Solubility of Ibuprofen with Poloxamer 407 and L-leucine in Water and Ethanol Co-solvent

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

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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.

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Approval

The project titled "Solubility of ibuprofen with poloxamer 407 and L-leucine in water and ethanol co-solvent" submitted by Rubaiya Hossain (15146089) of Spring, 2015 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on 22nd August, 2019.

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Ethics Statement

The study does not involve any kind of animal or human trial.

Abstract

Ibuprofen is a drug with very poor aqueous solubility and high permeability. Its poor aqueous solubility is one of the major problems when formulating a dosage form with it. This study was conducted by considering its poor aqueous solubility and solely concentrated on increasing the solubility. In this study the solubility of ibuprofen was examined by dissolution method using water, 10% ethanol and 20% ethanol as solvents. Poloxamer 407 and L-leucine were used as excipients. The whole study was conducted at 25ºC. Ibuprofen was found to show a significant enhancement in solubility in addition with poloxamer 407 in three of the solvent system up to a certain poloxamer 407 concentration (2%). L-leucine did not affect the solubility of ibuprofen significantly, the increment in the solubility were irregular.

Keywords: Ibuprofen; Poloxamer 407; L-leucine; Solubility.

Dedication

This paper is dedicated to my beloved parents and my dear sister for their continuous support and unconditional affection.

Acknowledgement

I would like to begin by thanking The Almighty Allah for providing me with the strength and patience to overcome all the hindrance and accomplish this project. It would be impossible to complete my project work without His mercy.

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List of Acronyms

NSAID	Non-steroidal anti-inflammatory Drug
COX	Cyclooxygenase
PG	Prostaglandin
OTC	Over-the-counter
CheqSol	Chasing Equilibrium Solubility
TPGS	Tocopheryl polyethylene glycol succinate
BCS	Biopharmaceutical Classification System
GIT	Gastrointestinal tract
rpm	Rotation per minute
mg	Milligram
gm	Gram
µg	Microgram
nm	Nanometer
CMC	Critical Micelle Concentration

Chapter 1

Introduction

1.1 Background

Ibuprofen which belongs to NSAID drug class is one of the most widely used drugs in today's world. Along with anti-inflammatory action it also has antipyretic and analgesic activity. It is a popular choice of drug to treat pain, fever and inflammation such as headache, menstrual pain, dental pain, rheumatoid arthritis etc. Ibuprofen shows its activity in treating pain by inhibiting the formation of prostaglandin. Prostaglandin is a chemical which is produced via arachidonic acid pathway with the help of cyclooxygenase (COX) enzyme. COX convert the arachidonic acid into prostaglandin H2 (PGH2). This PGH2 later convert into prostaglandin and produces pain. Ibuprofen is a nonselective inhibitor of COX. It is available as both OTC and prescription dose. Tender pain to medium pain, fever, inflammation can be treated by three of them. Low dose ibuprofen is approved as OTC drug in many countries and has good safety profile compared to acetaminophen (Rainsford, 2009). OTC ibuprofen shows very few side effects therefore has a wide clinical use record and also known as "the mildest NSAID" (Rainsford, 2009).

The most common brand name of ibuprofen is Advil and Motrin. Ibuprofen is commonly taken by orally and parenterally. Also, rectal and topical administration is possible. Ibuprofen tablets, capsules, suspensions and solutions are available for oral administration. The 200-600 mg oral dose for every six hour is the most commonly used ibuprofen dose although if the necessity is increased, it can be increased up to 2.4-3.2 gm daily (Irvine, Afrose, & Islam, 2018). The sustained release capsule of ibuprofen is administered twice daily to give the required action and can last up to 12 hours. For IV route the daily maximum dose of ibuprofen is 3200 mg (Rainsford, 2009).

Ibuprofen shows very poor water-solubility. It shows higher solubility in neutral and basic environment, as well as in the organic solvents like ethanol, chloroform, acetone and so on. Usually, factors like molecular structure, temperature, pH, surface area, dosage form etc influence the drug solubility. Ibuprofen has a polar carboxyl group and non-polar alkyl group and benzene ring. The latter two moiety reduces its polarity. This makes it significantly insoluble in polar water. Alcohol is less polar than water so ibuprofen is more soluble in it. The poor dissolution of ibuprofen affects the oral bioavailability of the drug and leads to various adverse effects, which is often seen with the higher dose of ibuprofen. As stated by Biopharmaceutical Classification System (BCS) all drugs are classified into four classes: class I (↑ soluble and ↑ permeable drugs), class II (↓ soluble and ↑ permeable drugs), class III (↑ soluble and ↓ permeable drugs) and class IV (↓ soluble and ↓ permeable drugs). Ibuprofen is a class II compound following its low solubility and high permeability (Fernandes et al., 2017). The poor water solubility is the major disadvantage of ibuprofen. Many processes have been used to increase its aqueous solubility such as microparticles spray drying process (Wikarsa, Durand, Delarbre, Baylac, & Bataille, 2008), wet granulation with β-cyclodextrin (Ghorab & Adeyeye, 2001), ibuprofen nanocrystal development by 2^2 factorial design experiment (Fernandes et al., 2017) and so on.

In this work report, the solubility of ibuprofen is compared by using Poloxamer 407 and L-leucine as excipients in both water and ethanol co-solvent at 25ºC. Pluronic F127 also known as poloxamer 407. Poloxamer 407 or Pluronic F127 is a triblock copolymer. It contains one central hydrophobic moiety and two hydrophilic moieties (Dou, Karim, & Loh, 2016). Because of the existence of both hydrophilic and hydrophobic moieties it demonstrates amphiphilic nature and thus preserves surfactant properties (Dumortier, Grossiord, Agnely, & Chaumeil, 2006). The aqueous poloxamer solution exhibits a thermoreversible property, which occupy a great attention in drug formulation strategy (Dumortier, Grossiord, Agnely,

& Chaumeil, 2006). It was found to have various properties including solubilisation, stabilising, adhesive property, gel strength and so on (Dumortier et al., 2006). L-leucine is one of the amino acids of protein, which is hydrophobic in nature (Pedroso, Zampieri, & Donato, 2015). It is more commonly used as lubricant in the pharmaceutical manufacturing (Pedroso, Zampieri, & Donato, 2015).

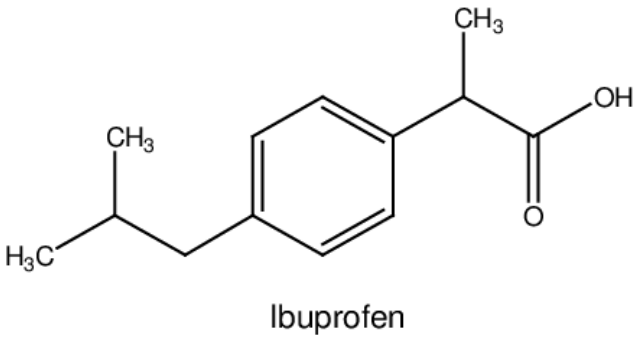

Figure 1 Structure of ibuprofen (Stoyanova, Vinarov, & Tcholakova, 2016)

1.2 Aims/ Objectives

This study aspires to improve the solubility of ibuprofen by using the excipients. The objective of this study implies on the following things-

- To elevate the ibuprofen solubility in aqueous medium.
- To examine the effect of poloxamer 407 and L-leucine in the solubility of ibuprofen in water-ethanol co-solvent.
- To find out if a better dosage form of ibuprofen can be obtained with addition of these two additives.

1.3 Significance

Ibuprofen is a poorly water-soluble drug. Ibuprofen which is a BCS class II drug, its bioavailability is restricted by the solvation rate. To be able to absorbed or diffused through small intestine the drug needs to be dissolved in the physiological medium. Since ibuprofen is a poorly soluble drug it cannot be absorbed properly which leads to a poor bioavailability. So, enhancement of ibuprofen solubility can lead to better bioavailability. Better solubility and better bioavailability lead to better pharmacological effect. Also, it is possible to develop a better dosage form of ibuprofen with enhanced solubility. Enhancement in ibuprofen solubility can lead to reduction in dose and dose frequency, which shows an overall improvement in patient's quality of life, patients' satisfaction and costs.

Chapter 2

Literature review

2.1 History of ibuprofen

Ibuprofen which belongs to NSAID drug class is a phenyl alkanoic acid compound. It is a pain reliever and widely used to treat rheumatoid arthritis. Ibuprofen is one of the newer NSAIDs that was introduced around late 1960s (Ehrlich, 2000). During 1950s and 1960s aspirin was the main drug of choice to relief pain and was available as OTC drugs (Rainsford, 2013). Stewart Adams and his team discovered ibuprofen in 1961, before that aspirin and cortisone were the first choice of drugs for treating rheumatoid arthritis (Ehrlich, 2000).

The first clinical trials with ibuprofen was inspected in six patients who were suffering from rheumatoid arthritis in Northern General Hospital, Edinburgh by Dr Tom Chalmers (Ehrlich, 2000). In 1969, ibuprofen launched in UK as Brufen™ (Rainsford, 2011). In 1974, the FDA gave approval to ibuprofen and was being marketed under the trademark Motrin™ in United States (Ehrlich, 2000). Later in 1983 (UK) and in 1984 (USA), ibuprofen got approval to be marketed as OTC drug and is now available over 80 countries (Rainsford, 2013).

2.2 Mechanism of action of ibuprofen

Prostaglandins are produced via COX pathway and are the end products of fatty acid metabolism (Rao, Knaus, Road, & Jolla, 2008). They are the major pathological and physiological arbitrator in pain, inflammation, pyrexia, cancer and other neurological disease (Peesa, Yalavarthi, Rasheed, & Mandava, 2016a).

