Significance of using Poloxamer 407 and Lactose in ibuprofen in vitro solubility enhancement

By

Fahima Akhter
12346004

A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy

Department of Pharmacy
Brac University
22 August, 2019.

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Fahima Akhter
12346004

Approval

The project titled "Significance of using Poloxamer 407 and Lactose in ibuprofen in vitro solubility enhancement" submitted by, Fahima Akhter (12346004) Summer 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on 22/08/2019.

Examining Committee:

Supervisor:
(Member)

_____

Dr. Afrina Afrose
Assistant Professor, Department of Pharmacy,
Brac university.

Program Coordinator:
(Member)

_____

Dr. Hasina Yesmin
Associate Professor, Department of Pharmacy,
Brac university

Departmental Head:
(Chair)

_____

Professor Dr. Eva Rahman Kabir
Chairperson, Department of Pharmacy,
Brac University

Ethics Statement

This project did not harm any animal or human**.**

Dedication

This work is dedicated to my parents for their love and constant support.

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Abstract

Ibuprofen is a widely used NSAID drugs dealing with mild to moderate pain formulated in numerous dosage forms. But ibuprofen has very poor solubility in water associated with minimal drug absorption hence leading to infrequent and low bioavailability. The following project was taken to determine the solubility profile of the drug in presence of poloxamer 407 and L- lactose as excipients since dissolution of orally taken dosage form principally depends on the solubility. While using poloxamer 407, ibuprofen solubility increases in presence of both co-solvents water and ethanol (in 10%and 20%). On the other hand, while using lactose, ibuprofen shows increased solubility profile in water. But even though ibuprofen has better solubility in ethanol, using lactose in 10% and 20% ethanol for ibuprofen did not show any significant solubility profile that may because of inadequate solubility of lactose in ethanol leads to super saturation of ethanol by lactose.

Keywords: Ibuprofen; NSAIDs; Poloxamer; Lactose; Solubility.

Dedication

This work is dedicated to my parents for their love and constant support.

Acknowledgement

I would like to begin by thanking Dr. Afrina Afrose, Assistant Professor of Department of Pharmacy, Brac University, for giving me continuous support and guidance since the first day of this project-work. As a person, she has endlessly encouraged and motivated me with her knowledge on Pharmaceutical Technology which made me more passionate about the project when it began. I would also like to thank her for her untiring patience in me during every stage of project, at the same time as I learned and performed in the lab. I would also like to thank Dr. Eva Rahman Kabir, Chairperson of Department of Pharmacy, Brac University, for providing me with an opportunity to carry out the project at an individual level and for making Dr. Afrina Afrose, my project supervisor. Additionally, I would like to thank all the lab officers and lab assistants for their continuous guidance pertaining to lab-work. All these would not have been possible without the Grace and Mercy of The Almighty, Allah, who has allowed me to complete this project-work in good health. Last but not the least; I would like to thank the faculties of Department of Pharmacy at Brac University, my friends and my family for their moral support, motivation and patience that altogether enabled me to complete my project successfully.

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List of Acronyms

NSAID	Nonsteroidal anti-inflammatory drugs
BCS	Biopharmaceutics Classification System
OTC	Over the Counter
Gm.	Gram
FDA	Food and Drug Administration
ER	Extended-release
COX	Cyclooxygenase
PG	Prostaglandins

Chapter 1

Introduction

1.1 Background

Ibuprofen is a kind of non-steroidal anti-inflammatory (NSAID) drug widely used to treat mild to moderate aching, fever, arduousness and soreness, alongside menstrual cramps, migraines and autoimmune disorder like rheumatoid arthritis. Moreover dealing with mild to moderate pain related to post-operative and to control spondylitis, Osteo-arthritis and soft tissue disorders, Racemic Ibuprofen and the S (+)-enantiomers are mainly used (Park, 2005). The drug is a derivative of propionic acid therefore extensively used in recent remedial as pyrogenic feverishness and for all progression related to darting pain also continuous pain and tenderness (More, 2015).

It has very slight solubility in water related to minimal drug absorption hence leading to scarce and mutable bioavailability (Bushra, Shoaib, & Aslam, 2008 ; Abraham et al., 2005). There are several dosage forms of ibuprofen having well established therapeutics and their mechanism of action is well established. Ibuprofen is an alternate choice of Indomethacin as a therapy as it also cyclooxygenase inhibitor but has fewer side effects as indomethacin may cause reduced blood flow to several organs (Afrose et al., 2018). Ibuprofen dosage form is marketed as tablets, capsules, suspensions as oral administrable therapeutics particularly in controlled and extended released dosage form. Oral dose of taking the drug is about 200-600mg that is most frequent otherwise considering severity of disease the dose can be increased up to 2.4-3.2g on daily basis (Bushra & Aslam, 2010). Likely The obligatory prescribed dose for curative measure in an adult is roughly 20–30mg, however the provided dose is more than tenfold as it has first pass metabolism and inadequate drug absorption due to low solubility (Dixit Mudit, 2011).

Drug shows its indicted therapeutics in desired concentration present in systemic circulation after dissolution to get efficient pharmacological response. Dissolution of orally taken dosage form principally depends on the solubility hence solubility is one of the most important constraints to reach in circulation. Moreover Therapeutic efficacy of a drug depends on the bioavailability in addition eventually upon the solubility of drug particles (Rita & Fernandes, 2016). According to an research paper, investigation of solubility enhancement in research laboratory is a vigorous topic at present as only 8% of new drugs have high solubility and permeability therefore in emerging the most desirable dosage forms the aqueous solubility of drugs is frequently a warning factor (Science, Badjatya, Bodla, & Moon, 2011).

1.2 Aim

a. This project aims to determine the solubility of ibuprofen in case of using Poloxamer 407

b. Using lactose as excipient in presence of ethanol and aqueous medium at different concentrations (mentioned in the methodology chapter) to determine the solubility profile of ibuprofen.

Chapter 2

Literature Review

This chapter instigates the therapeutic uses of ibuprofen, their fate of absorption followed by their importance regarding enhancement of solubility for better drug onset.

2.2 Therapeutics of Ibuprofen

The IUPAC name for ibuprofen is „2-methylpropylphenylpropanoic acid". The compound is also known as isobutyl phenyl propionic acid as it has a methyl propyl group $[CH_3CH(CH_3)CH_2]$ bonded to a phenyl group (C_6H_4) bonded to a propanoic acid group $(CH_3CHCOOH)$ (Bushra & Aslam, 2010).

NSAID like ibuprofen can also be used in case of mitigation of ache and agony with peripheral anti- inflammatory activity along with a decreased opioid dose thus progress repossession.

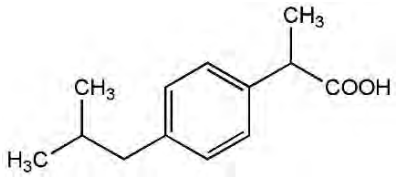

Figure 1 Ibuprofen

Ibuprofen is a propionic acid derivative having anti inflammatory, analgesic, and antipyretic properties.

