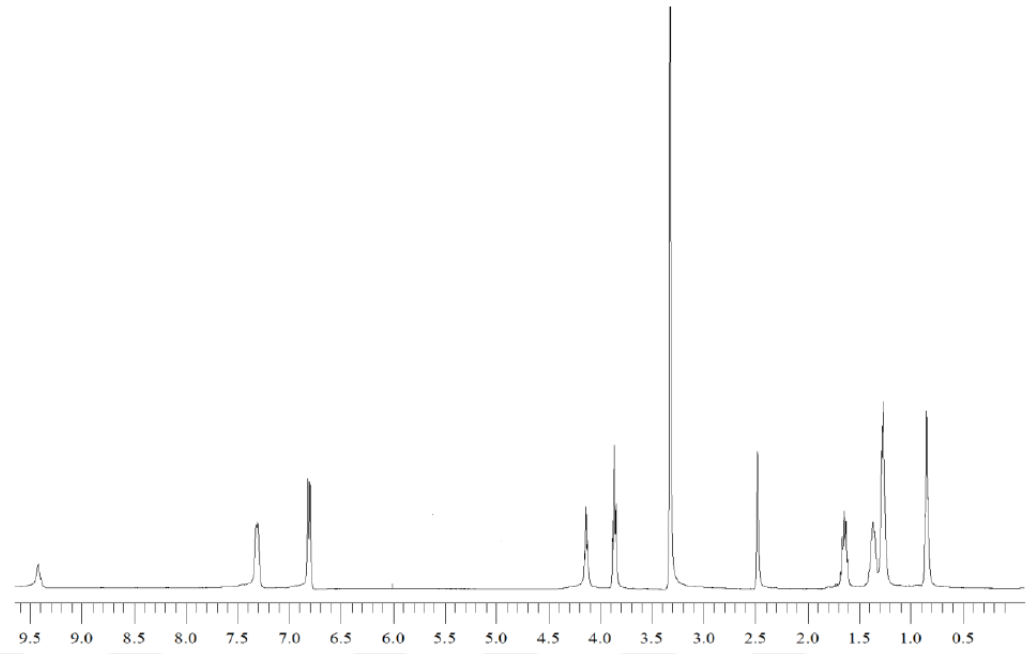

Figure 3.16. 400 MHz ^{1}H NMR spectrum of **3-OHex** (solvent= DMSO-d_6).

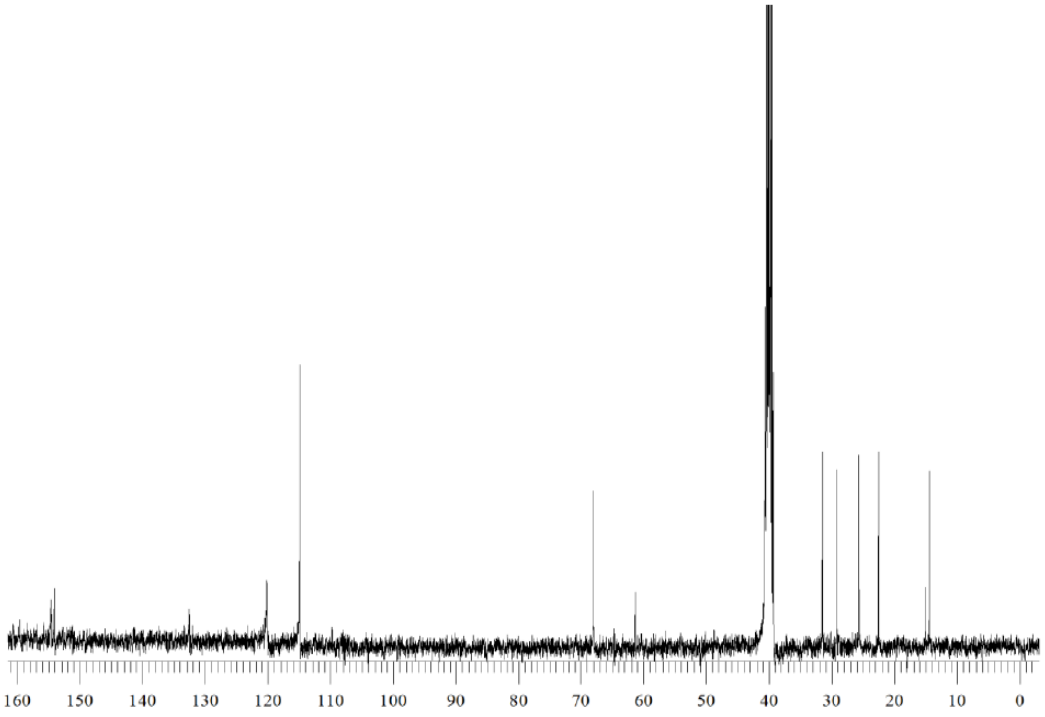

Figure 3.17. 100 MHz ^{13}C NMR spectrum of **3-OHex** (solvent= DMSO-d_6).

3.2.5 1,3-Bis[N-(*p*-octylphenyl)-carbomoyloxy]propane (3-Oct)

Compound 1,3-Bis[N-(*p*-octylphenyl)-carbomoyloxy]propane **(3-Oct)** was prepared according to the general procedure using 0.73 g (3.42 mmol) *p*- octylphenyl isocyanate, 0.10 g (1.43 mmol) 1,3-propanedioland 10 ml toluene.

White solid; yield (pure): 0.55 g (79%); Mp 123-125^{0}C.

^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.89 (t, 6 H, CH_3), 1.30 (br m, 20 H, CH_2),1.59 (m, 4 H, CH_2),2.08 (m, 2 H, CH_2), 2.57 (t, 4 H, CH_2), 4.33 (t, 4 H, OCH_2), 6.55 (s, 2 H, NH), 7.13 (d, *J*= 8.5 Hz, 4 H, CH), 7.28 (d, *J*= 8.5 Hz, 4 H, CH), ^{13}C NMR (75 MHz, $CDCl_3$): δ= 153.7, 138.3, 135.3, 128.9, 118.9, 61.8, 35.3, 31.9, 31.6, 31.4, 29.5, 29.3, 28.6, 22.7, 14.1.IR (pure): 3312, 3040, 2957, 2924, 2853, 1697 cm^{-1}.

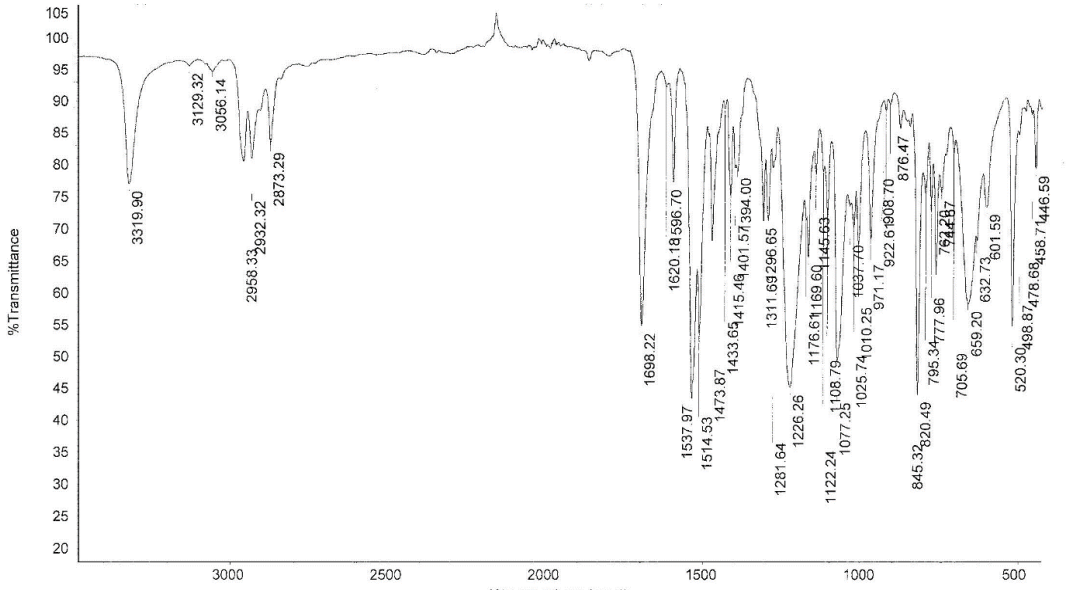

Figure 3.18. 3-Oct compound IR spectrum

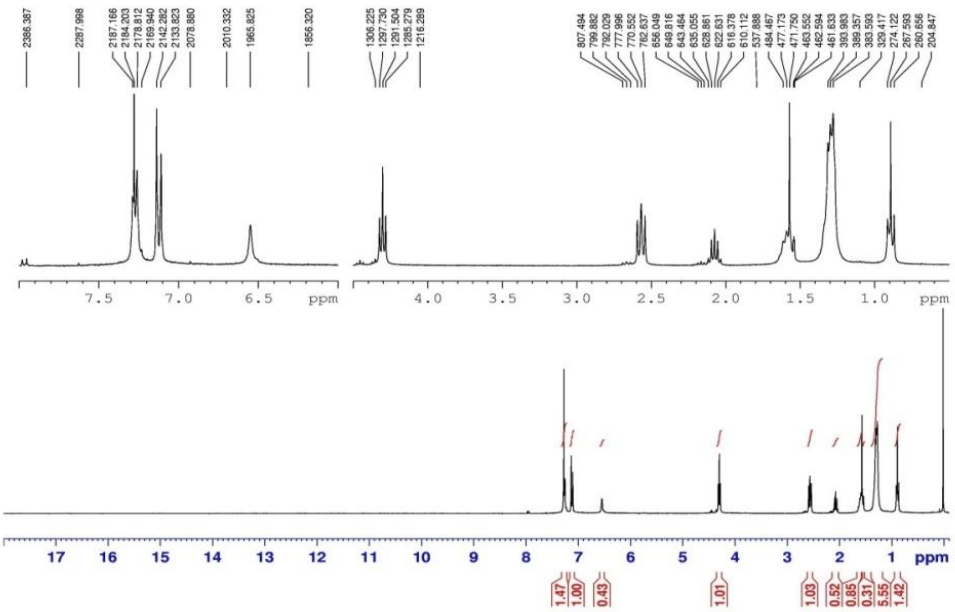

Figure 3.19. 400 MHz ^{1}H NMR spectrum of **3-Oct** (solvent= $CDCl_3$).