Arachidonic acid, an unsaturated 20-carbon fatty acid is immersed as a phospholipid ester in cell membrane (Rao et al., 2008). Membrane bound arachidonate is liberated into free

arachidonic acid by phospholipase A2 and is the precursor of prostaglandin synthesis (Peesa, Yalavarthi, Rasheed, & Mandava, 2016b; Vane & Botting, 1996).

COX is an enzyme with dual role incorporates in both cyclooxygenase and peroxide reductase activity (Vane & Botting, 1996). In the COX pathway, the free arachidonic acid by COX-1 and COX-2 is converted into prostaglandin G2, which further undergoes reduction to form prostaglandin H2 (Peesa et al., 2016b). This PGH2 is further converted into PGD2, PGE2, PGI2, PGF2 and thromboxane A2 (Peesa et al., 2016b). NSAIDs like ibuprofen restrict the activity of COX-1, COX-2 and LOX enzymes to inhibit the biosynthesis of prostaglandin, leukotrienes, thromboxane which are responsible for inflammation, fever and pain.

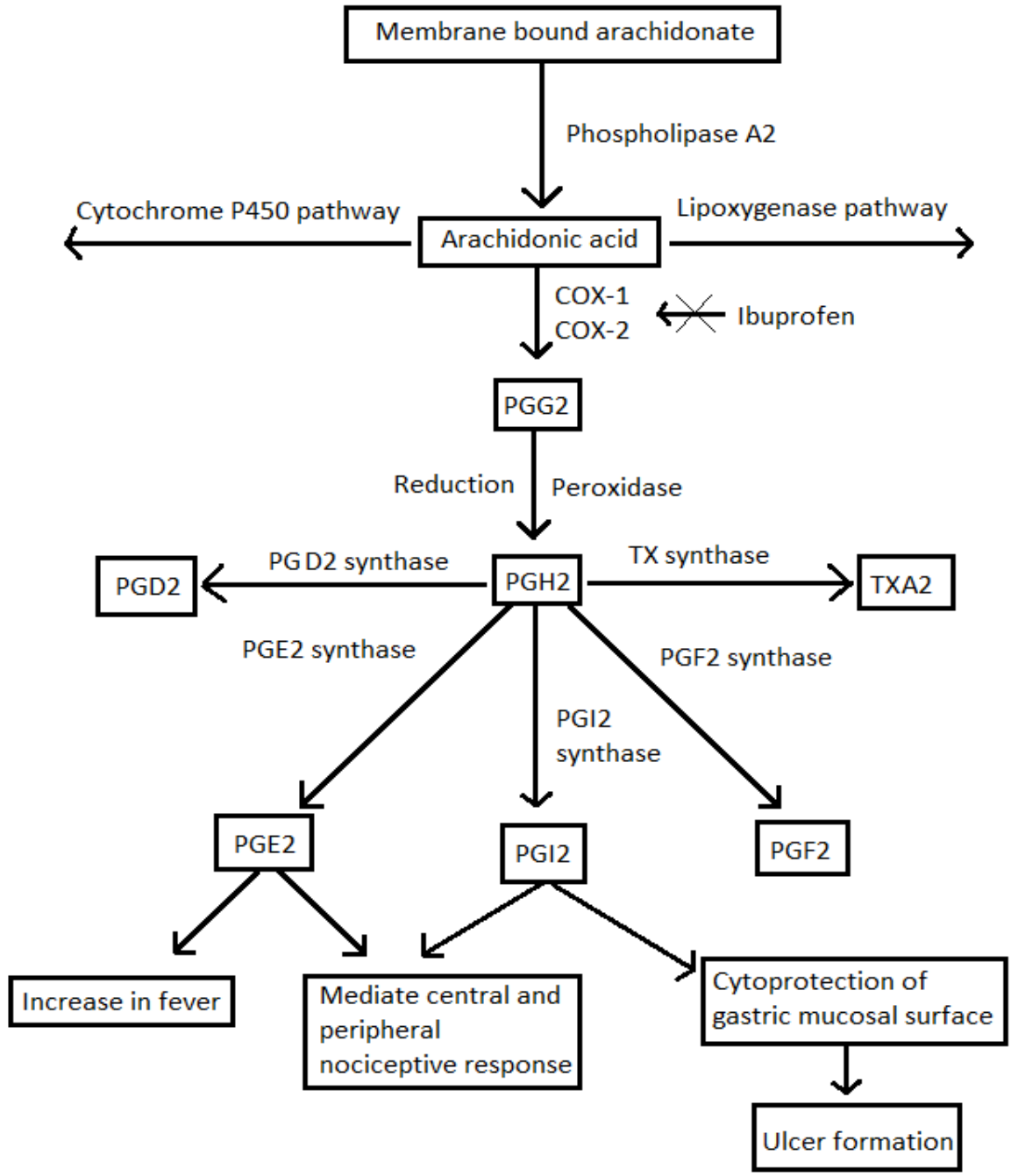

Figure 2 Mechanism of action of ibuprofen (Peesa et al., 2016)

2.3 Ibuprofen solubility

Ibuprofen shows quite insolubility in water but great solubility in many organic solvents like ethanol, methanol, acetone and dichloromethane. Ibuprofen contains two functional group (Fig. 1):

1. Carboxyl group (-COOH)
2. Aromatic group (Benzene ring)

Though ibuprofen contains the polar carboxyl group, but because of the non-polar alkyl groups and benzene ring the polarity of ibuprofen is significantly reduced ("Ibuprofen Chemistry Tutorial," n.d.). As water is quite polar, non-polar ibuprofen does not dissolve in it. On the other hand, it is more soluble in alcohols, since they are less polar than water.

Based on the solubility and permeability through bio membrane, Biopharmaceutical Classification System (BCS) categorized drugs into four categories as given below - (Kawabata, Wada, Nakatani, Yamada, & Onoue, 2011)

- Class I, belongs to high soluble, high permeable drugs

  Example: Paracetamol
- Class II, belongs to low soluble, high permeable drugs

  Example: Aceclofenac
- Class III, belongs to high soluble, low permeable drugs

  Example: Cimetidine
- Class IV, belongs to low soluble, low permeable drugs

  Example: Bifonazole

Class I Highly permeable Highly soluble	Class II Highly permeable Poorly soluble
Class III Poorly permeable Highly soluble	Class IV Poorly permeable Poorly soluble

Figure 3 Categorization of drugs according to BCS (Kawabata, Wada, Nakatani, Yamada, & Onoue, 2011)

As stated by Biopharmaceutical classification system (BCS), following its low solubility and high permeability through bio membrane ibuprofen is a member of class II (Fernandes et al., 2017). The rate limiting step of BCS class II drugs including ibuprofen is dissolution (Kawabata, Wada, Nakatani, Yamada, & Onoue, 2011).

2.4 Importance of solubility study

It is very important to perform the solubility studies for any pharmaceutical compound which can show thermodynamic properties of them. Especially for the new drug compounds performing solubility test is an important prerequisite at their early stage of development as poor soluble drugs are becoming more manifested. Most of the new chemical entities (> 40% of them) are found to be insoluble in water (Savjani, Gajjar, & Savjani, 2012). Around 60-70% drug molecules are found to show insufficient amount of solubility in aqueous media and have very low permeability to be sufficiently absorbed from the GIT upon oral absorption (Gupta, Kesarla, & Omri, 2013). For getting absorbed drugs need to be available to the absorption site in form of solution, which is a challenge for poor water-soluble drugs. If the highest strength of a drug substance is soluble in 250 ml or less of aqueous media within a

pH range of 1.0-7.5 it is considered highly soluble and it is considered poor soluble drug in vice versa (Ramesh et al., 2016). Most of the drugs are taken orally and after that they reach the GI tract, then go to the stomach then intestine. The pH in stomach is enormously low with a range of 2-4. The drug needs to be soluble at all of these pH conditions. Solubility plays very significant role in defining intestinal absorption, bioavailability, efficacy, dosing strategy and so many other parameters. Poor solubility of drugs leads to numerous difficulties concerning poor absorption and bioavailability regarding oral dosing, deficient solubility in IV, demonstration of low activity. Product development issues become a big problem due to low solubility making the product development more expensive. Also, it become a big concern for the patient as they have to take the drug quiet often as the bioavailability and absorption is poor. Various technique is being adopted to uplift the solubility problem of poor water-soluble drugs, including physical and chemical modification, reduction in the particle size, crystal engineering, salt formation, solid dispersion, use of surfactant, complexation and so on (Savjani et al., 2012).

2.5 Solvent used for solubility studies

Solubility occurs under dynamic equilibrium, it results from the concurrent and contradictory processes of dissolution and phase joining (Savjani et al., 2012). A drug is soluble or not mainly relies on the solvent used and along with the temperature and pressure (Savjani et al., 2012). Usually, the solvent used is liquid and can be either a pure solvent or a mixture of two liquids. For executing solubility studies various solvent is usually being used such as many pure solvents, water-organic cosolvent mixture or other organic cosolvents.