2.2 Metabolism of Ibuprofen

Mechanism action of ibuprofen therapeutics is accredited by in cooperation with both cyclooxygenase 1 and cyclooxygenase 2 (COX1 and COX2) inhibitor. Ibuprofen is metabolized utterly through oxidative reaction into inactive metabolites subsequent elimination in the urine. These two metabolites are carboxy-ibuprofen and 2-hydroxy-ibuprofen. Nevertheless, 10-15% of ibuprofen is glucuronidated to ibuprofen-acyl glucuronide happened to the patients taking the drug orally. Hence ibuprofen-acyl glucuronide subsidizes to both analgesic and anti-inflammatory activities (Logu et al., 2019).

2.3 Solubility of oral dosage form

Under precise ailment of temperature, pH and pressure optimum drug solubility is obtained when maximum concentration of drug solute dissolved in saturated solution the drug dissolution rate is a spirited property that describes more meticulously to the bioavailability rate (Ventosa-andrés & Fernández, 2012).

Therapeutic efficiency of a drug hinge on the bioavailability and eventually upon the solubility of drug molecules. Aqueous solubility of a therapeutically active substance is a key property as it directs dissolution, absorption and thus the efficiency in situ. Again solubilization may be demarcated as the grounding of a thermodynamically constant solution of a substance that is normally insoluble or very little soluble in a specified solvent by the starter of one or more amphiphilic composite (Mission, 2011). Assortments of new drugs & their spinoffs are available due to advanced research and development. But unfortunately, more than 40% of drugs nosedive to grasp market due to poor bioavailability, nevertheless these drugs are lipophilic and have competence potential pharmacodynamic activities (Savjani, Gajjar, & Savjani, 2012a).

Ibuprofen has low solubility leading to inadequate drug concentration in systemic circulation thus lowers the therapeutics. To overcome solubility problem or to enhance solubility there are so may techniques have been used such as according to a thesis work, particle engineering or crystallization technologies can boost drug solubility (Gadade, 2017).

The purpose of my study is to determine the solubility of ibuprofen in case of using Pluronic F 127 and L- lactose as excipient in presence of ethanol and aqueous medium at different concentrations.

Drug discovery has amended so much is this era but still enhancement of drug dissolution in gastrointestinal tract is nothing less than a challenge (Khadka et al., 2014).

Orally taken dosage forms produced in combinational chemistry bring the drugs in market having higher lipophilicity, poorer water solubility and higher molecular weight all of which are not advantageous for oral absorption. On the other hand, drugs forming stable crystals are also a challenge to the pharmacists as well.

The basic aim of my project is to enhance the drug (Ibuprofen) bioavailability at proper site of action within optimum dose. Ibuprofen is widely used throughout the world and to evaluate the solubility profile it is essential to know its physicochemical possessions for instance solubility in different solvents, in solvent mixtures and their interconnections as this knowledge will smoothens the design process of liquid pharmaceutical dosage forms (Wei & Sadus, 2000).

Additionally, the physicochemical features of a drug are really important to identify as it has imperative involvement to the process of solubilization therefore solubility trait in aqueous solvent or mixture of co-solvent is equally significant (Alkowsky, 1999).

Moreover, in order to attain comprehensive statistics of physicochemical properties of a drug

It is significant to regulate drug solubility in plasma. These statistics enables to develop and exploration about new drug product in pharmaceuticals (Garz & Mart, 2004).

On the other hand, temperature plays an vital role in thermostatic inspection giving us resultant data about mechanisms involving solubilization process (Bagheri, Ghader, & Hatami, 2019). Drug solubility can be amended by physical, chemical or other modifications on the drug molecules and subsequently a large variety of techniques exist to overawed poor water solubility of the drug.

Substantial and chemical alteration of drug molecules or alteration in element size, consuming diverse polymorphs or crystals of drug molecules enhance drug dissolution nonetheless nebulous solid dispersions generate easily dissolving drug particles. Besides pH variation, derivatively for instance formation of salt etc. are prominent chemical alterations owing to improver drug dissolution (Maleki et al., 2017). Using co-solvents, salt form of drug, generating prodrugs or initiating cyclodextrins may enhance drug solubility on molecular level whereas using emulsions, micro emulsions or lipid-based preparations enhance solubility on colloidal level. Besides, nanosizing and metastatic polymorphs plays vital role in particulate level drug dissolution (Hu, Johnston, & Iii, 2004).

Within a porous structure preserving loaded drug in its amorphous form yields beneficial controllable properties in the fate of drug absorption significantly enhances dissolution behavior. According to the cited journal this action required to amorphous form owe to fortification of the drug molecules from hydrolysis, oxidation and other dilapidation processes through prohibiting access from the adjacent environment (Skrdla, Floyd, & Dell‟Orco, 2019).

2.4 Techniques required enhancing solubility

Many techniques are used in order to enhance solubility are discussed as follows some of which might support ibuprofen solubility as well.

- Hydrotrophy (Shete, Yadav, Dabke, & Sakhare, 2010), (Science et al., 2011).
- Micronization (Patel, Rathod, Patel, & Modasiya, 2012).
- Nanonisation(Gadade, 2017).
- Super critical fluid recrystallization
- Cryodesiccation or lyophilization (Yasmin, Tan, Bremmell, & Prestidge, 2014).
- By using surfactants (Gadade, 2017).
- By using salt forms of the drug
- By using precipitation inhibition

Besides, according to some articles (mentioned in citation), drug solubility may also be increased while on up surging surface area by means of plummeting particle size (Khadka et al., 2014), forming inclusion compounds by using water soluble transporters, hydrotrophy (Abraham, Deveswaran, Furtado, Bharath, & Madhavan, 2014), using surfactants, forming solid dispersions to avoid crystallinity, using etc. (Dixit Mudit, 2011).

However, the above all the techniques are not as equally important for drug dissolution and in practical observation there are some limitations (Kapsi & Ayres, 2001).

Although particle size reduction is commonly used to increase the dissolution rate, there is a practical limit to the size reduction that can be achieved by such commonly used methods as controlled crystallization and grinding. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wet-ability. Salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs which are weakly acidic or weakly basic may often not be practical. Even when salts can be

prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because e of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and co solvents leads to liquid formation that is usually undesirable from the viewpoints of patient acceptability and marketing4. Solid dispersions have been widely used to enhance the solubility, dissolution rate, and bioavailability of poorly soluble drugs.

Solid dispersion system is one of the ways to exceed the drug solubility. Different drugs have different physical states therefore solid dispersion systems are categorized accordingly. This dispersion system perhaps a homogeneous multicomponent solid solution either crystalline particles in an amorphous carrier matrix, or dispersion of solid or an amalgamation of a solution (Gadade, 2017). Increase of aqueous solubility upsurges by increasing efficiency or by reducing contraindications of certain drugs (Ali et al., 2012).

Another solubility augmentation technique enhancing solubility to many times is using hydrotropes like sodium salt of benzoic acid, sodium salts of citric acid, carbamide, nicotinamide, etc. has a lot of recompenses (Bharath, Madhavan, Furtado, Deveswaran, & Abraham, 2014); (Abraham et al., 2014). Moreover, it is not necessary to do any chemical adjustment of hydrophobic drugs, use of organic solvents, or preparation of amalgam (Savjani, Gajjar, & Savjani, 2012b). The widespread uses of hydrotrophy method can work for parenteral topical and oral dosage forms as well (Jain, Goel, Sharma, & Parmar, 2010b). In another article, it increases solubility is much higher than other techniques making it preferable in industrial choice (Sampath Kumar, Raja, & Jayakumar, 2014). For an example in case of bioavailability enhancement of Griseofulvin drug hydrotrophy is favorable choice for formulation of suspensions owing to give longevity (Shete et al., 2010). Another investigation shows, hydrotropic solubilizing agent (30% of Urea and 20% of Sodium Citrate) was employed to solubilize Aceclofenac from its fine powder and tablet form to carry

out Spectrophotometric analysis (Jain, Goel, Sharma, & Parmar, 2010a).