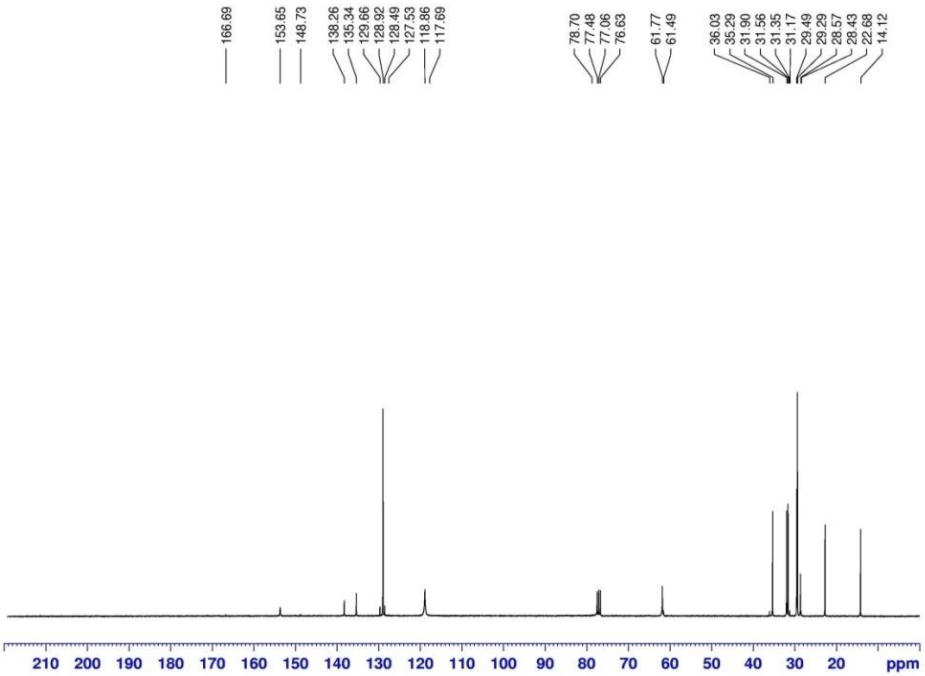

Figure 3.20. 100 MHz ^{13}C NMR spectrum of **3-Oct** (solvent= $CDCl_3$).

3.3 Gel preparation

A weighted amount of gelator and a measured volume of organic solvent were transferred into a vial whose diameter is 15 mm with a screw cap and the system was heated over hot plate until the solid was completely dissolved in organic solvent. The resulting solution was left to cool to room temperature in air for one day then the gelation was tested by test tube inversion method.

3.3.1 Test tube inversion (inverse flow) method and determination of minimum gelation concentration (mgc)

Mixtures of each derivative in organic solvents were heated until the solid was completely dissolved. Then the solution was slowly allowed to cool at room temperature and gelation was visually observed. It is considered that gelation was taken place only with a homogeneous solution without any gravitational flow. The minimum concentration of the homogeneous gel sample without gravitational flow is known as minimum gelation concentration (mgc) (Demir-Ordu, et al, 2015).

4. RESULT AND DISCUSSIONS

4.1 The Synthesis of 1,3-bis[N-(*p*-aryl)-carbamoyloxy]propanes (3-Oct, 3-OBu, 5-OBu, 3-OHex, 5-OHex)

The purpose of the present work is to use bis-carbamate derivativesin order to remove drugs from aqueous solutions. In this study, *p*-octyl, *p*-butoxy and *p*-hexyloxy bis-carbamate derivatives were used for this purpose. Because of this the first step is to synthesize these derivatives.

Bis-(*p*-aryl) carbamates **(3-Oct, 3-OBu, 5-OBu, 3-OHex, 5-OHex)** were synthesized by the reaction of 1,3-propanediol or 1,5-pentanediol with suitable *p*-aryl isocyanates in 79-97% yields (Scheme 3.1.)(Table 4.1.).

Table 4.1. The yields of the synthesized Bis-(*p*-aryl)-carbamates

Compound	Z	n	Yield (g / %)		Melting point (°C)
3-Oct	Octyl	3	0.55	79	123-125
3-OBu	Butoxy	3	0.79	82	157-158
5-OBu	Butoxy	5	0.89	83	152-153
3-OHex	Hexyloxy	3	0.71	97	153-155
5-OHex	Hexyloxy	5	0.74	96	150-151

4.2. Structure Elucidation of Bis-carbamateDerivatives by IR and NMR Spectroscopy

The structures of the compounds **(3-Oct, 3-OBu, 5-OBu, 3-OHex, 5-OHex)** were characterized by IR, ^{1}H NMR and^{13}C NMR spectroscopy. IR spectra of these compounds exhibited common characteristic absorption bands at 3312-3333 cm^{-1}(NH) and 1639-1627 cm^{-1}(Carbonyl) for carbamate functionality. The IR spectrum of compound **3-OBu** was shown as an example in Figure 4.1, the IR data for all compounds was tabulated in Table 4.2.

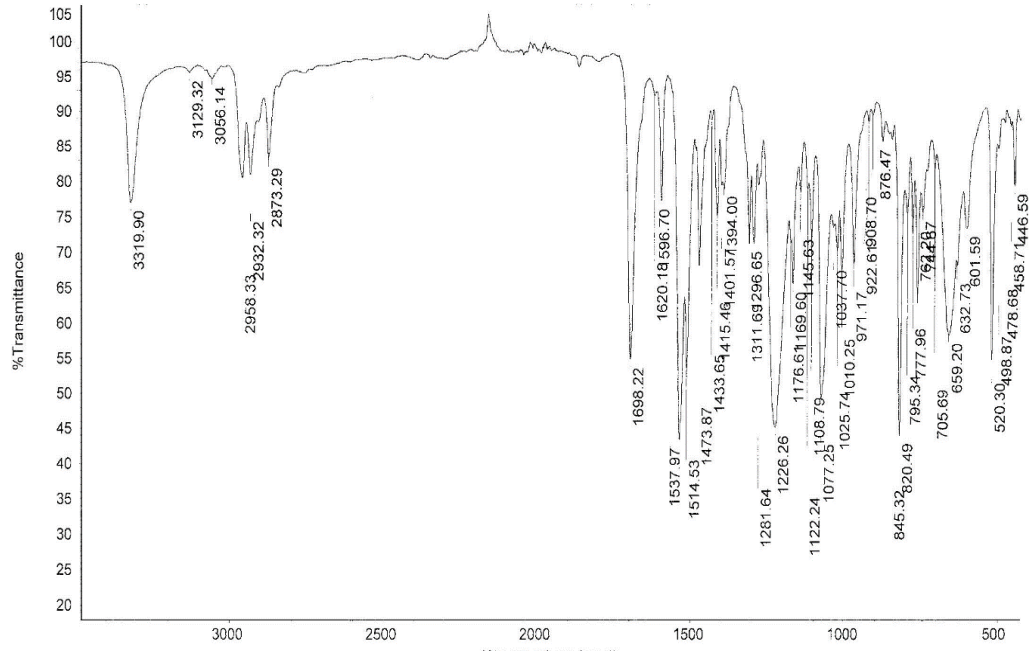

Figure 4.1. IR spectrum of compound **3-OBu**

Table 4.2. IR data for the compounds **3-Oct, 3-OBu, 5-OBu, 3-OHex** and **5-OHex**

Compound	N-H Stretching	Ar-H	C-H Stretching	Carbonyl
3-Oct	3312	3040	2957-2853	1697
3-OBu	3320	3056	2958-2873	1698
5-OBu	3335	3081	2956-2869	1697
3-OHex	3319	3056	2954-2870	1694
5-OHex	3333	3055	2951-2867	1697

The structures of the compounds were also characterized by NMR spectroscopy. In this study, all compounds had a *p*-substituted aromatic ring, a spacer with three or five methylene units and carbamate functionality in common (Table4.1). For all compounds, the NH proton signals of the carbamate unit wereobserved at 9.36-9.42 ppm as broad singlets in DMSO-d_6 and 6.55 ppm in $CDCl_3$.The ^{1}H NMR spectrum of compound **5-OBu** was chosen as an example and given in Figure 4.2. The detailed ^{1}H and ^{13}C NMR data were given in the experimental part for each studied compound.