The Hildebrand's solubility parameter for pure solvents shows that the cohesion of the solvent has great impact on the ibuprofen solubility, as the cohesive forces of solvent increases the ibuprofen solubility decreases (Filippa & Gasull, 2013). In binary aqueous

system a non-ideal behaviour occurs and has a significant influence of solvent-solvent interactions in determining solubility (Filippa & Gasull, 2013). For aqueous organic cosolvent mixture, ibuprofen is preferentially solubilized by organic cosolvent, because of the existence of an interaction between water and organic cosolvent (Filippa & Gasull, 2013). In water- ethanol cosolvent mixture, it is found out that the solubility of ibuprofen decreases as water content increases and ibuprofen originated phase separation occurs over a broad-spectrum of water-ethanol cosolvent mixtures at 40ºC (Rashid, White, Howes, Litster, & Marziano, 2014). Cyclohexane is a pure non-polar lipophilic hydrocarbon solvent, if it is used with ibuprofen interacts with the drug by dispersion forces unlike other organic and pure solvents (Garzón & Martínez, 2004).

2.6 Enhancing solubility by decreasing particle size

It is possible to enhance the dissolution by decreasing the particle size. As the size become smaller the surface area becomes higher, which leads to greater interaction to the solvent and finally solubility increases (Savjani et al., 2012).

2.6.1 Micro-ionization

Micro-ionization is the most popular method for reducing the particle size due to its fast and easy scale-up and low production cost, however it shows electrostatic effects and broad particle size distribution (Wikarsa et al., 2008). It leads to an expansion in the solubility by elevating the surface area but does not increase equilibrium solubility (Savjani et al., 2012). At very low saturation solubility the attained expansion in dissolution rate cannot conduct to a adequately high bioavailability (Jacobs, Kayser, & Muller, 2001).

2.6.2 Nanosuspension system

However, it is possible to improve the overall bioavailability by uplifting the surface area and saturation solubility through particle size reduction in a nanosuspension system (Jacobs et al.,

2001). Also, it is possible to overcome various carrier related problem by nanosuspension system for instance limitations in drug load along with problem caused by matrix ingredients of the carrier particles (Westesen, 2000). Nanosuspension technology has been established as an auspicious contender for the competent conveyance of hydrophobic drugs and are used for drugs that are insoluble in both oil and water (Savjani et al., 2012). A pharmaceutical nanosuspension refers to a biphasic system comprising of nanosized drug particles steadied by surfactants designed for either oral and topical use or parenteral and pulmonary administration (Savjani et al., 2012). The main difference that differentiate conventional suspension and nanosuspension is the particle size distribution of the solid particles, in nanosuspension which is generally < 1μm with an mean particle size range of 200-600 nm (Fahr & Liu, 2007). Various methods are used to prepare nanosuspension such as precipitation technique, media milling, high pressure homogenization, combined precipitation and homogenization (Savjani et al., 2012).

2.6.3 Spray drying

It is another important method for preparing microparticles of dried active solutions or micro suspensions (Wikarsa et al., 2008). It relies upon mechanical stress for disaggregating the active compounds, so thermal pressure which may occur due to it is an alarm when dealing with active compounds that are thermosensitive or unstable (Savjani et al., 2012). Spray drying is also useful in altering a drug nanosuspension into a tablet dosage form which shows stability regarding drug content and in vitro dissolution profiles under both ambient and accelerated storage condition (Sun, Ni, Zhang, Li, & Mao, 2015). Another advantage is that microparticles of ibuprofen produced by spray drying shows better dissolution rate and are stable for at least six months from the date of production (Wikarsa et al., 2008). It is also considered as an economic way for enhancing solubility since the conventional mechanical stress is used to disaggregate the active ingredients (Savjani et al., 2012).

2.6.4 Hydrophobic microparticles with excipients

To increase the dissolution one way is to prepare hydrophobic ibuprofen microparticles with the addition of various excipients such as l-leucine, Pluronic F127, HPMC and D-mannitol by a controlled crystallization technique (Afrose et al., 2018). The higher number of hydroxyl group of these excipients specially D-mannitol and HPMC get distributed around the ibuprofen particles and increase the drug-solvent interaction and thus increases the dissolution (Afrose et al., 2018).

2.7 Cheqsol method

Solubility determination using the Chasing Equilibrium Solubility (CheqSol) method is considered one of the novel swift solubility screening techniques for ionisable compounds (Etherson, Halbert, & Elliott, 2014). It requires very little amount of sample and time (less than 2 hours) to do the operation. In this method three excipients were used. Which includes poloxamer 407, poloxamer 188 and hydroxypropyl-β-cyclodextrin. The CheqSol method is capable of measuring the intrinsic solubility by chasing equilibrium. As it is capable of determining the intrinsic solubility, it should have the capability to ascertain the impact of non-ionisable soluble excipients in this framework (Etherson et al., 2014). In this method, a increment in the intrinsic solubility of all the inspected compounds (ibuprofen, atenolol, propranolol, gliclazide) were found out in the presence of poloxamer 407 and 188 (highest with poloxamer 407) in a poloxamer concentration reliant manner (Etherson et al., 2014). Also, increment was obtained in the measured kinetic or solubility in a linear concentration reliant manner at a rate larger than the intrinsic solubility (Etherson et al., 2014).

Though, this method helps to detect the excipient's impact on supersaturation via kinetic solubility but then again great variation was found in the measured value (Etherson et al., 2014).

2.8 Solid dispersion system

To advance the solubility and bioavailability of ibuprofen solid dispersion system is another method that widely used. Solid dispersion ascribes to an assembly of solid compounds comprising of at least two entities, usually a hydrophilic matrix and a hydrophobic drug (Savjani et al., 2012). The most commonly used hydrophilic carrier that is used in solid dispersion polyvinylpyrrolidone (PVP), polyethylene glycols (PEGs), plasdone-S630 and surfactants like Tween-80, docusate sodium, Myrj-52, pluronic-F68 and sodium lauryl sulphate (Savjani et al., 2012). Park Young-Joon and his team developed an innovative ibuprofen-loaded solid dispersion with aqueous solution to expand ibuprofen solubility (Park et al., 2009). Solid dispersion can be made by numerous methods for instance fusion method, solvent evaporation method, lyophilization method, spray drying, co-precipitation, kneading method, co-grinding method and hot melt extrusion method, the use of surfactant (Nikghalb, Singh, Singh, & Kahkeshan, 2012; Ramesh et al., 2016; Savjani et al., 2012).

An ibuprofen loaded solid dispersion can be made by using water, poloxamer and HPMC and the impact of HPMC and poloxamer on ibuprofen can be inspected to see if it has any effect on the solubility of ibuprofen. In this way, little amount of carrier is required to prepare the dispersion system of ibuprofen by spray drying method. It is better than other method for example melting method, solvent evaporation method and solvent wetting method which were formerly reported for preparing the solid dispersion (Ali et al., 2012). In the solid dispersion system, single or additional active ingredients may exist at solid form in a carrier or matrix and have a better solubility than crystalline material. The active ingredients or drugs that are dispersed in the carrier may attain a peak chance of decrease in their particle size, which lead to the growth in surface area (Craig, 2002). The higher the surface area become, the greater the solubility occurs because the molecules with larger surface area has better contact with the solvent.

These solid dispersions of ibuprofen show sophisticated initial plasma concentrations, Cmax and AUC of drug compared to the ibuprofen powder; however Tmax, Kel and $T_{1/2}$ values of drug from solid dispersion were not meaningfully changed (Park et al., 2009). So, the use of such dispersion is only limited in those case where fast absorption is required in the initial phase. Major disadvantage of solid dispersion system is their unsteadiness; it shows variations in crystallinity and a reduction in dissolution rate with maturity (Kumar, 2017). Also, solid dispersion is more prone to get deteriorated by temperature and moisture and because of their tackiness handling is different.

2.8.1 Fusion or hot melt method

Fusion or hot melt method to develop solid dispersion of ibuprofen is a simple and an economic way (Savjani et al., 2012). It was developed to formulate solid dispersion dosage form that provide fast drug release (Savjani et al., 2012). To uplift the solution and dissolution rate of ibuprofen this method had been examined in a study with block copolymer of poloxamer 407 (Dugar, Gajera, & Dave, 2016). This approach allows to mix the drug and polymer without any organic solvent at a molecular level. Here, dual mixtures of ibuprofen and poloxamer 407 were formulated with minor levels of polymer providing a possibility of advanced drug loading without uplifting the ultimate formulation weight (Dugar et al., 2016). In this study maximum increased solubility was found in the acidic media but ibuprofen mostly remains unionized in acidic pH. To develop solid dispersion of ibuprofen by fusion method both drug and carrier need to have thermostability and the mixture of the drug and carrier in liquefied form is another prerequisite (Savjani et al., 2012).

2.8.2 Solvent evaporation method

To prepare solid dispersion by solvent evaporation the precondition is that drug and carrier both should show mutual solubility in solvent (Kar & Ahmed, 2017). In case of solvent

evaporation method for preparing solid dispersion, the benefit is that thermal breakdown of drugs and carrier can be prohibited since for evaporating organic solvent low temperature is sufficient; however, the higher preparation cost, struggle in entirely eradicating organic solvent, difficulty in reproducing crystal forms, the choice of a usual volatile solvent are some of the demerits of this method (Ramesh et al., 2016; Savjani et al., 2012). Kar and Ahmed studied the solubility of ibuprofen with a solid dispersion of ibuprofen containing PEG 20000 in combination with poloxamer 407 in a proportion of 1:3:3 made via solvent evaporation method, which showed 95.09% drug release within 60 minutes (Kar & Ahmed, 2017). Compared to ibuprofen solid dispersion formulated with PVP K30 and PEG 6000 carriers individually, the solid dispersion of ibuprofen formulated via solvent evaporation method with a combination of PEG 6000-PVP K30 exhibited a notable enhancement for both solubility and drug dissolution in in-vitro dissolution study with enough stability throughout the study (Hasnain & Nayak, 2012).