Besides cyclodextrines are recently used in the pharmaceuticals together with liposomes, microparticles, nanoparticles consisting of more than a few glucose molecules (Boyd et al., 2019). Their characteristic feature is they have similar polarity like ethanol thus ensuring favorable milieu for lipophilic drugs where outer surface is hydrophilic surface attributing to further modification to improve the water solubility (Savjani, Gajjar, & Savjani, 2012c) . Using Cyclodextrins in BCS class II drugs (high permeability, low solubility drugs. Example: aceclofenac)., enhance solubility and also make the drug more stable avoiding chemical deterioration thus bioavailability enhanced with minimized contraindications (Wankar et al., 2017).

Water insoluble compound has very few bioavailability because of poor dissolution yet nanosuspensions are used to enhance bioavailability like usage of lipidic system in formulation. however, nanosuspensions also improve aqueous solubility of drugs which are not soluble in water even not in oil (Grau, Kayser, & Mu, 2000). Moreover, nanosizing advantageous that the drug crystals are condensed hence, dose up can be achieved as compared to cyclodextrins.

In the pharma industries formulating poor soluble drugs for oral delivery is one of the burning challenges therefore poorly water-soluble drugs results rate limiting dissolution rate of absorption. Furthermore, tremendously hydrophobic drug having aqueous solubility lesser than 0.1mg/ml at body temperature shows enormous bioavailability glitches predominantly because of inadequate absorption from GIT.

2.5 Ibuprofen solubility enhancement procedures

Solubility enhancement of the drug ibuprofen is a concern as it is poorly water-soluble drug. So, to get the optimum therapeutic window at the possible minimal dose solubility

enhancement assessments are needed. A lot of thesis work have been done already to get most optimal therapeutics in different dosage forms. In my thesis work, I focused mainly on two of the most available excipients that are lactose and poloxamer and their subsequent effects on drug solubility.

Research works done about using hydrotropes to enhance ibuprofen solubility and indicating enhancement of ibuprofen solubility due to hydrotropes. As it is acknowledged that hydrotropes enhance solubility of ibuprofen by many folds to specific solutes which may parsimoniously soluble in water under typical circumstances (Nidhi et al, 2011).

In case of ibuprofen amongst all hydrotropes momentous augmentation in solubility was detected using sodium benzoate. Even though ibuprofen itself is poorly water soluble but increased sodium benzoate concentration significantly rise the solubility of the ibuprofen in aqueous medium (Nidhi et al., 2011).

Ibuprofen has better gastro intestinal permeability but because of its solubility availability in body fluids is not optimum therefore gastric emptying time required about is 30 min to 2 hr.

According to an article „Solubility enhancement of ibuprofen using hydrotropic agents" surfactants were added to the aqueous release media owing to increase aqueous solubility (Mission, 2011). However, this method is inappropriate for polymeric micelle systems as they are very sensitive to surfactants since even a very small amount of surfactant may abolish their micellar assembly in addition garble their release profiles. So, in that case to upsurge solubility a good substitute could be a hydrotropic agent (Stoyanova, Vinarov, & Tcholakova, 2016).

From an article „Improving ibuprofen solubility by surfactant-facilitated self-assembly into mixed micelles" ibuprofen solubility in aqueous solvent basically used only four nonionic

surfactants that are polysorbate 20, 40, 60 and 80 likely two anionic surfactants that are SDS 405 and SLES-3EO (Stoyanova et al., 2016).

The reason behind poor dissolution of Ibuprofen owed to its hydrophobic chemical structure. Moreover, it has extreme cohesively resulting low flow ability (Hussain, Khan, Irfan, Pedge, & Ermolina, 2018).

This hydrophobicity of drug may be treated by using Polymeric micelles formation as an effective substitute to surge the solubility and bioavailability while hydrophobic part of drugs is stable in surfactant with lower Carboxymethylcellulose owing to sluggish rate of dissociation.

I decided to use L- Lactose and Pluronic F- 127 or poloxamer as excipients to perceive whether the solubility enhanced or not in different temperature and concentrations as it could be a new way to investigate the solubility of Ibuprofen.

The disaccharide Lactose is composed of one galactose in addition one glucose molecule. Lactose has outstanding compressibility properties in tablets formulations. In pharmaceuticals to formulate dry-powder inhalations lactose could also be used as diluent powder. Likely it is extensively used as a filler or binder in the production of pharmacological tablets and capsules (Jamal Altamimi, Wolff, Nokhodchi, Martin, & Royall, 2018).

Pluronic F-127 is commonly used in the field of cosmetic, pharmaceutical, and biomedical industries as excipients (Dixit Mudit, 2011). it is a made up of lipophobic outer surface that is polyethylene oxide, with a hydrophobic center unit that is polypropylene oxide. it has exclusive thermo rescindable gelling competency. It occurs as single chain polymers at truncated temperature in solution. Biocompatible Pluronic is very desirable for drug delivery system hence is lipophobic making it corporeal barrier to avert scar tissue development. Studied found that the drug delivery of ibuprofen in Pluronic F- 127 or in Pluronic F- 68

cross-linked with alginate as a physical barrier for adhesion prevention in situ action resulting a stable gel at 30 °C with delayed release of ibuprofen exceeds up to 45% of total loading quantity. Ibuprofen gel using pluronic as excipient was shown to be an effective material to prevent tissue adhesion establishment. Therefore, it has been proposed to prevent adhesion injecting Pluronic after spinal surgery while giving antibiotics.

Chapter 3

Research Methods

3.1 Chemicals

3.1.1 Model drug

Ibuprofen (BP).

Lot No: W010011898.

Source: Beximco Pharmaceuticals Ltd.

3.1.2 Excipients

3.1.2a) Kolliphor® P 407 micro (Geismar),

Lot No: GNB28621CT.

Source: BSF Bangladesh.

3.1.2b) L-lactose USP.

Source: Beximco Pharmaceuticals Ltd.

3.1.3 Solvent

3.1.3a) Ethanol (Merck Germany; GR grade)

3.1.3b) Distilled water; prepared in lab.

3.2 Apparatus and Instruments

3.2. a) Incubator Shaker (Germany); this is used to incubate the drug (Ibuprofen) along with excipient in different concentration for the solubility study.

3.2. b) UV spectrophotometer (Model:2910, Hitachi, Japan); this is used to detect the absorbance of the drug solution with the excipients to get the final solubility profile.

3.2. c) Balance (Model: PA2/3, Ohaus, Corp, USA).

3.2. d) Microsyringe Filter (China):

Pore size: 0.45µm

Diameter: 25mm.

3.3 Stock Solution Preparation

The laboratory test for obtaining the solubility profile of Ibuprofen required the measurement of concentration be detected in a spectrophotometer. Spectrophotometer is only capable of measuring the amount of light being permitted to pass through the cuvette so, their readout devices display % of light transmitted solitarily or mathematically derived absorbance. One of the methods of obtaining concentration from absorbance is determination of a standard curve. For the research work, standard curve is well-defined as a graph with absorption plotted on the Y axis, in addition increasing concentrations of standard along the X axis.