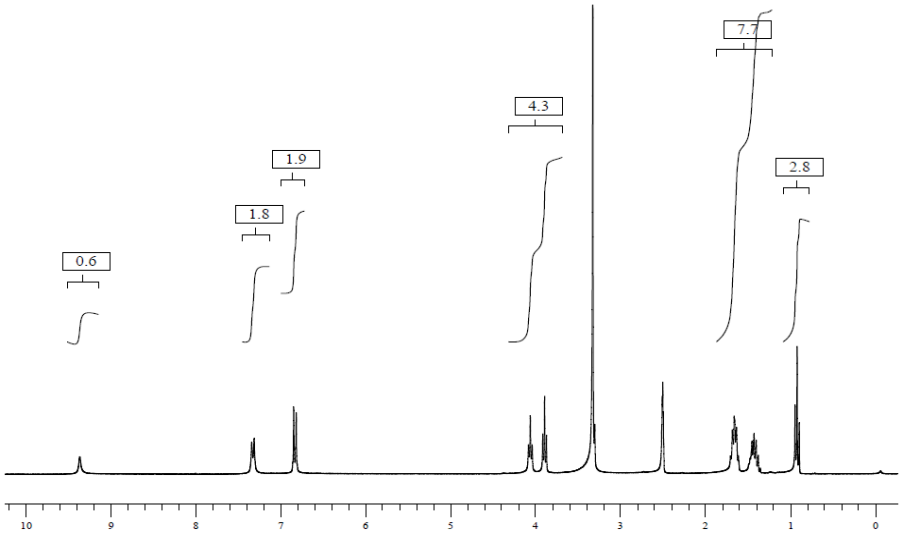

Figure 4.2. 300 MHz ^{1}H NMR spectrum of **5-OBu** (solvent= DMSO-d_6).

4.3. Gelation properties of 3-Oct, 3-OBu, 5-OBu, 3-OHex, 5-OHex derivatives in organic solvents

In a previous work it was found that the lenght of the spacer was effective on gelation (Demir-Ordu, 2015). While odd number of methylene units resulted in gel formation, the even-numbered methylene spacer did not form gel structure for *p*-alkoxy substituted bis-carbamate derivatives. For alkyl substituted compounds, decreasing the length gave rise to gel formation. Gelation of *p*-butoxy and *p*-hexyloxy derivatives was achieved with lower mgc values. Gelation abilities of the compounds in tested organic solvents were given in Table 4.3. In addition to this SEM images represented that **3-OBu**, **5-OBu**, **3-OHex**, **5-OHex** derivatives formed 3D network structures with fibers (Figure 2.2-2.6). Because of these results **3-Oct**, **3-OBu**, **5-OBu**, **3-OHex**, **5-OHex** derivatives were chosen as candidates for drug removal experiments.

Table 4.3. Bis-carbamate compounds gelation behavior in different solvents (n-Butyl palmitate (NBP), Ethyl laurate (EL), Isopropyl myristate (IPM))

			SOLVENT						
Compound No	Ar	n	Toluene	NBP	EL	IPM	Olive oil	Corn oil	Sunflower oil
3-Oct	*Octylphenyl*	3	ppt	G(11)	soln	soln	G(34)	G(59)	G(43)
3-OBu	*Butoxyphenyl*	3	G(20)	G(17)	G(13)	G(13)	G(8)	G(10)	G(12)
5-OBu	*Butoxyphenyl*	5	G(25)	G(16)	G(18)	G(14)	G(11)	G(12)	G(14)
3-OHex	*Hexyloxyphenyl*	3	G(28)	G(14)	G(9)	G(7.5)	G(8.5)	G(8.5)	G(13)
5-OHex	*Hexyloxyphenyl*	5	G(22)	G(2)	G(6)	G(3.5)	G(4.5)	G(11)	G(9.5)

[a] G: gel (Minimum gelator concentration (mg ml^{-1}), Ppt: precipitate, ins: insoluble

4.4. Drug Removal studies by gels

4.4.1. Drug Removal studies by dry gels (Xerogels)

Drug removal studies were first tried by dry gels (xerogels) obtained by evaporation of the gelation solvent from the wet gels at room temperature. To the aqueous drug solution, a weighed amount of xerogel was added. After gentle shaking the solution was stayed at room temperature and samples were taken at certain time intervals for UV experiment.

4.4.1.1. Removal of paracetamol

Removal of paracetamol was first tried by using 3-Oct xerogels obtained from evaporation of CH_2Cl_2, toluene and xylene from the wet gels at room temperature. As can be seen in Tables 4.4-4.6 and Figures 4.3-4.5, no significant absorbance changes were obtained.

Table 4.4. Absorbance changes for the removal of paracetamol by 21.1 mg **3-Oct** CH_2Cl_2-xerogel

λ Max	Time	Max. Absorbance
257 nm	First Day*	0,415
256 nm	First Day**	0,455
246 nm	1 Day Later**	0,419
242 nm	15 Day Later**	0,443
242 nm	35 Day Later**	0,423
*: standart solution **: after addition of the xerogel		

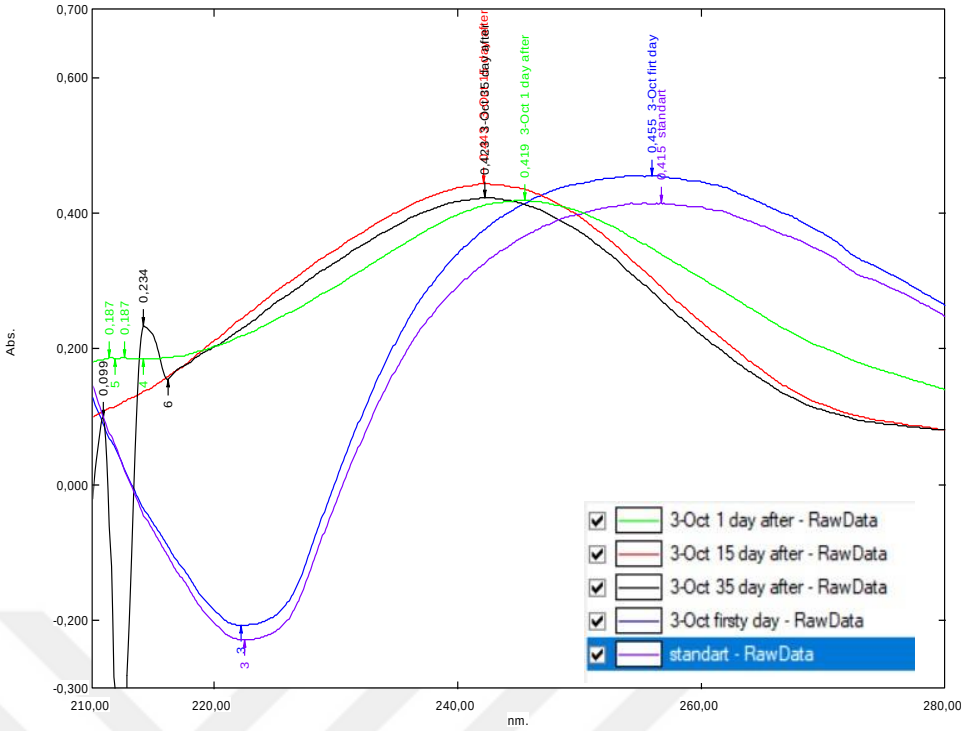

Figure 4.3. The UV spectra for paracetamol removal by 21.1 mg **3-Oct** CH_2Cl_2-xerogel

Table 4.5. Absorbance changes for the removal of paracetamol by 21.2 mg **3-Oct** toluene-xerogel

λ Max	Time	Max. Absorbance
257 nm	First Day*	0,415
256 nm	First Day**	0,436
255 nm	1 Day Later**	0,439
245 nm	15 Day Later**	0,400
243 nm	35 Day Later**	0,406
*: standart solution **: after addition of the xerogel		

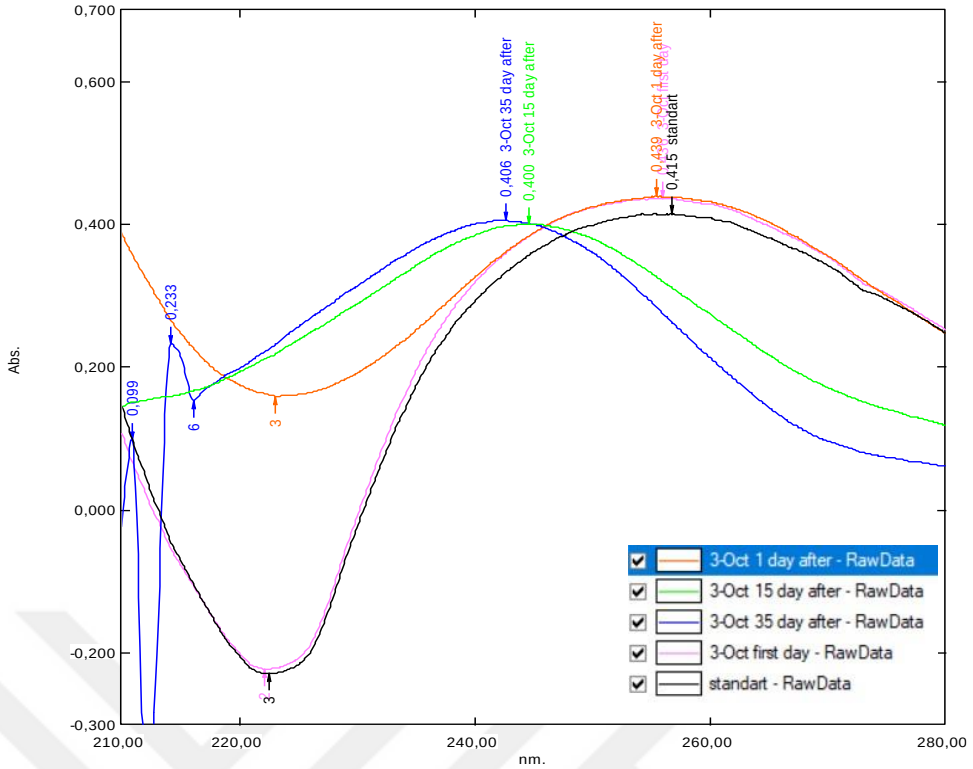

Figure 4.4. The UV spectra for paracetamol removal by 21.2 mg **3-Oct** toluene xerogel