2.8.3 Hot-melt extrusion method

Hot-melt extrusion method for preparing solid dispersion shows similarity to fusion method excluding the extreme mixing of components, which is generated by the extruder (Savjani et al., 2012). In the dispersion the concentration of drug is 40% at all times (W/W) (Nikghalb et al., 2012; Ramesh et al., 2016). Gryczke and his team formulated an orally disintegrating tablet comprising ibuprofen via hot melt extrusion method, which came out with a better dissolution rate and the hot melt extrusion processing masked efficiently the unpleasant taste of the active ingredients without negotiating tablet palatability (Gryczke, Schminke, Maniruzzaman, Beck, & Douroumis, 2011).

Compared to traditional fusion method, it is more appropriate for extensive manufacturing due to its ability of continuous processing (Savjani et al., 2012). However, the drugs and matrix miscibility can become problematic, also it can be a problem for the materials which

are incompatible to heat because in the extruder the high shear forces generates high local temperature (Savjani et al., 2012).

2.8.4 Lyophilization or freeze-drying method

Lyophilization or freeze drying involves the transmission of heat and mass to and from the product under groundwork (Nikghalb et al., 2012; Ramesh et al., 2016). It is used as an alternative for solvent evaporation method (Nikghalb et al., 2012; Ramesh et al., 2016). Abdul-Fattah and N. Bhargava prepared solid dispersion of halofantrine via both solvent evaporation technique and lyophilization process, the solid dispersion of halofantrine prepared by lyophilization showed better dissolution compared to the one prepared by solvent evaporation method (Abdul-fattah & Bhargava, 2002). It had been assumed of a molecular mixing practise where both drug and carrier are co-dissolved in a shared solvent, frozen and forwarded to attain a lyophilized molecular dispersion (Nikghalb et al., 2012; Ramesh et al., 2016).

2.9 Use of surfactant to enhance solubility

Use of surfactant to expand the ibuprofen solubility is the oldest technique. Surfactants like tween-80, sodium lauryl sulphate, spans, polyglycolide glyceride, pluronic-F68, myrj-52, polyoxyethylene stearates are usually accustomed to formulate solid dispersion of poorly soluble drugs like ibuprofen (Ramesh et al., 2016; Savjani et al., 2012). Solid dispersion can be several types but the one that contains surfactant accompanied by drug and a polymeric carrier is called the ternary solid dispersion (Ramesh et al., 2016). Binary solid dispersion contains only the drug and a polymeric carrier. Addition of a surfactant in the binary solid dispersion make it more effective to improve the dissolution of ibuprofen (Giri, Badwaik, Alexander, & Tripathi, 2010).

Surfactant has the ability to reduce the surface tension which is necessary for drug solubility.

Cheng Yiyun and Yang Jiepin examined the influence of tween series surfactants on the solubility of some poor soluble NSAIDs including ibuprofen at 37ºC (Yiyun & Jiepin, 2006). The result showed that the solubility of the drugs depend on the concentration and HLB value of the surfactants, the ability range of surfactants were: Tween 80> Tween 60> Tween 40> Tween 20 (Yiyun & Jiepin, 2006). The concentration of surfactant on top of the critical micelle concentration (CMC) allows the micelle genesis, which leads to the entrapment of the drugs into the micelle. This process is called micellization, another way to expand the solubility of poorly soluble drugs (Savjani et al., 2012). Stoyanova, Vinarov and Tcholakova examined the water solubility and bioavailability of ibuprofen drugs by solubilizing it in micellar surfactant solution (Stoyanova, Vinarov, & Tcholakova, 2016). These authors found out that a strong improvement in the ibuprofen solubility occurred with SDS, SLES-3EO which are anionic surfactants and non-ionic tween 80; this is because the ibuprofen generates assorted micelles with all those surfactants and with tween 80 the maximum mole fraction of the drug in the assorted micelles was attained (Stoyanova et al., 2016).

2.10 Use of poloxamers to enhance solubility

Poloxamers are a collection of non-ionic copolymers, comprises of poly (ethylene oxide) (PEO) and poly (propylene oxide) (PPO) copolymers and organised as a triblock edifice. Based on the PEO/PPO ratio variety of poloxamers with different molecular weight are commercially available. The excipient poloxamers serves in the formulation of drugs in various way but most commonly as surfactant. Due to their immense role in the drug formulation they are considered as “functional excipients” (Patel, Patel, & Patel, 2009).

In aqueous solution, the thermoreversible gelation properties of poloxamers with high PEO content such as poloxamer 407 has a huge impact in the formulation of drug more specifically to promote the prolonged release of drugs (Dumortier, Grossiord, Agnely, &

Chaumeil, 2006b; Ivanova, Lindman, & Alexandridis, 2000; Patel et al., 2009). By using this property, it is possible to develop more advance and promising drug delivery technologies.

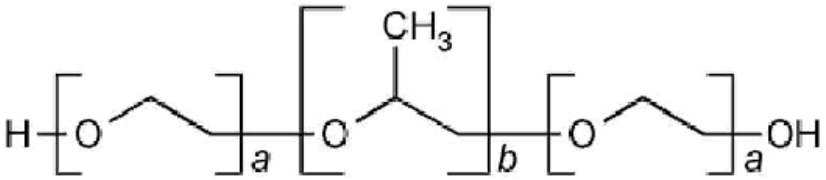

Figure 4 Poloxamer 407 structure (Grimaudo et al., 2018)

Since the PEO and PPO copolymers of poloxamer are soluble in low temperature the poloxamer aqueous solution shows a unimer status at low temperature and poor polymer concentration, an growth in the temperature propels to progress in the hydrophobicity of PPO block and results in generation of micelle (Wu, Liu, Chu, Schneider, & Graziano, 1997). Pluronic unimers are able to inhibit the drug efflux transporter in both small intestine and BBB and the incorporation of drug in the core of micelle can enhance solubility, metabolic stability and circulation time of the drug (Kabanov, Batrakova, & Yu, 2002). Nevertheless, at a suitable concentration and temperature the polymer solution can lead to the formation of micelles and their intersection conduct the development of a gel like medium with supramolecular crystalline structure (Wu et al., 1997). Poloxamer copolymers show a wide variety of microstructure and phase behaviour as a ternary system with selective solvents and co-solvents such as water and organic solvent (Ivanova et al., 2000). Ivanova along with some other co-workers in their work showed that, with propylene carbonate 2 lyotropic liquid crystalline phase (normal hexagonal and normal micellar cubic) was obtained and with triacetin 4 lyotropic liquid crystalline phase (normal micellar cubic, normal hexagonal, normal bicontinuous and lamellar) was obtained (Ivanova et al., 2000). In the work statement

of Liu and Chu, it was found out that 20-40% concentration of poloxamer 407 shows a face cantered cubic (FCC) structure in water and biological buffer; with higher concentration such as 50% of poloxamer 407 shows a body cantered cubic (BCC) structure of micelles (Liu & Chu, 2000)(Wu et al., 1997). Oils for instance butyl acetate or xylene and glycols such as glycerol or ethanol can reform the self-assembly of the block copolymer dur to their desire to situate in the diverse areas of the microstructure based on their respective polarity (Ivanova et al., 2000).

For enhancing the brain penetration of drugs various poloxamer technologies are used in the drug formulation. Many drugs have low permeability through the blood brain barrier (BBB) in the central nervous system (CNS). The presence of specific efflux transport system and macromolecules from the endothelial cells may remove or limit the penetration of drugs or other macromolecules through the BBB (Kabanov, Batrakova, & Miller, 2003). Kabanov along with some other co-workers designed a strategy to improve the drug efflux through the BBB by using pluronic co-polymers. Which just does not focus on uplifting drug BBB permeability by momentarily shifting the constructional solidarity of brain micro vessel endothelial cell (BMVEC) and neither on altering the physicochemical assets of the drug itself to enhance the diffusion, it required more information and clinical studies to show an satisfactory result (Kabanov et al., 2003).

P-glycoprotein is a membrane bound efflux pump which contribute to the multidrug resistance (MDR) by leading to an energy-dependent drug efflux and a reduction in the drug concentration (Chavanpatil et al., 2007). This P-glycoprotein mediated drug efflux can be inhibited by nanoparticles formulated with polymers like polyalkylcyanoacrylates, also pluronic block co-polymers are able to constrain the action of drug efflux transporter p-glycoprotein as micellar delivery system both in tumour cells and brain capillary endothelial cells (Chavanpatil et al., 2007; Kabanov et al., 2003). Miller and Kabanov in their study

report addressed the advantages of polymer preparations to uplift the distribution of the drugs through brain. First, the modification of the physicochemical properties of therapeutic agent is less important; second, the use of polymer micelle as drug carrier provides more favourable drug to carrier ratio than the drug-ligand conjugates and lastly, the capability of polymers to hinder the efflux transport system provides further mechanism to improve the drug conveyance to the central nervous system (Miller & Kabanov, 1999).

The addition of poloxamer in pharmaceutical encapsulation such as liposomes, nano capsule or inclusion can significantly can enhance the drug release profile; also it is considered as an optimistic polymer for ophthalmic use in combination with other polymers (Dumortier et al., 2006b). However, incompatibility or serious alteration problem may occur as poloxamer can interact with other copolymers or other components and specifically in elevated copolymer concentrations the unsuitability among copolymer can become momentous which may lead to phase separation (Dumortier et al., 2006b; Liu & Chu, 2000).