3.4 Dilution of the Stock Solution

The stock solution of ibuprofen was made in the laboratory by using Ibuprofen active drug powder in the 50% aqueous ethanol. For making the stock solutions theoretically we decided to take concentrations as following: 1500µg, 1200µg, 1000µg, 800µg, 600µg, 400µg and 200µg in total volume of 10gm.To make a fixed amount of a dilute solution from a stock solution, we used the formula:

$C_1V_1 = C_2V_2$, where:

V_1 = Volume of stock solution needed to make the new solution

C_1 = Concentration of stock solution

V_2 = Final volume of new solution

C_2 = Final concentration of new solution

For instance, to make a 10gm of stock solution having 1500µm concentration we used the formula:

$C_1V_1 = C_2V_2$

$V_{2 = C1V1/ C2}$

3.5 Calibration Curve Preparation

For the calibration curve preparation, I took 50% of aqueous ethanol as solvent for Ibuprofen as it has slight solubility in water. Ibuprofen solution for the standard curve was made in different concentrations of 1500 µg/gm, 1200 µg/gm, 1000 µg/gm, 800 µg/gm, 600 µg/gm, 400 µg/gm, 200 µg/gm and 100 µg/gm hence, the absorbance was taken through UV spectrophotometry. Data for the standard curve of ibuprofen in 50% ethanol:

Table 1 Absorbance of ibuprofen in different concentration for standard curve

IBP Concentration (µg/ gm)	Absorbance at 264 nm
63.10	0.078
202.17	0.287
401.74	0.516
794.23	1.037
955.06	1.219
1215.44	1.595
1507.94	1.868

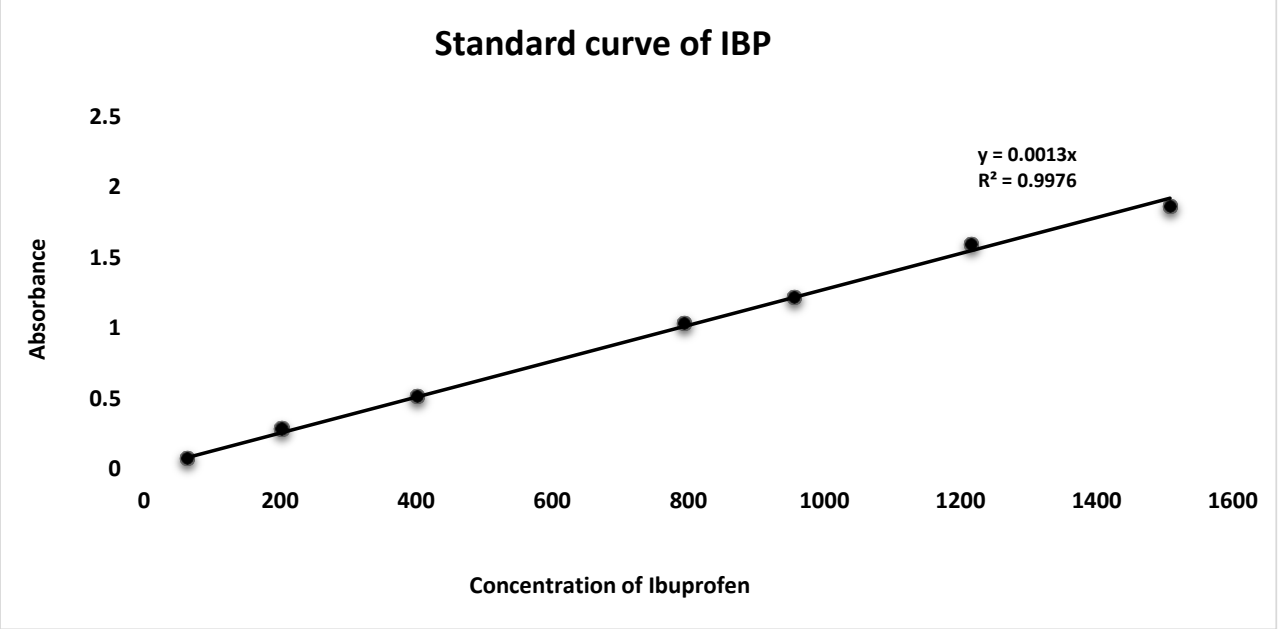

Figure 2 Standard curve of ibuprofen

So, the above standard curve of ibuprofen shows the absorbance of Ibuprofen in different concentrations obtains a straight line of regression demonstrating that it follows the Beer-Lambert‟s law.

3.6 Solubility of Ibuprofen in Addition with Poloxamer 407

3.6.1 Preparation of poloxamer 407 sample solutions

Poloxamer 407 solution was prepared by Poloxamer 407 in different concentrations by using co- solvent water, 10% and 20% aqueous ethanol respectively.

Theoretically we calculated to make 0%, 1%, 1.5%, 2%, 2.5%, and 3% Poloxamer 407 in distilled water, 10% and 20% ethanol distinctly.

3.6.2 Shaking of the poloxamer 407 solution in addition with ibuprofen API

At first, the poloxamer 407 solution using distilled water was made in previously mentioned concentrations. After few minutes poloxamer was completely dissolved in the distilled water. Then the active drug powder Ibuprofen was added in the poloxamer 407 solution to make it

supersaturated and subsequently shake it in the shaker for up to six hours.

Followed by ibuprofen also added in poloxamer 407 by using alcohol as a solvent and shake in the incubator shaker for minimum 6 hours to dissolve the drug into the solution.

3.7 Solubility of Ibuprofen in Addition with L-Lactose

3.7.1 Preparation of L-lactose solution

Lactose solution was prepared by lactose in different concentrations in distilled water, 10% and 20% aqueous ethanol respectively. Theoretically we calculated to make 2%, 4%, 6%, 8%, 10% lactose in distilled water and in 10% ethanol while in concentrations of 0.5%, 1%, 1.5%,2%, 3%, 3.5% in 20% ethanol distinctly because at these mentioned concentrations lactose was completely dissolved in the respective solvents.

After preparing L-lactose solution, ibuprofen was added and kept the solution in the incubator shaker for 6 hours.

Chapter 4

Results

4.1 Poloxamer 407 solution in water

Poloxamer 407 and distilled water solution was made to determine the solubility profile of Ibuprofen resulting that poloxamer vigorously increase solubility of ibuprofen though Ibuprofen itself is poorly soluble in water.