Table 4.6. Absorbance changes for the removal of paracetamol by 21.1 mg **3-Oct** xylene-xerogel

λ Max	Time	Max. Absorbance
257 nm	First Day*	0,415
255 nm	First Day**	0,445
247 nm	1 Day Later**	0,400
241 nm	15 Day Later**	0,414
243 nm	35 Day Later**	0,432
*: standart solution **: after addition of the xerogel		

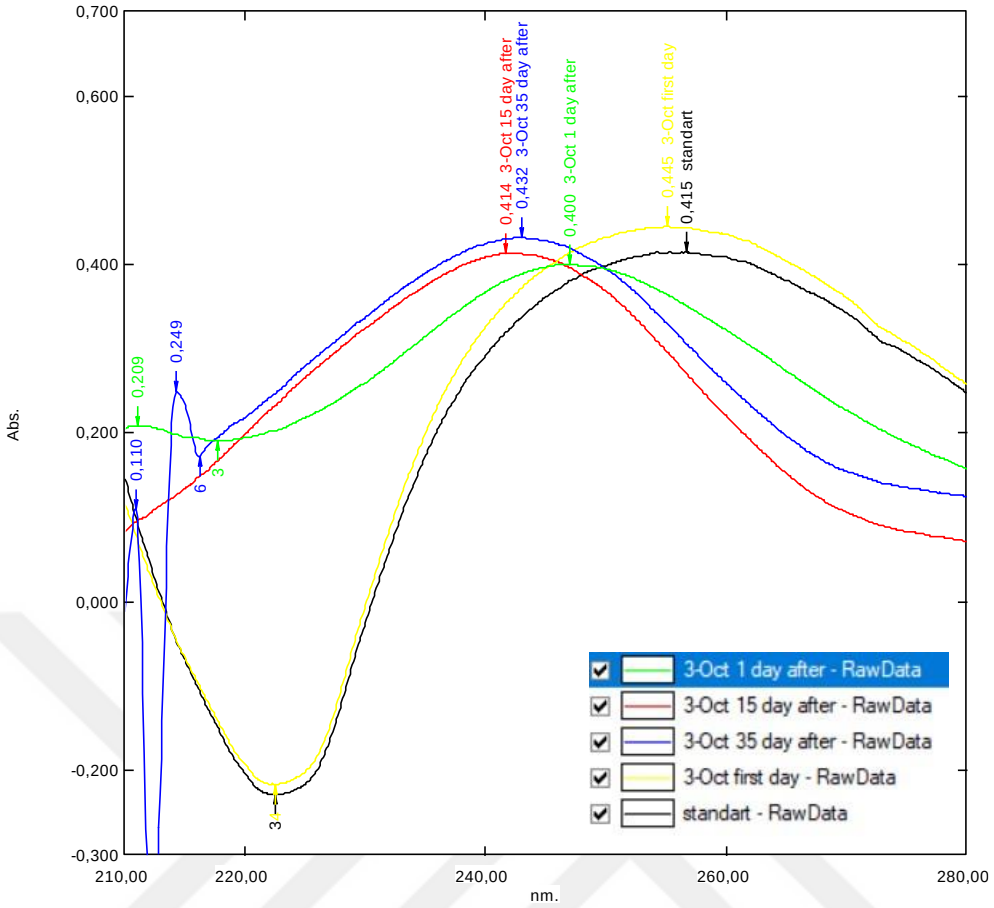

Figure 4.5. The UV spectra for paracetamol removal by 21.1 mg **3-Oct** xylene xerogel

4.4.1.2.Removal of ibuprofen

Removal of ibuprofen was only tested by **3-OBu** toluene xerogel. Due to the unstability of the solution at room temperature, the solution could only be analyzed after 2 hours. Almost no change was observed as can be seen in Figure 4.6. and Table 4.7.

Table 4.7. Absorbance changes for the removal of ibuprofen by 25,1 mg **3-OBu** toluene xerogel

λ Max	Time, hr	Maximum Absorbance
221 nm	0*	0,414
221 nm	2**	0,408
*: standart solution **: after addition of the xerogel		

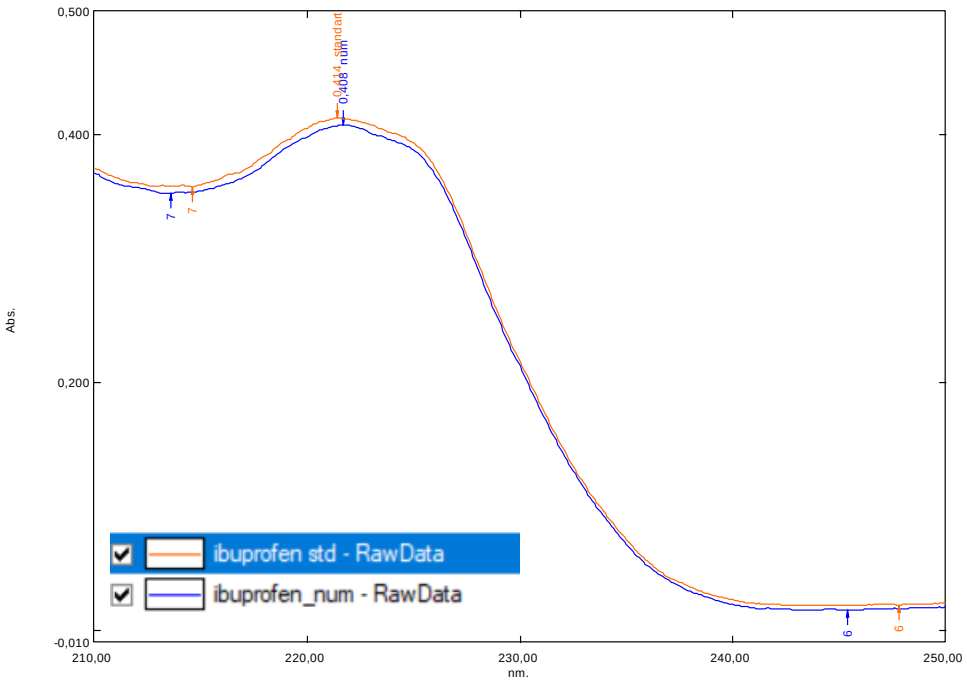

Figure 4.6. The UV spectra for ibuprofen removal by 25,1 mg **3-OBu** toluene xerogel

4.4.1.3.Removal of Ciprofloxacin HCl

Removal of Ciprofloxacin HCl was only tested by **3-OBu** toluene xerogel. Due to the unstability of the solution at room temperature, the solution could only be analyzed after 2 hours.Almost no change was observed as can be seen in Figure 4.7. and Table 4.8.

Table 4.8. Absorbance changes for the removal of Ciprofloxacin HCl by 25,0 mg **3-OBu** toluene xerogel

λ Max	Time, hr	Maximum Absorbance
277 nm	0*	0,702
277 nm	2**	0,707
*: standart solution **: after addition of the xerogel		

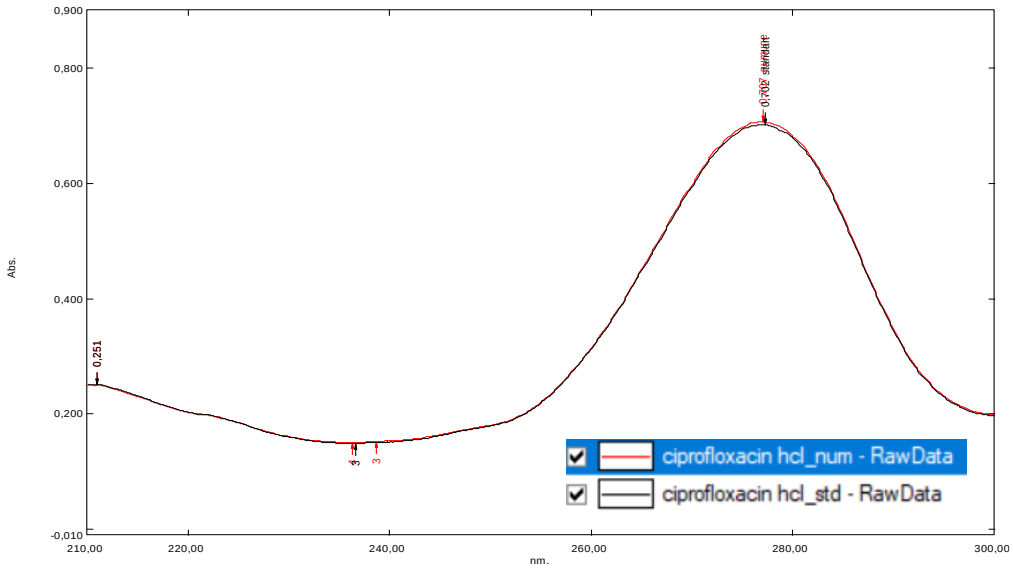

Figure 4.7. The UV spectra for Ciprofloxacin HCl removal by 25,0mg **3-OBu** toluene xerogel

4.4.1.4.Removal of Dexketoprofen Trometamol

As a result of instability of the drugs; Ciprofloxacin HCl and ibuprofen, the removal of Dexketoprofen Trometamol which is soluble in water without the need of acidic or basic solutions was chosen and tested using **3-OBu**, **3-OHex**, **5-OBu** and **5-OHex** toluene xerogels. No removal was observed as can be seen in Figures 4.8 - 4.11. and Tables 4.9-4.12.