By using poloxamer in topical preparation better result had been found, a gel containing 1% piroxicam and poloxamer 407 showed better anti-inflammatory activity when studied in rats (Shin, Cho, & Oh, 2000). Use of poloxamer in nasal and parenteral formulation is not considered suitable. The slow release kinetic can become a disadvantage at the nasal absorption site and the parenteral administration of poloxamer can lead to alteration on lipid metabolism and renal filtration (Dumortier et al., 2006b).

2.11 Microemulsion system

Emulsified formulations have a somewhat longer antiquity and have revealed their ability to improve the absorption of poorly water-soluble drugs (Humberstone & Charman, 1997). However, emulsion are thermodynamically unstable and this downside can be overcome via formulating emulsions into dry powder emulsions (Fahr & Liu, 2007). Various studies have

showed that for delivering poorly water-soluble drugs microemulsion is a brilliant choice. Microemulsion is a liquid combination of oil, water, surfactant and cosurfactant. The main difference between emulsions and microemulsions is that unlike emulsion, microemulsion is thermodynamically stable, also microemulsion preparation requires less input of energy than emulsion (Fahr & Liu, 2007). Liandong Hu and some other authors performed pharmacokinetic study of a microemulsion of ibuprofen containing Labrafil M 1944CS, Cremophor RH40/, Transcutol P and 55% water on rats and found out that the oral bioavailability was 1.9-fold superior than the granule preparation of ibuprofen because ibuprofen discharged quickly in the microemulsion because of exalted solubility (Hu, Yang, Liu, & Li, 2010). Hiroshi Araya and his team performed a solubility study of nine poorly water-soluble drugs including ibuprofen on fasted rats by preparing a microemulsion containing 5% oil, 1-5% lipophilic surfactant, 5-1% hydrophilic surfactant, 5% anhydrous ethanol and 80% PBS; the result showed a 60-20,000 time solubility that to water (Araya, Tomita, & Hayashi, 2005). The amount of surfactant used in microemulsion should be sufficiently enough as excess amount can lead to side effects. Study has showed that the use of mixed oils in the microemulsion can reduce the amount of surfactant thus reduce the chance of side effects induced by elevated surfactants, also the use of excess surfactants in microemulsion does not boost up the oral in vivo bioavailability or in vitro cellular uptake (You et al., 2014). For preparing microemulsion for poorly soluble drugs the most eligible surfactants are Pluronic P84, Tween 80, BL-9EX, HCO-40 and HCO- 60; also sodium dodecyl sulphate and sodium deoxycholate is used to improve the solubilization capacity of oils (Kawakami et al., 2002). For oil, propylene glycol monoalkyl ester and glycerol monoalkyl ester are more suitable as they get solubilized easily by surfactants in aqueous medium; propylene glycol dialkyl ester can be solubilized by blending it with glycerol mono alkyl ester in 1:1 proportion (Kawakami et al., 2002).

2.12 Crystal engineering

Crystal engineering method, which can possibly be employed for a widespread range of crystalline materials, propose a substitute and efficiently productive method for upgrading the solubility, dissolution rate and bioavailability of poorly soluble drugs (Blagden, Matas, Gavan, & York, 2007). It proposes a number of routes to advance the solubility and dissolution rate, which can be accepted over an detailed information of crystallization process and the molecular assets of active pharmaceutical ingredients (Savjani et al., 2012). It comprises the formulation of hydrates and solvates for uplifting the dissolution rate, also it is likely to confine molecules of the solvent inside the lattice during crystallization (Savjani et al., 2012). The challenge of poor aqueous solubility provides an perfect condition for the implementation of crystal engineering techniques for uplifting bioavailability while also formulating steady and vigorous pharmaceutical products (Blagden et al., 2007). Traditional methods for crystallization are sublimation, crystallization from solutions, evaporation, thermal treatment, desolvation and grinding/milling; the process includes dissolving the drug in a solvent and precipitating in a skilful way to develop nanoparticles via addition of an anti-solvent typically with water (Savjani et al., 2012).

2.13 Solid lipid nanoparticles system

Solid lipid nanoparticles (SLNs) system is another widely performed system for uplifting the solubility of poorly soluble drugs like ibuprofen. Solid lipid nanoparticles are colloidal drug transporter system which are similar to nano-emulsions but with a different lipid character in which the liquid lipid portion of emulsion is substituted by a solid lipid at 25ºC such as glycerides or waxes with high melting point (Uner, 2007). They are a particulate system with a mean particle diameter ranging 50-1000nm and the overall components for SLNs comprise solid lipid(s), emulsifier(s) and water (Fahr & Liu, 2007). The use of SLNs as an innovative particle technology is growing day by day due to its capability as an substitute carrier system

towards conventional colloidal carriers for instance emulsions, liposomes and polymeric microparticles and nanoparticles; also because of their likelihood to be used in numerous routes of drug delivery (Gohla, Ma, & Mu, 2000). Various methods are used for preparing SLNs such as cold/hot homogenization, solvent emulsification-evaporation, solvent emulsification-diffusion, disintegration of o/w microemulsion, solvent injection, w/o/w emulsion, high shear homogenization and ultra sound dispersion (Khadka et al., 2014). Among all of them high pressure homogenization is regarded as ideal due to its several advantages over other methods (Khadka et al., 2014).

SLNs have adhesive properties which enables them to be adhered in gut wall and liberates the drug precisely where absorption should occur helping in enhanced bioavailability (Muller & Keck, 2004). Several studies had been done to investigate the efficiency of SLNs in uplifting solubility of poorly water-soluble drugs. In a study it was found out that the incorporation of all-trans retinoic acid (ATRA) into SLN significantly improves the oral bioavailability of ATRA by enhancing the absorption (Hu, Tang, & Cui, 2004). SLNs have several advantages such as improved drug targeting, possibility to be developed as controlled drug release delivery systems, enhanced drug solidity, no chance of bio-toxicity by carrier and capability to combine both lipophilic and hydrophilic drugs into the carrier (Khadka et al., 2014). SLNs provide a device which is both cost-effective and patient-amiable for administrating drugs via numerous routes, coating of SLN with hydrophilic elements is very auspicious for treating several diseases for instance cancer and tuberculosis; also statements on surface qualification of SLN by PEG coating have markedly significant scrutiny of numerous investigation groups with the purpose of elevating drug bioavailability (Uner, 2007). However, SLNs show some disadvantages such as poor drug loading capacities and steadiness difficulties during storage or administration (gelation, particle size increase, drug expulsion from SLN) (Khadka et al., 2014).

2.14 Use of L-leucine to enhance solubility

L-leucine had been used as coating material to uplift the ibuprofen solubility. In one of the techniques where 1% of the dry coating of L-leucine alongside with magnesium stearate, sodium stearyl fumarate and silica-R972 was applied onto ibuprofen powder by mechanofusion (Qu et al., 2015). From this experiment the dissolution rate of coated ibuprofen powder was attained at a rate higher than the raw ibuprofen powder, indicating surface coating effect improves both bulk flow and drug dissolution (Qu et al., 2015). Further it was found out that the ibuprofen powder which is coprocessed with a coating material (L-leucine), binder and super-disintegrate via mechanical dry coating shows lower disintegration time and acceptable tensile strength along with better dissolution (Qu et al., 2017). The coprocessing is done in single step.

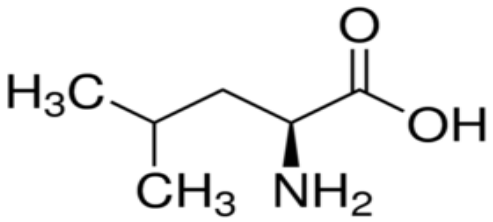

Figure 5 Chemical structure of L-leucine (Pedroso, Zampieri, & Donato, 2015)

2.15 Use of co-solvent/ lipophilic vehicles

Many NSAIDs like ibuprofen are organic acids with a pH level 3-5 and will get ionized at the pH of skin surface, but in the deeper layer of the skin due to less acidic environment and the degree of ionization increases along with solubility and permeation (Watkinson et al., 2009). Use of cosolvents such as ethanol can influence the ionization and permeability of ibuprofen into and through the skin, so an increase in the amount of the cosolvent ethanol can increase the solubility of ibuprofen relative to its aqueous solubility (Watkinson et al., 2009).

The use of lipophilic vehicles such as coconut oil [Miglyol (MG)] and light mineral oil (MO)

also influences ibuprofen transportation in silicon and human skin (Watkinson, Guy, Oliveira, Hadgraft, & Lane, 2010). In silicon, saturated ibuprofen solutions in lipophilic vehicles show high flux values than propylene glycol (PG) vehicles and lower than ethanol and ethanol abundant vehicles, also in skin from MO, MG or combination of both ibuprofen permeates more efficiently than the permeation from PG and lower than ethanol (Watkinson et al., 2010).

2.16 Use of Vitamin E TPGS

Vitamin E TPGS which is derived from vitamin E and a water soluble derivatives of it, also a non-ionic surfactant which plays the role of solubilizer in formulating poorly soluble drugs (Ghosh & Michniak-Kohn, 2012). Previously a study was reported that a positive result was obtained for poor soluble drugs by using vitamin E TPGS/HPMC and other combination of polymer/solubilizer, which reported to uplift their solubility along with permeability through skin (Ghosh & Michniak-Kohn, 2012). In case of poor soluble drugs there is a higher chance of drug nucleation due to thermodynamic challenges. When a drug with poor solubility is dissolved in the intestine with high energy, it's concentration attains a higher supersaturated value and reaches a critical concentration, which results in initiation of nucleation (Ozaki, Minamisono, Yamashita, Kato, & Kushida, 2012). Specially for the poor soluble drugs nucleation is a very critical factor as it can affect the absorption. It was stated that supersaturated formulation of vitamin E TPGS can expand the solubility but not the permeability, the presence of polymer can delay the crystallization and the contact among the drug and polymer can inhibit the nucleation (Ghosh & Michniak-Kohn, 2012).