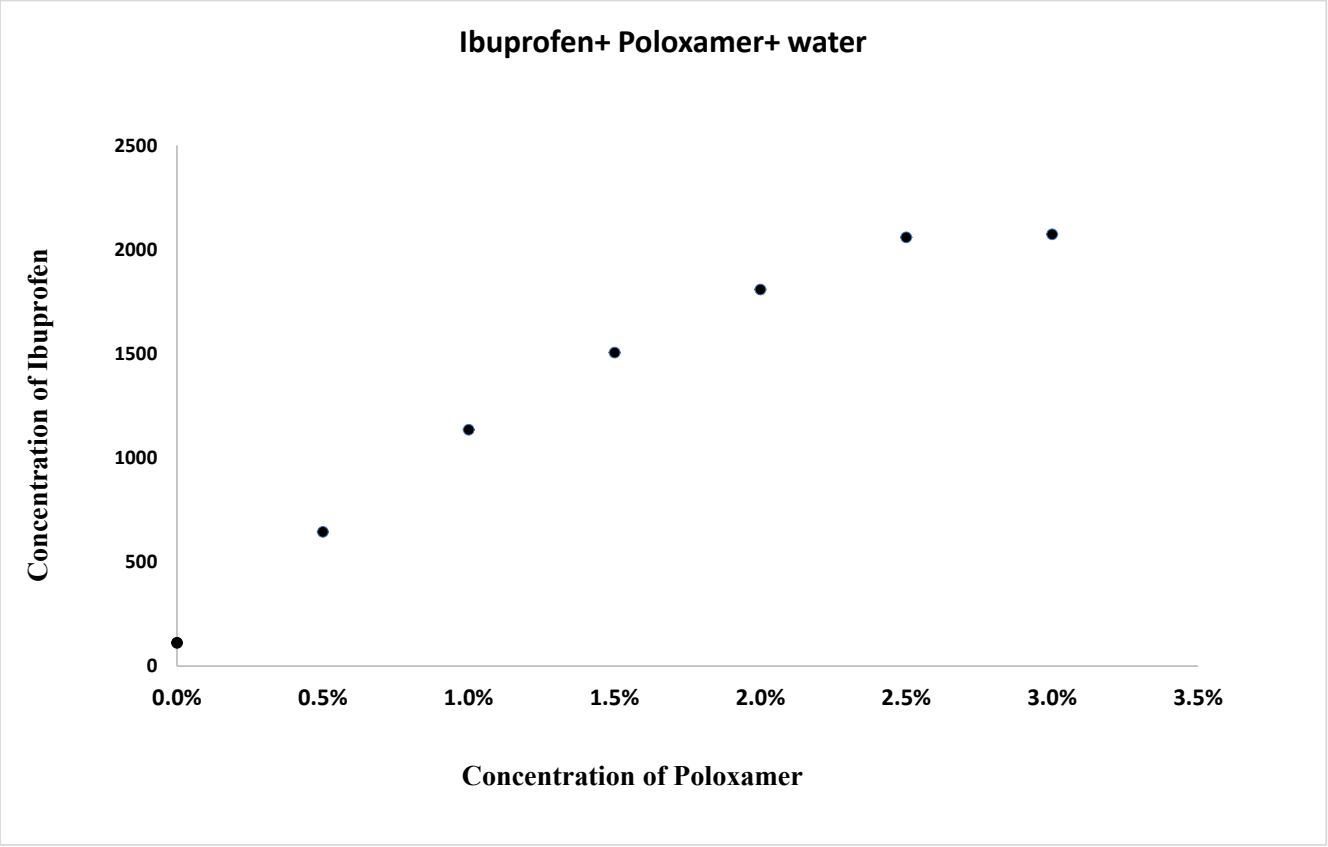

Figure 3 Solubility curve for ibuprofen in presence of poloxamer and water

The above graph (figure 3) is plotted concentration of poloxamer 407 vs ibuprofen concentration in presence of water from the laboratory data that are present in Appendix 1. The absorption of ibuprofen is gradually increased with increasing the concentration of

poloxamer 407 (up to 2.5% conc.) proving that ibuprofen has better solubility profile in presence of poloxamer as an excipient. In 3% concentration of poloxamer in water, ibuprofen solubility decreases a little that indicates the solution became saturated. So, poloxamer 407 did not use in concentration more than 3%.

4.2 Poloxamer solution in 10% aqueous ethanol

Poloxamer 407 was taken in 10% aqueous ethanol in the concentration of 0%, 0.5%, 1.0%, 1.5%, 2%, 2.5%, 3% and in 3.5%. Then in the solution Ibuprofen was taken in a maximum amount until no saturation occurred.

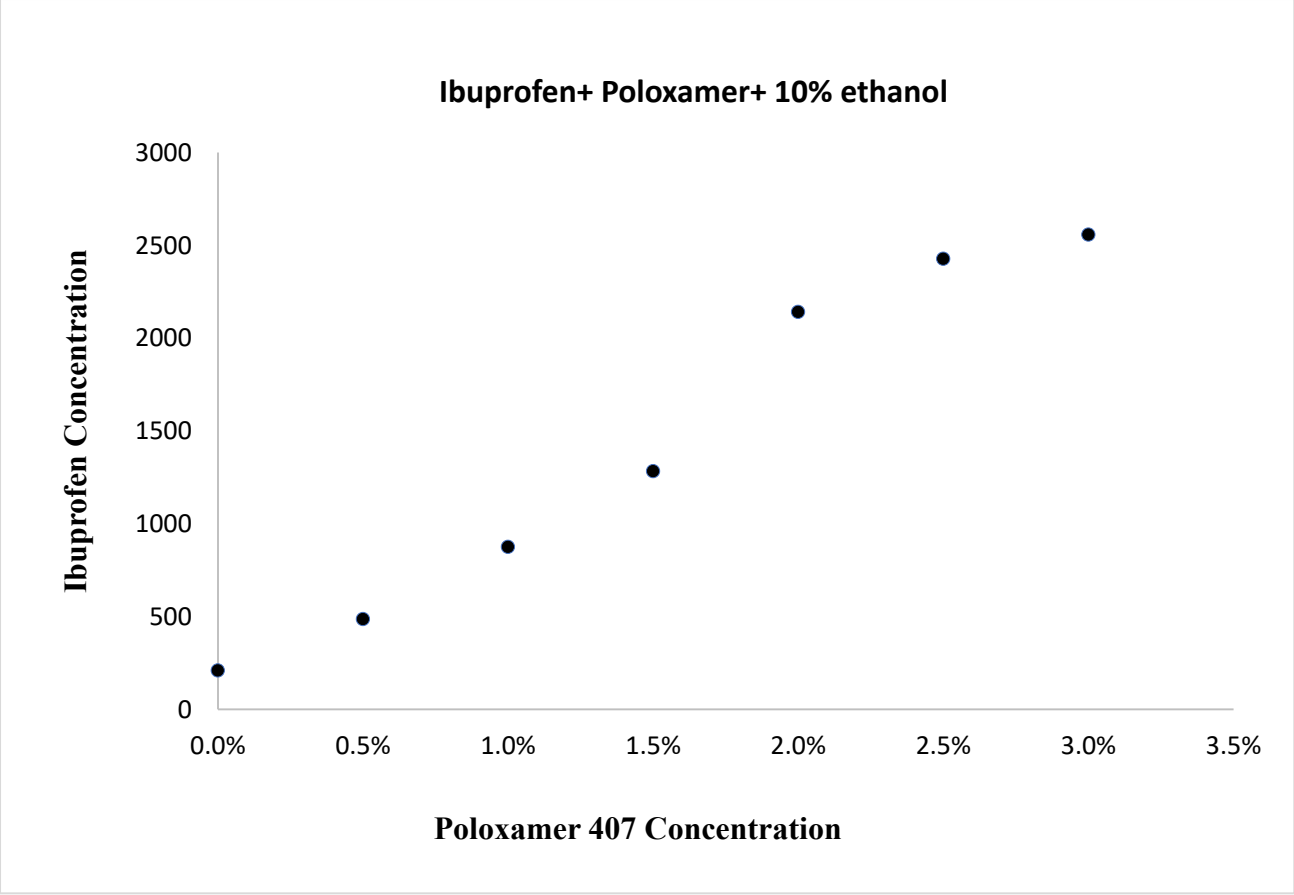

Figure 4 Solubility curve showing ibuprofen absorbance in presence of poloxamer and 10% ethanol

Data from Appendix 2, the above solubility curve is plotted (figure 4). From the above graph in presence of 10% ethanol, the solubility of ibuprofen is gradually increased with increasing

the concentration of poloxamer 407. The above solubility profile of ibuprofen in poloxamer 407 explains that Ibuprofen has a significant solubility in presence of poloxamer 407 in 10% ethanol.