Table 4.9. Absorbance changes for the removal of Dexketoprofen Trometamol by 25.5 mg **5-OBu** toluene xerogel

λ Max	Time	Maximum Absorbance
260 nm	First Day*	0,446
247 nm	First Day(2 hour)**	1,150
249 nm	7 Day Later**	0,624
241 nm	1 Month Later**	1,581
*: standart solution **: after addition of the xerogel		

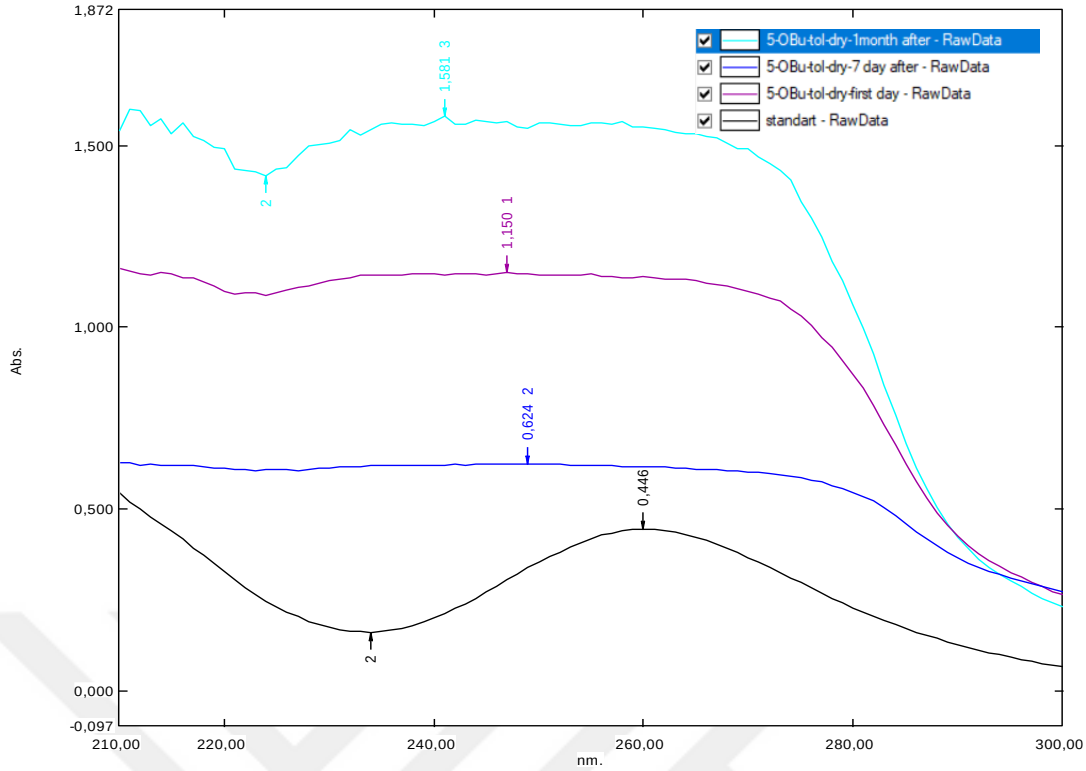

Figure 4.8. The UV spectra for Dexketoprofen Trometamol removal by 25.5 mg **5-OBu** toluene xerogel

Table 4.10. Absorbance changes for the removal of Dexketoprofen Trometamol by 25.1 mg **5-OHex** toluene xerogel

λ Max	Time	Maximum Absorbance
260 nm	First Day*	0,446
249 nm	First Day (2 hour)**	0,414
249 nm	7 Day Later**	1,601
248 nm	1 Month Later**	1,793
*: standart solution **: after addition of the xerogel		

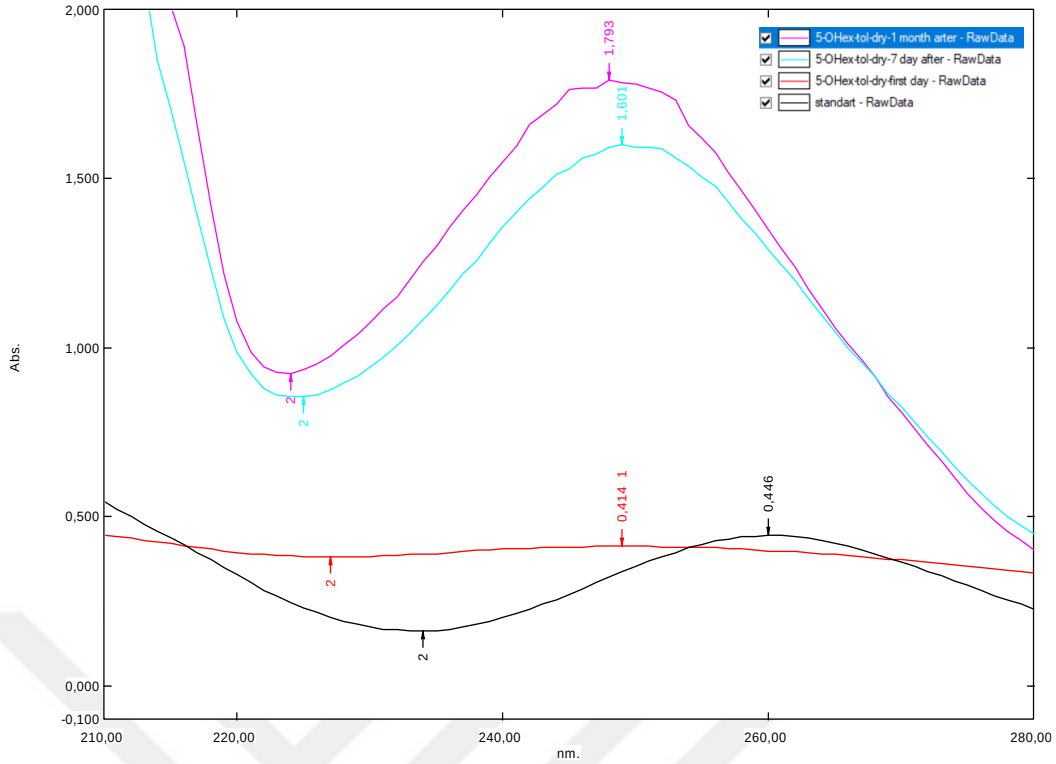

Figure 4.9. The UV spectra for Dexketoprofen Trometamol removal by 25.1 mg **5-OHex** toluene xerogel

Table 4.11. Absorbance changes for the removal of Dexketoprofen Trometamol by 25.0 mg **3-OBu** toluene xerogel

λ Max	Time	Maximum Absorbance
260 nm	First Day*	0,446
260 nm	First Day**	0,559
261 nm	7 Day Later**	0,583
259 nm	1 Month Later**	0,408
*: standart solution **: after addition of the xerogel		

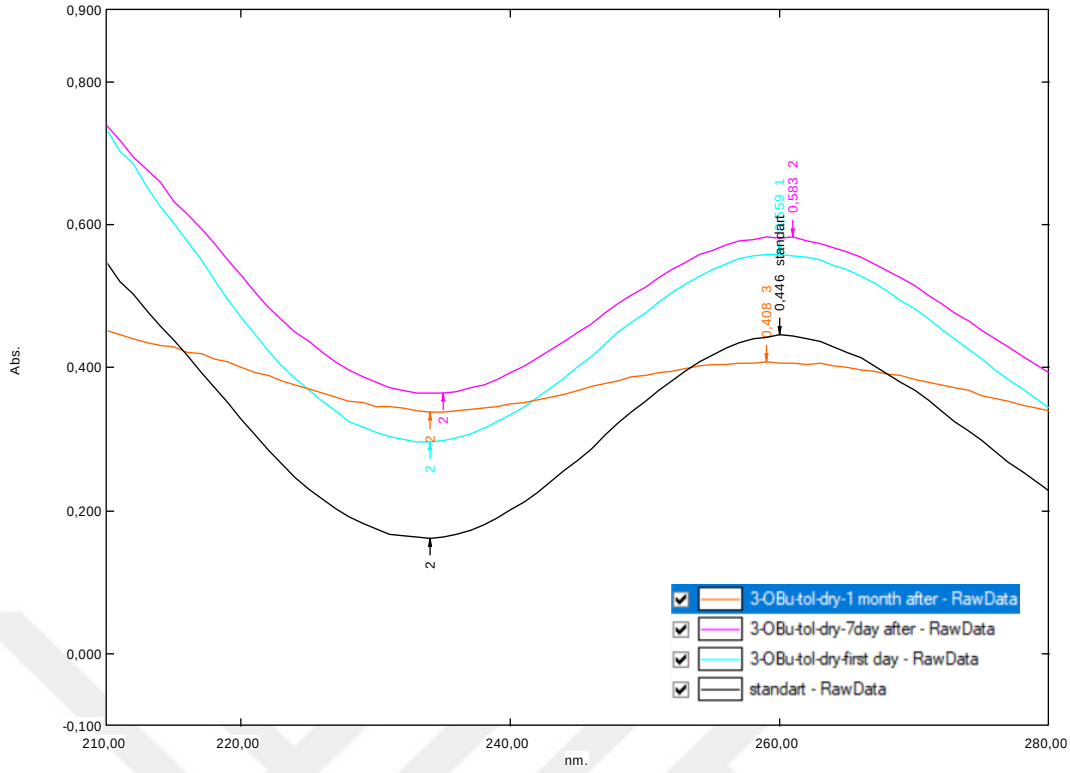

Figure 4.10. The UV spectra for Dexketoprofen Trometamol removal by 25.0 mg **3-OBu** toluene xerogel