2.17 The effect of different buffer media

The effect of different buffer media composition were also examined to increase the solubility and permeation coefficient of ibuprofen (Levis, Lane, & Corrigan, 2003). The

buffer media can influence the solubility of the drug when saturated with the drug, different pH of buffer and the existence of micelles and divalent ions are responsible for the different solubility (Levis et al., 2003).

2.18 Prodrug approach

Other approaches for instance reduction in the particle size, use of surfactants, complexation, solid dispersion when are not able to improve solubility at the expected level, prodrug approach is another option. A prodrug refers to poorly active or inactive compound and after administration it is metabolized into active drug through biotransformation or chemical or enzymatic cleavage. It has several advantages such as increased chemical or metabolic stability, less local irritation, patent line extension, reduced toxicity, improved local or oral absorption, enhanced brain penetration (Bonn, 2009). Mainly prodrugs are categorized in two groups:

1) Carrier-linked prodrugs and

2) Bio precursors.

Macromolecular prodrug is a form of carrier-linked prodrug and most frequently casted-off in designing prodrug that will be split through a cell and in specified drug-transporting systems for improving drug solubility, stability, drug release and pharmacokinetics (Jornada et al., 2016). Though it is an excellent approach for improving drug solubility but it requires extensive study to ensure the safety of prodrug.

2.19 Inclusion complex formation technique

Among all techniques that is used in solubility enhancement, inclusion complex formation technique has been used more firmly for improving the water solubility, bioavailability, dissolution rate of poorly soluble drugs (Savjani et al., 2012). In this process two principle

things are guest part and host part. The non-polar molecule or the non-polar part of a molecule is the guest part, which is installed into the cavity of host part which is another molecule or group of molecules (Savjani et al., 2012). Cyclodextrins are most frequently used as host molecules (Savjani et al., 2012). Cyclodextrins are starch derivatives and most widely used excipients to uplift the solubility of poorly water-soluble drugs (Krishnaiah, 2014). They belong to oligosaccharides with 6-8 dextrose units, all are attached by 1-4 C-C bonds (Fahr & Liu, 2007). Cyclodextrins have a relatively hydrophobic interior and a relatively hydrophilic exterior; they are capable to install the non-polar molecules or part of it into their hydrophobic part which leads to betterment in stability, water solubility, bioavailability and decreases side effects (Duchêne, Wouessidjewe, & Ponchel, 1999).

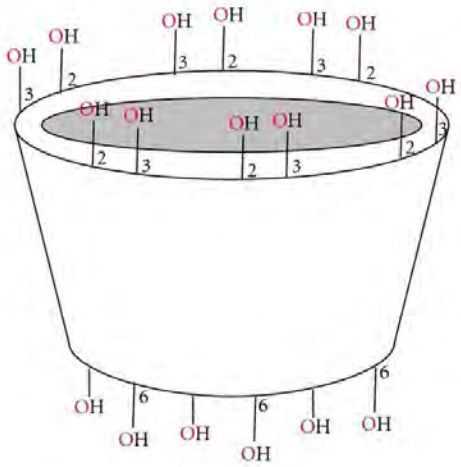

Figure 6 Representation of cyclodextrin with its hydrophobic cavity and hydrophilic outer surface (Savjani et al., 2012)

β-cyclodextrin was the very first derivative of cyclodextrin that was employed to improve the solubility of poorly water-soluble drugs but it's low aqueous solubility and nephrotoxicity led to the evolution of 2-hydroxypropyl-β-cyclodextrin, methyl-β-cyclodextrin and sulfobutyl ether-β-cyclodextrin which are less toxic and more water soluble (Fahr & Liu, 2007). The addition of poorly water soluble drugs complex with cyclodextrin can be equipped by

numerous approaches for example kneading method, lyophilization, microwave irradiation method (Savjani et al., 2012).

The topical administration of ibuprofen by solid dispersion incorporated gels along with 2-hydroxy-propyl-β-cyclodextrins and β-cyclodextrin as carriers showed better solubility and penetration through skin (Lakshmi, Kumar, Sridharan, & Bhaskaran, 2011). The oral administration of tablets comprising ursodeoxycholic acid and 2-hydroxypropyl-β-cyclodextrin complex showed upgraded dissolution rate and bioavailability in human stereotype (Panini, Vandelli, Forni, Pradelli, & Salvioli, 1995). To increase the ibuprofen dissolution rate wet granulation with β-cyclodextrin can be also used by using granulating solvents: ethanol, water and isopropanol (Ghorab & Adeyeye, 2001). Oven dried granules show much faster dissolution but can enhance the ibuprofen-β cyclodextrin complexation in solution due to dehydration of β cyclodextrin, but air dried granules does not cause the dehydration of β cyclodextrin and increases the dissolution (Ghorab & Adeyeye, 2001).

The drug-cyclodextrin complex is usually equipped via freeze-drying, spray-drying, co-precipitation of a cyclodextrin/drug solution or by simply making a drug slurry and cyclodextrin by using mortar and pestle (Carrier, Miller, & Ahmed, 2007). These approaches may comprise single or additional organic solvent, as a result there is chance of final product containing remaining noxious solvents; also the variance in complex formation methodology can disturb the release kinetics as well as bioavailability (Carrier et al., 2007). So, these methods need to be carefully controlled for preparing drug-cyclodextrin complex.

2.20 Reason for choosing my work method

In my work report the solubility of ibuprofen was investigated by dissolution method in addition with excipients. The dissolution method is considered the simplest and the most trusted method for investigating or screening the aqueous solubility of any compounds or

chemical entities. Also, it is a universally accepted method for inspecting or improving the solubility of any compounds. Two excipients were used in my dissolution study to investigate the ibuprofen aqueous solubility. Diversification in material traits of excipients can influence dissolution, design and thus the performance of the product. So, the impression of excipient diversification should be reflected in product development.

Chapter 3

Materials and method

3.1 Chemicals

Pure chemicals and analytical tools were used throughout the experimental study. Following chemicals have been used in the experiment-

3.1.1 Model drug (IBP BP)

Ibuprofen BP (Fig. 1.1) was the active pharmaceutical ingredient (API) in this experimental work. Ibuprofen BP (Lot: w010011898) was provided by BEXIMCO PHARMACEUTICALS LTD (Tongi, Gazipur, Bangladesh). A quantity of 300gm was provided for research purpose.

3.1.2 Excipients

Following excipients were used in this study-

3.1.2a) Kolliphor® P 407 micro (Geismar)

Kolliphor® P 407 micro grades are the micronized poloxamer 407 (Fig. 2.3.), which was provided by BASF Bangladesh Ltd (SAM Tower, House#4, Road#22, Gulshan-1, Dhaka, Bangladesh). Poloxamer 407 is also known by its BASF trade name Pluronic F127. 500 gm plastic bottle of kolliphor® P 407 was provided (Product Number: 50424593, Lot: GNB28621CT).

3.1.2b) L-leucine USP

L-leucine (Fig. 2.4.) is an essential amino acid with the molecular formula $C_6H_{13}NO_2$ also known as 2-amino-4-methylpentanoic acid. L-leucine USP (Lot: w010000607) was provided by BEXIMCO PHARMACEUTICALS LTD (Tongi, Gazipur, Bangladesh). A quantity of

100 gm of L-leucine was provided for research purpose.

3.1.3 Solvent

3.1.3a) Ethanol

GR grade ethanol was used as solvent in this experimental work. It was manufactured by Merck, Germany.

3.1.3b) Distilled water

Distilled water was prepared in the Brac University lab (Room No: UB30802).

3.2 Apparatus and instruments

The apparatuses and devices used throughout the experiment are listed in Table 1.

Table 1 Total number of tools utilized throughout the study and their functions

	Instruments		Functions
i)	Dropper	i)	To transfer small quantities of liquid
ii)	Disposable Syringe (5ml)	ii)	To draw solutions from the volumetric flask and push it through the micro syringe filter
iii)	Micro syringe filter (Pore size: 0.45µm, Diameter: 25mm)	iii)	To eradicate any existed particles from the sample solutions prior to the analysis in the UV-vis spectrophotometer to dodge any damage to the device
iv)	Analytical balance (Model: PA213 Manufacturer: OHAUS, USA)	iv)	Measurement of weight

Instruments	Functions
v) UV-visible spectrophotometer (Model: U-2910, MT-230, P1102 Manufacturer: Hitachi, Japan)	v) To perform quantitative determination of concentrations of the absorber in the solutions
vi) Digital shaking incubator (Model: 110-OE+ OL30-ME Manufacturer: OVAN, Spain)	vi) To perform dissolution at a stable temperature condition

3.3 Stock solution preparation

At first, 1.5 gm ibuprofen was taken in a 100 ml volumetric flask. After that, 1.5 gm ibuprofen was dissolved with 50% aqueous ethanol and was made up to 100 gm at 25ºC.