4.3 Ibuprofen in Poloxamer 407 in 20% aqueous ethanol

Poloxamer 407 again was dissolved in the 20% aqueous ethanol to observe if it enhances solubility or not. Alcohol conc. was increased as ibuprofen has better solubility in alcohol than water. So, if the increased conc. of alcohol could also enhance the ibuprofen solubility in presence of alcohol or not was our objective in this case.

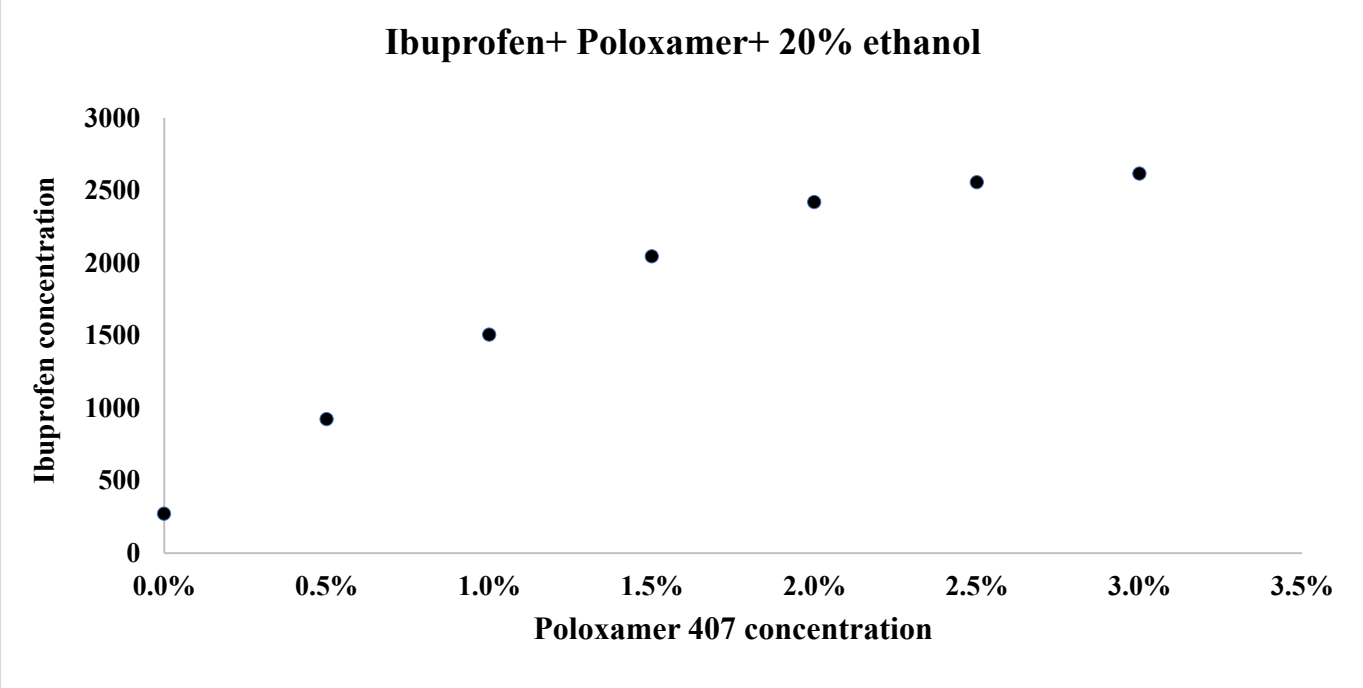

Figure 5 Solubility curve showing ibuprofen absorbance in presence of poloxamer and 20% ethanol

The solubility curve (figure 5) was plotted ibuprofen concentrations against the poloxamer 407 concentrations based on the data from Appendix 3. The above curve shows that initially the solubility increased with poloxamer 407 conc. (up to 1.5%) but then further increase in poloxamer 407 concentration, ibuprofen solubility was increased almost linearly.

4.5 Lactose in water

Lactose was dissolved in different concentrations in water. Then maximum amount of ibuprofen was added up to which it was dissolved in the lactose solution.

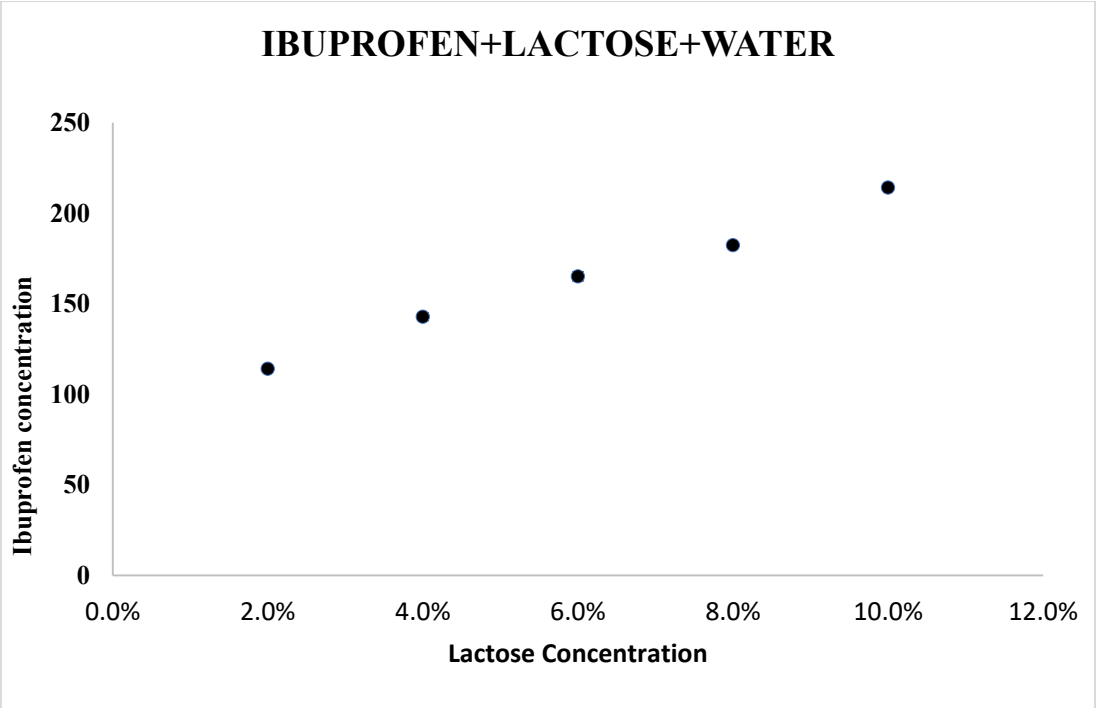

Figure 6 Solubility curve showing ibuprofen absorbance in presence of L-lactose and water

Data from Appendix 4 the above solubility curve was plotted. Through the solubility curve showing in figure 6, solubility of ibuprofen in L-lactose increases with the increased concentration of lactose even though ibuprofen itself has poor solubility in water. That is because, lactose has better solubility in water. Meanwhile proving that ibuprofen has an enhanced solubility profile in presence of lactose even in water.