Table 4.12. Absorbance changes for the removal of Dexketoprofen Trometamol by 25.0 mg **3-OHex** toluene xerogel

λ Max	Time	Maximum Absorbance
260 nm	First Day*	0,446
258 nm	First Day**	0,469
261 nm	7 Day Later**	0,618
261 nm	1 Month Later**	0,603
*: standart solution **: after addition of the xerogel		

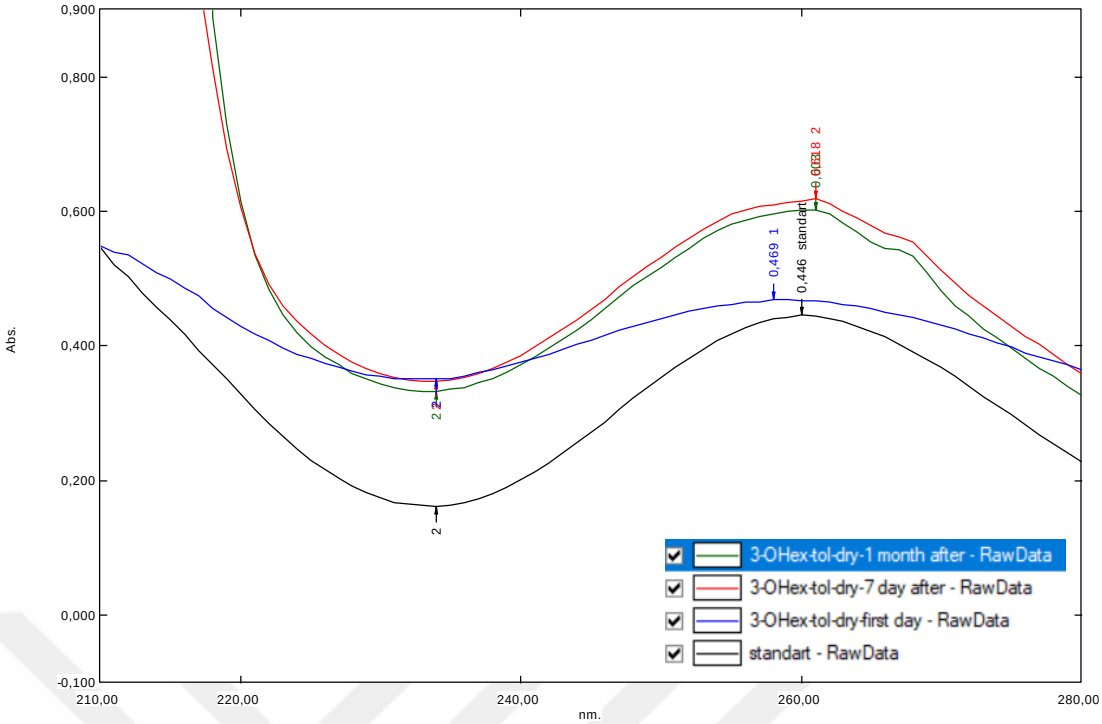

Figure 4.11. The UV spectra for Dexketoprofen Trometamol removal by 25.0 mg **3-OHex** toluene xerogel

4.4.2. Drug Removal studies by wet gels

In this study dried-gels (xerogels) were firstly used in drug removal experiments due to the 3D network or porous structure of the gels. However, the desired effect could not be obtained for the removal of Paracetamol, Ibuprofen, Ciprofloxacin HCl andDexketoprofen Trometamol. The reason might probably be the gel collapse during drying process and hence an insufficient pore size for sorption of the drug molecules. Because of this, secondly wet gels were tried for drug removal. Due to the fact that all *p*-alkoxy substituted organogelator molecules formed gel structure in toluene (Table4.3), the aquoeus drug solutions were added over the gels in a vial and shaked gently. After that the vial stayed at room temperature to obtain two separate layers before analysis. However, two distict layer formations could not be achived due to the limited miscibility of toluene and water, resulting in emulsion. Because of this result, ethyl laurate gels were chosen for drug removal experiments. In this study, Dexketoprofen Trometamol solution was the most stable drug to be analyzed at room temperature and for a long time. In addition to this, it is not soluble in ethyl laurate (Figure 4.12) thus eliminating the possibility for removal by extraction. As can be seen in Figure 4.12. no absorbance for Dexketoprofen Trometamol was obtained in ethyl laurate.

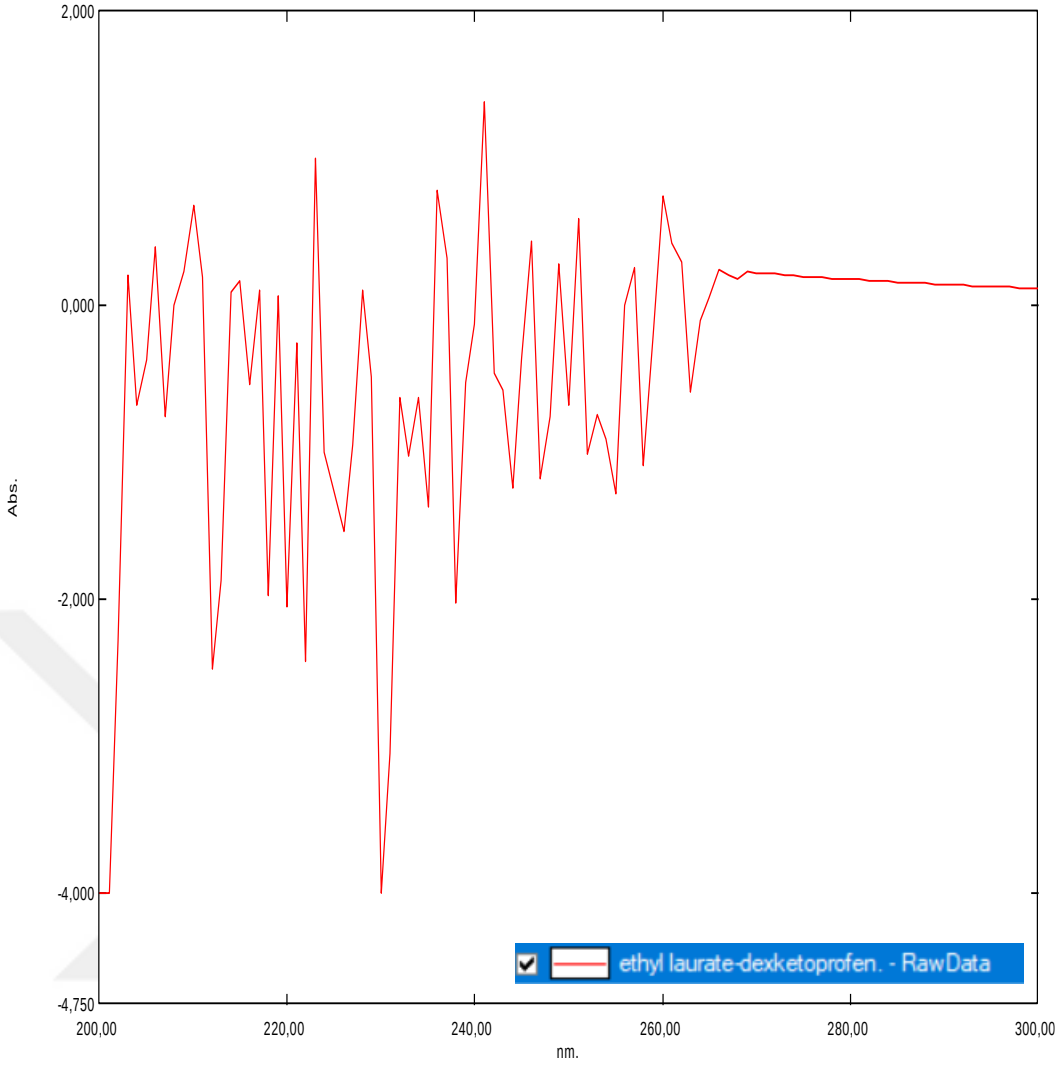

Figure 4.12. The UV spectrum of Dexketoprofen Trometamol in ethyl laurate

4.4.2.1. Removal of Dexketoprofen Trometamol

Dexketoprofen Trometamol removal was first tested by using 20.4 mg **5-OBu**/Ethyl laurate gel. The results were tabulated in Table 4.13 and the UV spectrum was given in Figure 4.13. The results showed that there was no drug removal by this gel.