Concentration of the stock solution:

1.5 gm/100 gm = 0.015/ gm = (0.015 × 1000 mg)/gm = 15 mg/gm = 15 × 1000 µg/gm = 15000 µg/gm

3.4 Dilution of the stock solution

Dilution is a process where the concentration of solute in a solution is decreased. It is usually done by adding more solvent without adding any solute. Mathematically the relationship can be shown by following equation:

$M_1 \times V_1 = M_2 \times V_2$

Here,

M_1 = Initial concentration

V_1 = Initial volume

M_2 = Final concentration

V_2 = Final volume

The dilution for each concentration was done in triplicate and here also the room temperature was maintained which is 25ºC. The 100-gm ibuprofen stock solution with a concentration of 15000 µg/gm was diluted seven times up to 10 gm. Where the concentrations were 1500 µg/gm, 1200 µg/gm, 1000 µg/gm, 800 µg/gm, 400 µg/gm, 200 µg/gm and 50 µg/gm.

3.5 Standard curve preparation

Standard curve or calibration curve is a type of graph that is used in quantitative research. To prepare this graph multiple samples with known concentrations are measured and graphed. As a result, it allows to find out the same properties for some unknown sample. The samples with known properties are called standards. UV-spectrophotometer is used in this study and a wavelength of 264 nm was used. Since, the dilution of the stock solution was done in triplicate, the absorbance was also taken in triplicate. Then the average absorbance was taken for each concentration. Here, also room temperature was maintained. After, utilizing the value of absorbance, a graph of absorbance against concentration was generated by using Microsoft Excel Software 2016. The obtained results are given below:

Table 2 Data for the standard curve of ibuprofen in 50% ethanol

Concentration (µg/gm)	Absorbance at 264 nm
1500 µg/gm	1.868 (±0.034117)
1200 µg/gm	1.595 (±0.076603)
1000 µg/gm	1.219 (±0.182954)
800 µg/gm	1.0373 (±0.023007)
400 µg/gm	0.5163 (±0.063066)
200 µg/gm	0.2873 (±0.007767)
50 µg/gm	0.0783 (±0.009866)

For these data, following standard curve was obtained:

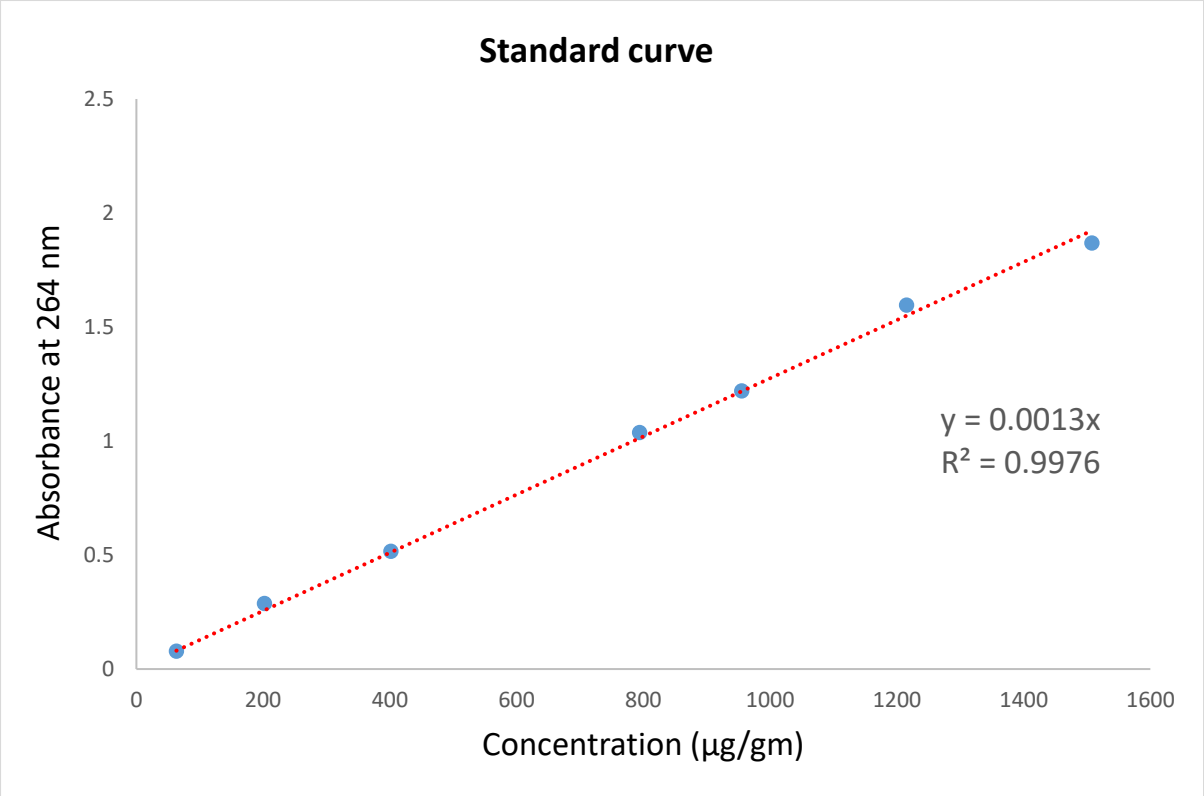

Figure 7 Standard curve of ibuprofen in 50% aqueous ethanol

3.6 Solubility of ibuprofen in addition with poloxamer 407

Kolliphor® P 407 micro grades poloxamer was used to check if it has any effect in the enhancement of the ibuprofen solubility.

3.6.1 Preparation of poloxamer solution

Three different types of poloxamer solutions were prepared with three different types of solvents. Water, 10% aqueous ethanol and 20% aqueous ethanol were used as solvent. For three of them the same poloxamer concentrations were maintained which were 0%, 0.5%, 1.0%, 1.5%, 2%, 2.5% and 3%. For three different types of solvents the solutions were prepared in triplicate. Room temperature was maintained at 25ºC throughout this procedure.

3.6.2 Shaking of the poloxamer solution in addition with ibuprofen API

Excess amount of ibuprofen API was added in each of the volumetric flask containing poloxamer solutions. Then the volumetric flasks were placed in the digital shaking incubator at 120 rpm for 6 hours (Afrose & Pharm, 2017, p. 54). Here, temperature was maintained at 25ºC as well.

After 6 hours the volumetric flasks were removed, then the solubility of ibuprofen was measured at room temperature.

3.7 Solubility of ibuprofen in addition with L-leucine

L-leucine USP was used to check if it has any effect in the enhancement of the ibuprofen solubility.

3.7.1 Preparation of L-leucine solution

Three different types of L-leucine solutions were prepared with three different types of solvents. Water, 10% aqueous ethanol and 20% aqueous ethanol were used as solvent. For three of them the same L-leucine concentrations were maintained which were 0.1%, 0.2%, 0.4%, 0.8%, 1.2% and1.5%. For three different types of solvents the solutions were prepared in triplicate. Room temperature was maintained at 25ºC throughout this procedure.

3.7.2 Shaking of the L-leucine solution in addition with ibuprofen API

Excess amount of ibuprofen API was added in each of the volumetric flask containing L-leucine solutions. Then the volumetric flasks were placed in the digital shaking incubator at 120 rpm for 6 hours (Afrose & Pharm, 2017, p. 54). Here, temperature was maintained at 25ºC as well.

After 6 hours the volumetric flasks were removed, then the solubility of ibuprofen was measured at room temperature.

Chapter 4

Result

Solubility limitations of ibuprofen were measured by means of linear regression, for all possible combinations of three different solvents and two excipients. All of the combinations did not always show rational results.

4.1 Solubility data of ibuprofen in addition with poloxamer 407

Solubility of ibuprofen was investigated in water and ethanol solvent in addition with poloxamer to see whether it increases the solubility or not. Positive results were observed with poloxamer.

(The detailed raw data for ibuprofen with poloxamer 407 in three solvent systems are provided in appendix A, B and C)

The investigation result for poloxamer 407 in ibuprofen solubility in various solvents is given below-