4.6 Ibuprofen in lactose in 10% ethanol

Since ibuprofen has better solubility profile in alcohol so lactose concentrations were taken to make solution with 10% alcohol to determine if it has any effect in ibuprofen solubility enhancement.

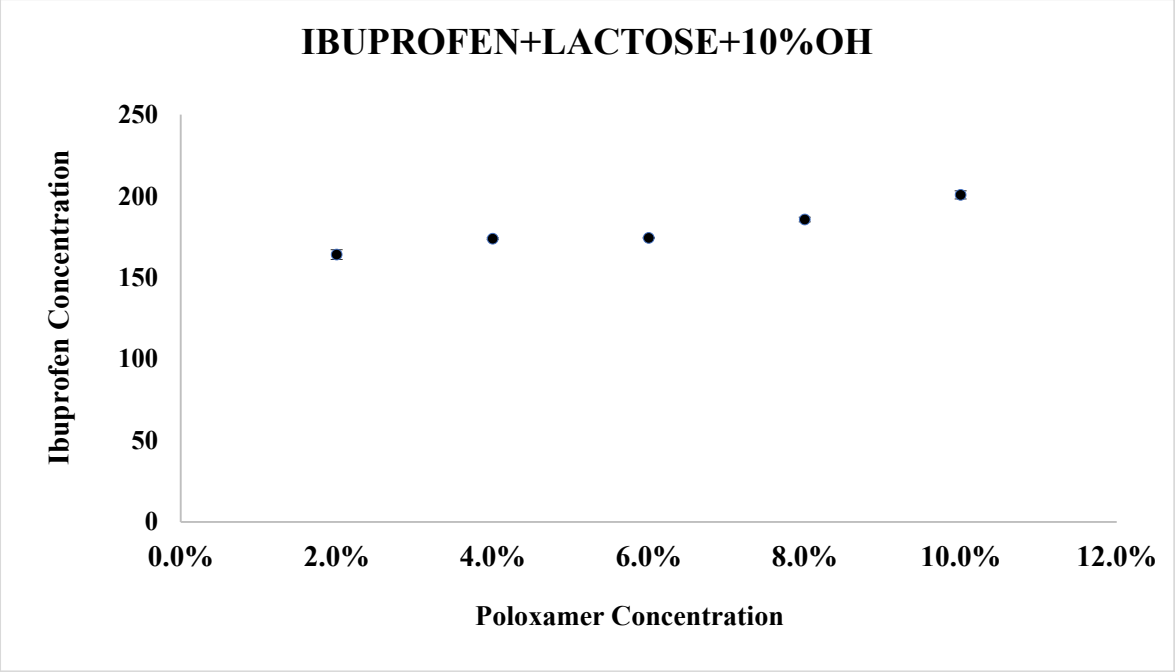

Figure 7 solubility profile of ibuprofen in presence of lactose in 10% ethanol

In figure 7, the solubility curve is plotted from the data of Appendix 5 where lactose is used in the ethanol followed by ibuprofen was added. Ibuprofen itself has better solubility in alcohol but the above curve (figure 7), the solubility does not show any significant enhancement because lactose has lower solubility in ethanol with increasing concentration. Likely, ethanol in the solution gets super saturated by lactose so it cannot dissolve ibuprofen.

4.7 Ibuprofen in Lactose in 20% ethanol

In 20% ethanol lactose concentrations were taken with ibuprofen to determine the solubility profile of ibuprofen.

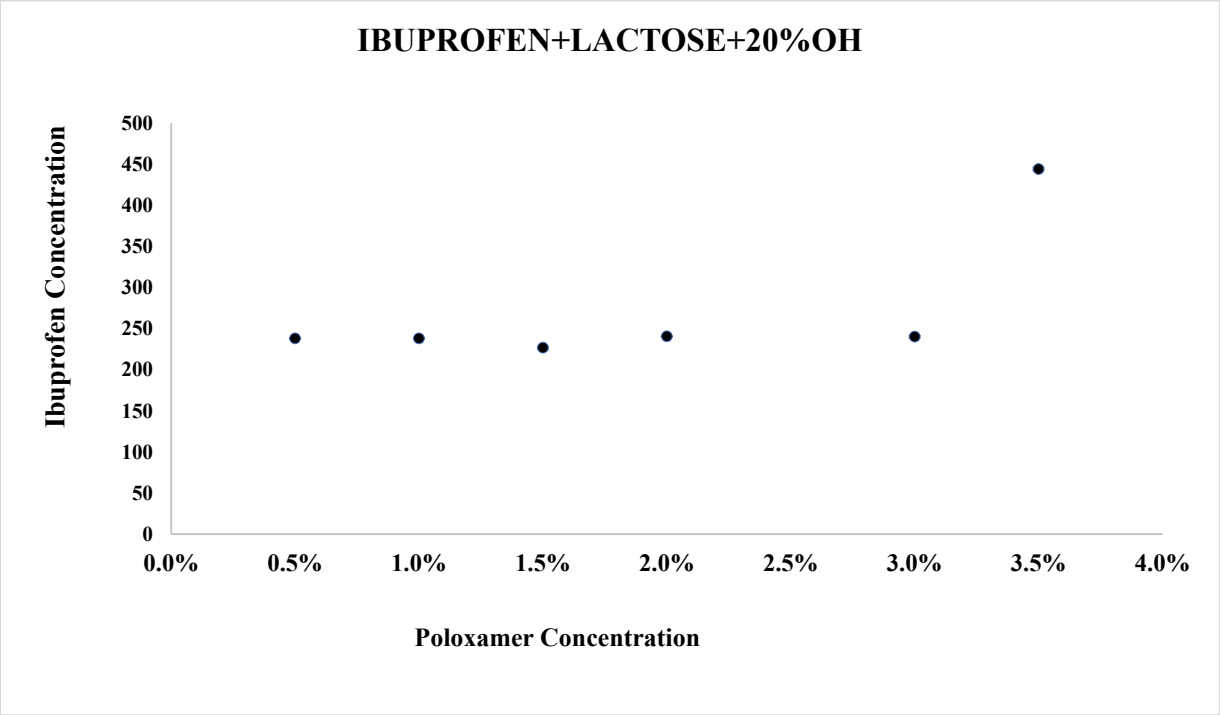

Figure 8 solubility curve showing ibuprofen absorbance in presence of L-lactose and 20% ethanol

Through figure 8 (plotted by using data from Appendix 6), the solubility profile of ibuprofen is irregular. Particularly in 3.5% the available ethanol gets super saturated by lactose making the solution not to dissolve ibuprofen. Though ibuprofen itself has better solubility in alcohol, lactose becomes less soluble by increasing concentration in alcohol. That is why in presence of 20% aqueous ethanol ibuprofen does not show enhancement of solubility profile.