Table 4.13. Absorbance changes for Dexketoprofen Trometamol removal by **5-OBu**/Ethyl laurate gel

λ Max	Time	Maximum Absorbance
260 nm	First Day*	0,446
250 nm	2 Day Later**	0,571
244 nm	20 Day Later**	0,401
246 nm	30 Day Later**	0,389
*: standart solution **: after addition of the gel		

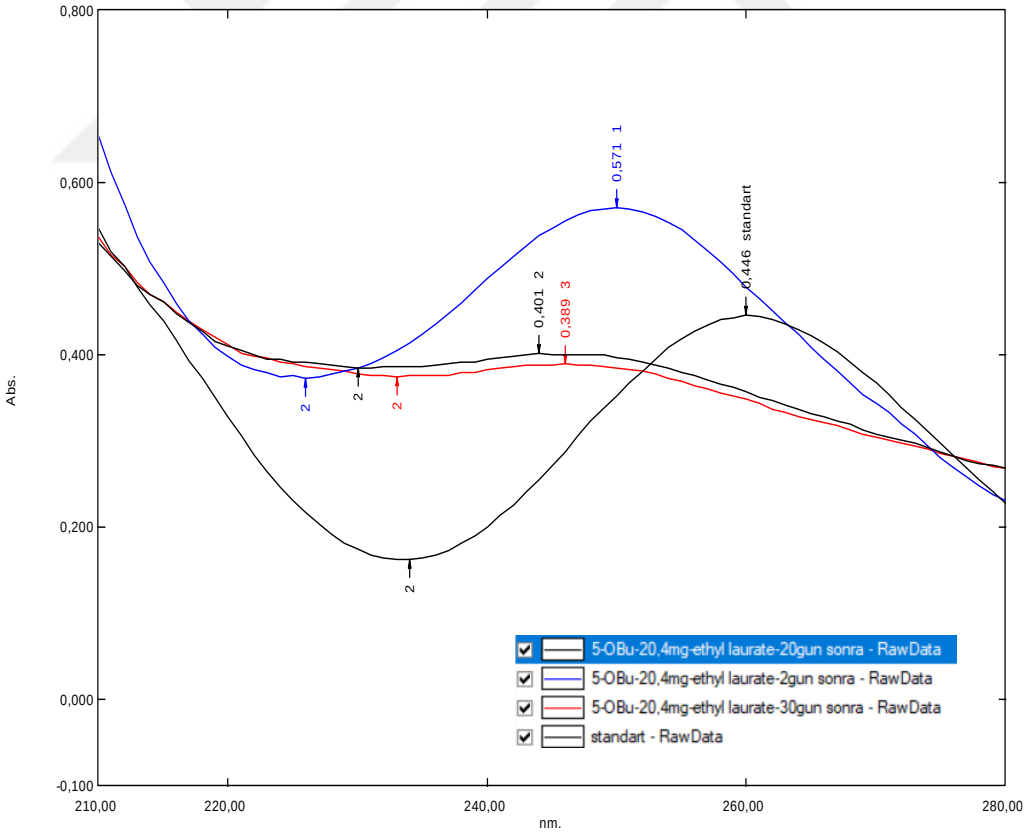

Figure 4.13. The UV spectra for Dexketoprofen Trometamol removal by **5-OBu**/Ethyl laurate gel

In order to compare *p*-hexyloxy derivatives with *p*-butoxy ones, Dexketoprofen Trometamol removal was also tested by 20.3 mg **5-OHex**/Ethyl laurate gel. The results were tabulated in Table 4.14 and the UV spectrum was given in Figure 4.14. As can be seen clearly in Figure 4.14 Dexketoprofen Trometamol could be removed from the aqueous solution by **5-OHex**/Ethyl laurate gel. After 2 days later the absorbance value decreased from 0,446 to 0,364. Further decreasing was also observed after 20 days to a value of 0,218. An increase from 0,218 to 0.252 was obtained after 30 days probably due to desorption.

Table 4.14. Absorbance changes for Dexketoprofen Trometamol removal by **5-OHex**/Ethyl laurate gel

λ Max	Time	Maximum Absorbance
260 nm	First Day*	0,446
256 nm	2 Day Later**	0,364
247 nm	20 Day Later**	0,218
249 nm	30 Day Later**	0,252
*: standart solution **: after addition of the gel		

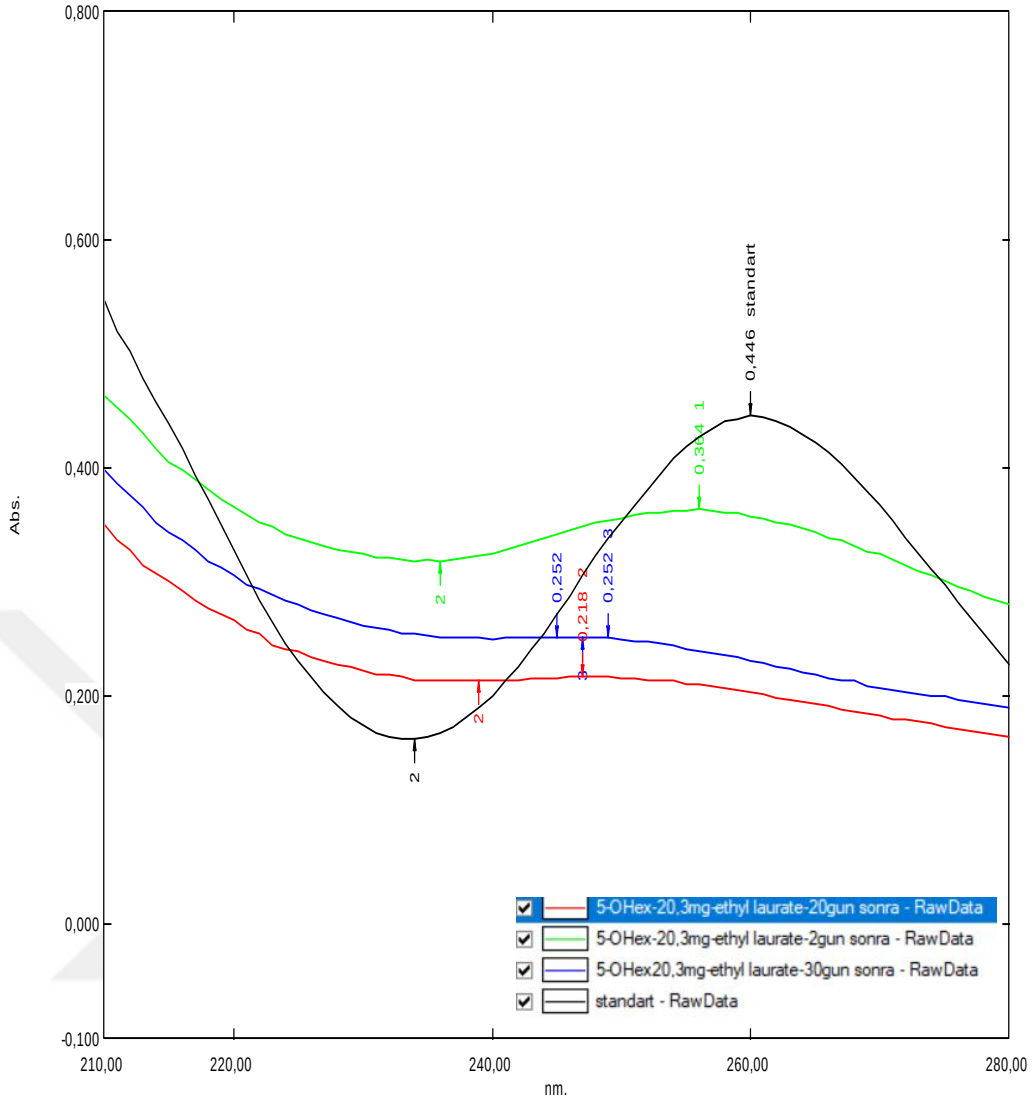

Figure 4.14. The UV spectra for Dexketoprofen Trometamol removal by **5-OHex**/Ethyl laurate gel

In order to compare derivatives having five methylene units (n:5) with the ones having three methylene, Dexketoprofen Trometamol removal was also tested by 20.6 mg 3-OBu/Ethyl laurate gel. The absorbance results were shown in Table 4.15 and the UV spectra were given in Figure 4.15. As can be seen, the absorbance value decreased from 0,446 to 0,434 after two days. The absorbance value for the samples taken after 20 and 30 days were 0,245 and 0,231 respectively.