Chapter 5

Discussion

5.1 Ibuprofen and Poloxamer 407

Ibuprofen is poorly soluble in water but when we use poloxamer as an excipient the solubility increases in lower concentrations of poloxamer. As poloxamer concentration gets higher (more than 3%) it will be saturated in water. Moreover, poloxamer having higher concentration is more likely soluble in alcohol rather than in water. In presence of 10% alcohol (in figure 3), solubility of ibuprofen is increased progressively within the poloxamer concentration reaches to 1.5%. in 2% concentration of poloxamer, ibuprofen has a rapid solubility profile and then the solubility increases gradually up to 3% of poloxamer concentration. In presence of 20% ethanol as solvent (showing in figure 4), ibuprofen solubility increases gradually in presence of poloxamer as both has better solubility in alcohol. In 20% alcohol, ibuprofen solubility increases rapidly when poloxamer concentration is up to 1.5%. After 1.5%, solubility increases sluggishly with the poloxamer concentration (in poloxamer 407 concentration of 2%, 2.5% and 3%). We did not take poloxamer concentration exceeding 3% as resulting saturation and has no solubility of drug.

5.2 Ibuprofen and Lactose

Ibuprofen is poorly soluble in water but lactose has a good solubility in water. So, in presence of water, lactose dissolves without any saturation. The calibration curve (figure 6) shows a rapid solubility profile of ibuprofen in presence of lactose using water. In presence of 10% alcohol (in figure 7), solubility of ibuprofen is very little increased within the lactose concentration reaches to 4%. Then in concentration 6% ibuprofen solubility decreases a little. But when lactose concentration increases to 8% and 10% solubility of ibuprofen again increases slowly. Solubility of ibuprofen in presence of 10% alcohol shows an irregular

profile as lactose has poor solubility in alcohol. In presence of 20% ethanol as solvent (showing in figure 8), solubility remains nearly persistent up to in 3% of lactose. But in 3.5% lactose concentration, lactose is not soluble in ethanol and it becomes super saturated.

Chapter 6

Conclusion

From the above discussion, poloxamer could be a good choice of ibuprofen solubility as solubility enhances in both aqueous and alcoholic media. Followed by, lactose could be a good choice of ibuprofen solubility only in aqueous media if it has no effect in ibuprofen solubility. On the other hand, lactose could be used in 10% ethanol but must use carefully with 20% ethanol. The objective I had set before starting my lab work is to determine if solubility of ibuprofen changes significantly in presence of poloxamer and lactose excipients or not. The above finding indicates both the excipients have significance in the drug‟s solubility. Particularly ibuprofen in lactose has shown a very satisfactory result while using water as a cosolvent, then solubility increases indicating a successful result. On the other hand, in 10% and in 20% ethanol solution using lactose makes the solution supersaturated. So, solubility of ibuprofen did not occur significantly.

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Appendix1:

Table 2: Poloxamer 407 solution in water

Lactose Concentration	Absorbance	Ibuprofen Concentrations	Average	%Err
0.0%	0.153	117.69	111.79	1.84
	0.141	108.46		
	0.142	109.23		
0.5%	0.874	672.30	645.12	1.51
	0.813	625.38		
	0.829	637.69		
1.0%	1.464	1126.15	1135.12	0.29
	1.485	1142.30		
	1.478	1136.92		
1.5%	1.956	1504.61	1505.64	1.76
	2.044	1572.30		
	1.872	1440.00		
2.0%	2.324	1787.69	1808.71	1.52
	2.451	1885.38		
	2.279	1753.07		
2.5%	2.731	2100.76	2058.71	0.74
	2.664	2049.23		
	2.634	2026.15		
3.0%	2.676	2058.46	2073.58	0.45
	2.68	2061.53		
	2.731	2100.76		

Appendix 2

Table 3: Poloxamer 407 solution in 10% aqueous ethanol

Lactose Concentration	Absorbance	Ibuprofen Concentrations	Average	%Err
0%	0.271	208.46		
	0.288	221.53	209.23	2.29
	0.257	197.69		
0.50%	0.624	480.00		
	0.622	478.46	486.41	1.03
	0.651	500.76		
1%	1.133	871.53		
	1.148	883.07	875.12	0.317
	1.13	870.76		
1.50%	1.70	1309.23	1282.56	0.725
	1.65	1270.01		
	1.64	1268.46		
2%	2.77	2137.69	2140.76	0.451
	2.81	2166.15		
	2.75	2118.46		
2.50%	3.12	2400.76	2427.17	0.379
	3.17	2440.00		
	3.17	2440.76		
3%	3.26	2514.61	2557.94	0.690
	3.32	2556.92		
	3.38	2602.30		

Appendix 3

Table 4: Poloxamer 407 solution in 20% aqueous ethanol

Poloxamer Concentrations	Absorbance	Ibuprofen Concentrations	Average	% Error
0%	0.343	263.84	270.01	1.213
	0.363	279.23		
	0.347	266.92		
0.50%	1.202	924.61	922.05	0.102
	1.198	921.53		
	1.196	920.01		
1%	1.921	1477.69	1505.38	1.027
	2.014	1549.23		
	1.936	1489.23		
1.50%	2.602	2001.53	2044.87	0.741
	2.682	2063.00		
	2.691	2070.02		
2%	3.136	2412.30	2418.97	0.297
	3.127	2405.38		
	3.171	2439.23		
2.50%	3.296	2535.38	2555.12	0.419
	3.361	2585.38		
	3.308	2544.61		
3%	3.405	2619.23	2615.12	0.266
	3.419	2630.01		
	3.375	2596.15		

Appendix 4:

Table 5: Ibuprofen in lactose in water

Lactose Concentration	Absorbance	Ibuprofen Concentrations	Average	%Err
2.0%	0.151	116.15	114.10	0.68
	0.146	112.30		
	0.148	113.84		
4.0%	0.195	150.02	142.82	2.18
	0.187	143.84		
	0.175	134.61		
6.0%	0.199	153.07	165.12	2.55
	0.224	172.30		
	0.221	170.01		
8.0%	0.234	180.01	182.30	0.44
	0.238	183.07		
	0.239	183.84		
10.0%	0.276	212.30	214.10	0.36
	0.281	216.15		
	0.278	213.84		

Appendix 5:

Table 6: Ibuprofen in lactose in 10% ethanol

Lactose Concentration	Absorbance	Ibuprofen Concentrations	Average	%Err
2.0%	0.225	173.07	164.10	3.03
	0.220	169.23		
	0.195	150.01		
4.0%	0.226	173.84	173.84	0.53
	0.229	176.15		
	0.223	171.53		
6.0%	0.227	174.61	174.35	0.27
	0.225	173.07		
	0.228	175.38		
8.0%	0.243	186.92	185.64	1.43
	0.249	191.53		
	0.232	178.46		
10.0%	0.244	187.69	200.76	2.48
	0.276	212.30		
	0.263	202.30		

Appendix 6:

Table 7: Ibuprofen in lactose in 20% ethanol

Lactose Concentration	Absorbance	Ibuprofen Concentrations	Average	%Err
0.5%	0.311	238.46	238.20	0.58
	0.314	241.53		
	0.305	234.61		
1.0%	0.31	238.46	238.20	0.45
	0.313	240.76		
	0.306	235.38		
1.5%	0.303	233.07	226.92	1.34
	0.298	229.23		
	0.284	218.46		
2.0%	0.311	239.23	240.76	0.22
	0.314	241.53		
	0.314	241.53		
3.0%	0.302	232.30	240.25	1.19
	0.315	242.30		
	0.321	246.15		
3.5%	0.556	427.69	444.35	1.46
	0.579	445.38		
	0.598	460.02		