Table 4.15. Absorbance changes for Dexketoprofen Trometamol removal by 3-OBu/Ethyl laurate gel

λ Max	Time	Maximum Absorbance
260 nm	First Day*	0,446
205 nm	2 Day Later**	0,434
287 nm	20 Day Later**	0,245
293 nm	30 Day Later**	0,231
*: standart solution **: after addition of the gel		

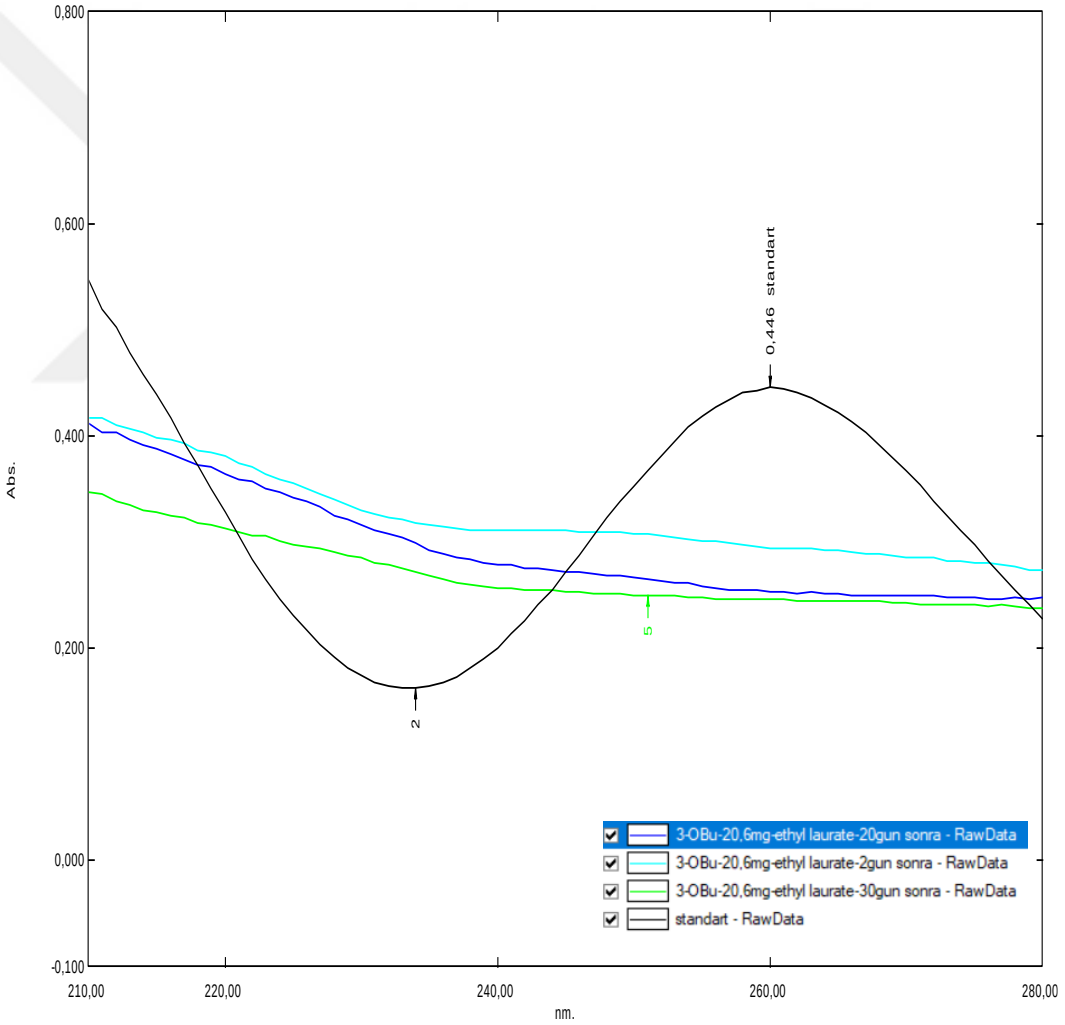

Figure 4.15. The UV spectra for Dexketoprofen Trometamol removal by **3-OBu**/Ethyl laurate gel

The last trial was done by 20.4 mg **3-OHex**/Ethyl laurate gel (Table 4.16, Figure 4.16). The absorbance value for the standart solution decreased from 0,446 to 0,331 after 2 days. Further decrease to 0,148 was observed after 20 days. However an increase was obsedved after 30 days, probably because of desorption.

Table 4.16. Absorbance changes for Dexketoprofen Trometamol removal by **3-OHex**/Ethyl laurate gel

λ Max	Time	Maximum Absorbance
260 nm	First Day*	0,446
259 nm	2 Day Later**	0,331
254 nm	20 Day Later**	0,148
259 nm	30 Day Later**	0,195
*: standart solution **: after addition of the gel		

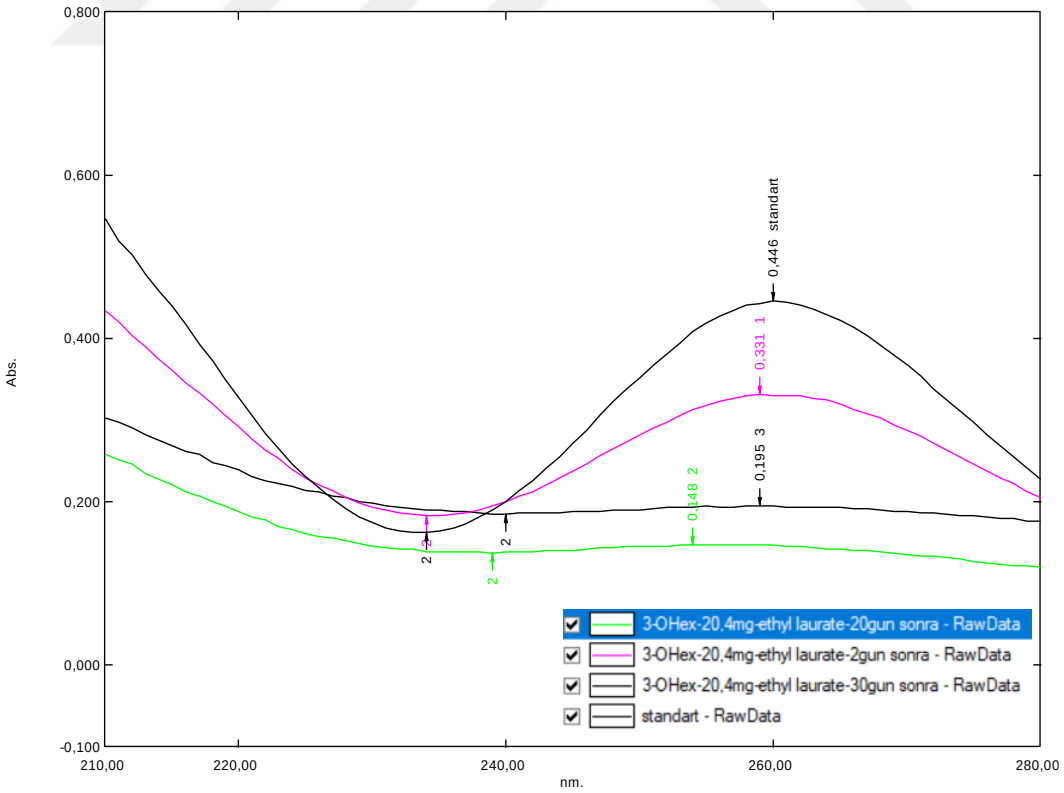

Figure 4.16. The UV spectra for Dexketoprofen Trometamol removal by **3-OHex**/Ethyl laurate gel

4.4.2.2. Calculation of dexketoprofen trometamol removal rates

Removal rates of dexketoprofen trometamol from aqueous solutions was calculated by using the following formula for **5-OBu**, **5-OHex**, **3-OBu** and **3-OHex** ethyl laurate gels.

$$Removal\ rate\ \varphi = \frac{C_o - C_e}{C_o} \times 100\%$$

Table 4.17. Removal rates of dexketoprofen trometamol

	λ Max	Time	Maximum Absorbance	Removal Rate%
Standart	260 nm	First Day*	0,446	
5-OBu	244 nm	20 Day Later**	0,401	10,09
5-OHex	247 nm	20 Day Later**	0,218	51,12
3-OBu	287 nm	20 Day Later**	0,245	45,07
3-OHex	254 nm	20 Day Later**	0,148	66,82
*: standart solution **: after addition of the xerogel				

	λ Max	Time	Maximum Absorbance	Removal Rate%
Standart	260 nm	First Day*	0,446	
5-OBu	246 nm	30 Day Later**	0,389	12,78
5-OHex	249 nm	30 Day Later**	0,252	43,49
3-OBu	293 nm	30 Day Later**	0,231	48,20
3-OHex	259 nm	30 Day Later**	0,195	56,27
*: standart solution **: after addition of the gel				

5. CONCLUSION

In the present work, *p*-alkyl and alkoxy substituted biscarbamate derivatives were obtained efficiently. Syntheses of 1,3-bis[N-(p-aryl)-carbamoyloxy]propanes (**3-Oct**, **3-OBu**, **5-OBu**, **3-OHex**, **5-OHex**) were carried out by the reaction of *p*-aryl isocyanates and 1,3-propanediol with a yield of 79-97%. The starting compounds *N*-*p*-aryl isocyanates were synthesized by Curtis rearrangement with a yield of 78-97%. Structures of the compounds were elucidated by IR, ^{1}Hand ^{13}C NMR spectroscopy. Formation of -N=C=O functionality was determined by IR spectroscopy and it was observed at around 2200 cm^{-1}.

After the sythesis of the compounds, their organogelation properties were tested in common organic solvents (toluene), vegetable oils (sunflower oil, olive oil, etc.), and esters used in pharmaceutical applications (NBP, E-L, etc.) by test tube inversion method.

For drug removal experiments, first dry gels (xerogels) obtained by evaporation of the organogelating solvent were used. Removal properties of paracetemol, ibuprofen. Ciproflaxin HCl and dexketoprofen trometamol were studied by the absorbance change of the drug molecule via UV spectroscopy. However, no removal was obtained for the studied drugs. The reason might probably be an insufficient pore or network size for the capture of drug molecules. Then, the wet organogels of *p*-alkoxy substituted bis-carbamates prepared in ethyl laurate were used in drug removal experiments. Only dexketoprofen trometamol was tested due to its stability at room temperature. All *p*-alkoxy derivatives (except **5-OBu**) showed an ability to remove the drug from aqueous solutions. Almost same capasities were obtained for **3-OBu** and **5-OHex** derivatives. **3-OHex** was the best having a higher capacity for the removal of dexketoprofen trometamol.

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