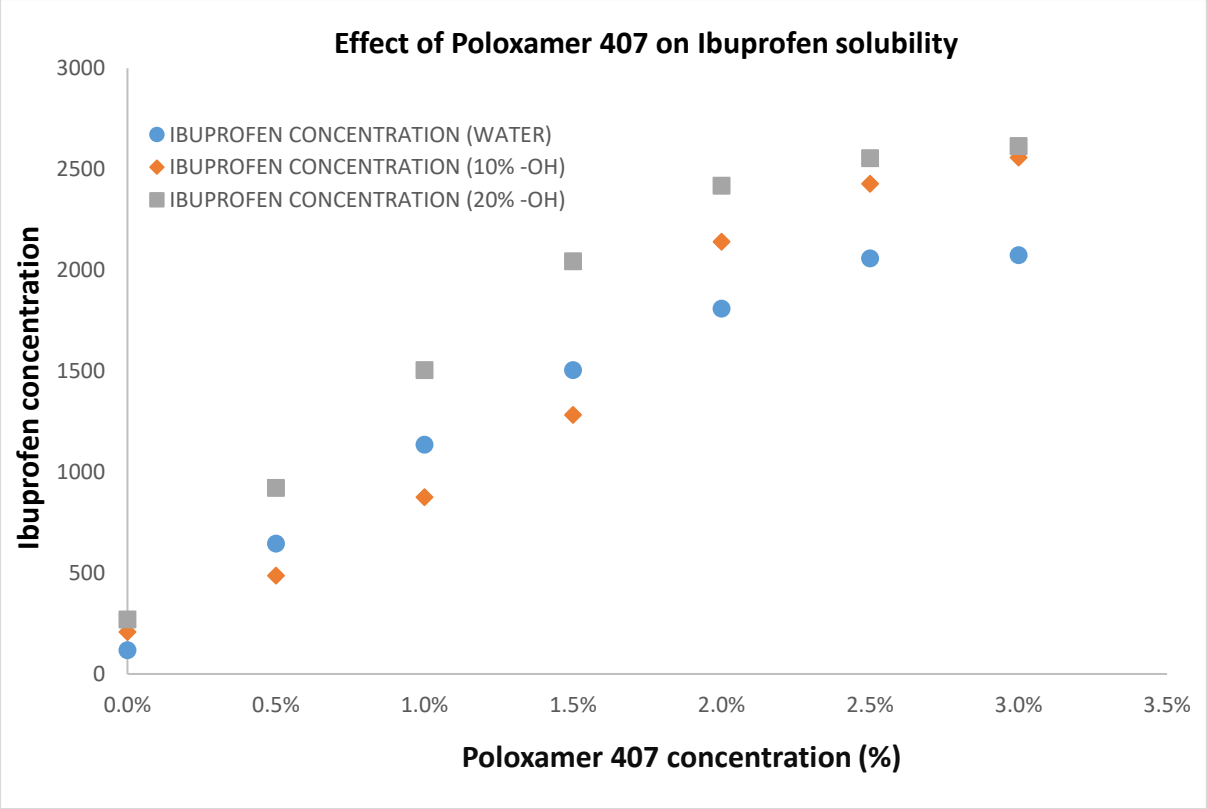

Figure 8 Effect of poloxamer 407 on Ibuprofen solubility (The blue rounds indicate the concentrations of ibuprofen in water. The orange diamonds indicate the concentrations of ibuprofen in 10% ethanol solvent. The grey squares indicate the concentrations of ibuprofen in 20% ethanol solvent)

As we can see from the graph that for poloxamer 407, the solubility of ibuprofen in water is increasing linearly up to 2.5% of poloxamer concentration and for other two solvents the solubility is increasing up to 2% of poloxamer 407 concentration. After those certain concentration values no significant change in ibuprofen solubility is happening.

4.2 Solubility data of ibuprofen in addition with L-leucine

Solubility of ibuprofen was investigated in water and ethanol solvent in addition with L-leucine to see whether it increases the solubility or not. It shows an erratic pattern of increase in ibuprofen solubility.

(The detailed raw data for ibuprofen with L-leucine in three solvent systems are provided in appendix D, E and F)

The investigation result for L-leucine in ibuprofen solubility in various solvents is given below-

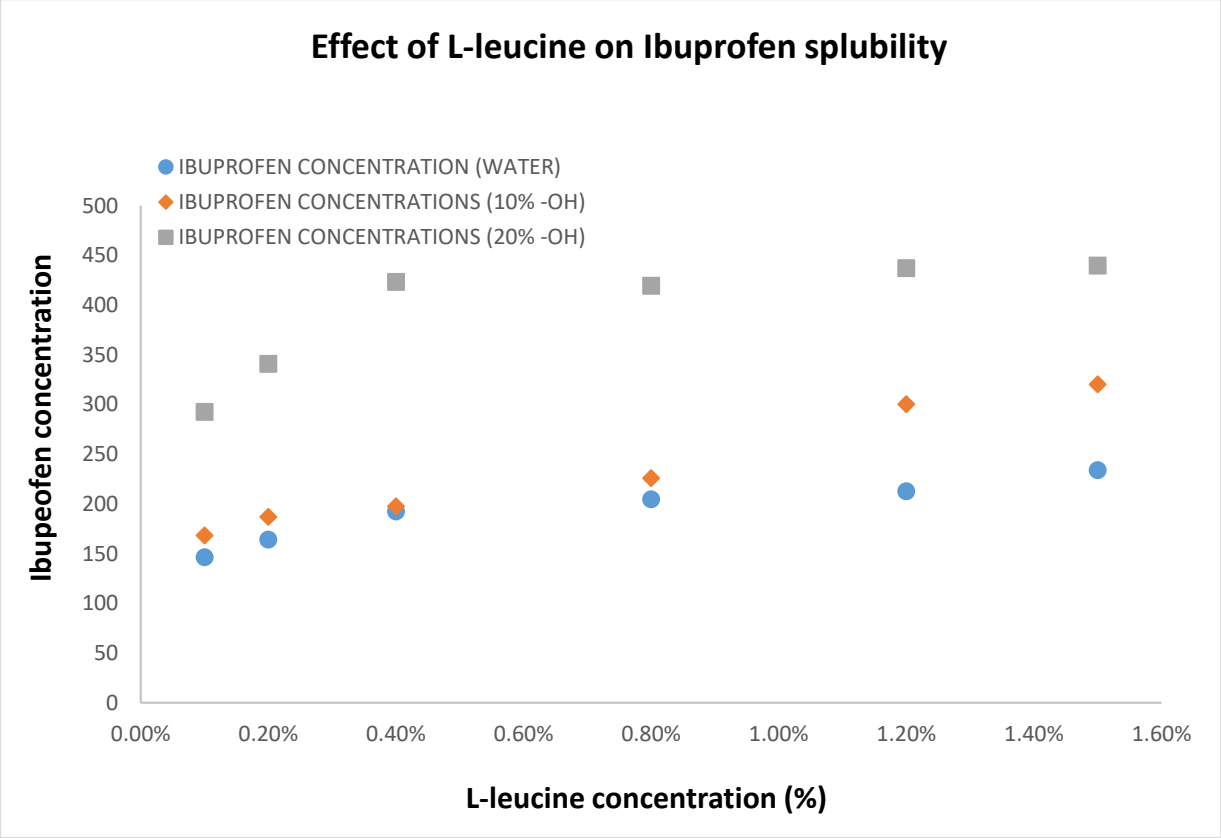

Figure 9 Effect of L-leucine on Ibuprofen solubility (The blue rounds indicate the concentrations of ibuprofen in water. The orange diamonds indicate the concentrations of ibuprofen in 10% ethanol. The grey squares indicate the concentrations of ibuprofen in 20% ethanol)

From the graph it was found that in three of the solvent the addition of L-leucine is increasing the ibuprofen solubility. However, it is not increasing linearly. The increment in the ibuprofen solubility is irregular in three of the solvents. The solubility is found to be increasing then gradual drop in increment was found and then it is increasing. So, the impact of L-leucine in the ibuprofen solubility remains insignificant.

Chapter 5

Discussion

The main purpose of this paper is to uplift the ibuprofen aqueous solubility which is a BCS class II drug with low aqueous solubility and high permeability. For this class of drug rate limiting step is dissolution. In chapter two (section 2.4) the importance of solubility study has been discussed. The poor aqueous solubility of ibuprofen leads to various problem more commonly seen with high dosage form. It leads to various problem regarding poor oral bioavailability, scarce solubility in IV dose, high production cost and patient's satisfaction. So many works have been conducted to uplift the aqueous solubility of ibuprofen and so many is still going on. This report focuses on elevating the aqueous solubility of ibuprofen in an easy, simple and satisfactory manner.

In my work study the aqueous solubility of ibuprofen was investigated by dissolution method in addition with two excipients. Poloxamer 407/ pluronic F127 and L-leucine were the choice of excipients. Throughout the experiment the room temperature was maintained at 25ºC and the samples in whole experiment was conducted in triplicate. At first a standard curve of ibuprofen was prepared by following the standard curve procedure in which the absorbance of ibuprofen was recorded at a wavelength of 264 nm. The standard curve was prepared in triplicate for ibuprofen concentrations 1500 µg/gm, 1200 µg/gm, 1000 µg/gm, 800 µg/gm, 400 µg/gm, 200 µg/gm and 50 µg/gm in 50% aqueous ethanol. The standard curve in Fig. 7 designates the linearity of the Beer-Lambert equation.

Then, sample solutions were prepared with Kolliphor® 407 which is a micro grade poloxamer 407. Sample solutions were prepared with water, 10% aqueous ethanol and 20% aqueous ethanol containing poloxamer concentrations 0%, 0.5%, 1%, 1.5%, 2%, 2.5% and 3%. In the volumetric flask containing the poloxamer sample solutions, excess amount of

ibuprofen was added then they were placed in digital shaking incubator for about six hours to ensure equilibrium. After six hours the solubility of ibuprofen was measured. Same procedure and same solvents were used for sample solutions containing L-leucine with different concentrations. In case of L-leucine the concentrations were 0.1%, 0.2%, 0.4%, 0.8%, 12%, 1.5% and 1.8%.

After investigating the effect of poloxamer 407 and L-leucine on ibuprofen solubility, it was found out that both of them show some positive effect on ibuprofen solubility. However, the results vary with the excipient concentrations.

In case of poloxamer 407, the ibuprofen solubility seems to increase linearly up to 2% of poloxamer concentrations in three of the solvent systems (Fig.8). After 2% the solubility seems to follow straight with a negligible increase. That means until 2% the poloxamer seems to have a remarkable effect in uplifting ibuprofen solubility but after that the change in ibuprofen solubility is not so noteworthy. Poloxamer 407 is a surfactant which can uplift the solubility of poor aqueous soluble drugs either by reducing the surface tension or by entrapping the drugs into micelle. So, up to 2% concentration of the existed surfactants in the solution are increasing the solubility of ibuprofen as unimer or by forming micelle. We know that until CMC the surface tension inclines to change quite dynamically due to the adsorption of surfactants at the interface. CMC is the critical micelle concentration above which the surfactant starts to form micelle. Above CMC when more surfactant is added or present, no more decline in the surface tension will occur rather they start to aggregate resulting in micelle (Dunn, Scamehorn, & Christian, 1985). Micellization is also another way to improve the aqueous solubility of drug (Savjani, Gajjar, & Savjani, 2012). Poloxamer 407 micelles entrap hydrophobic ibuprofen inside their hydrophobic PPO blocks and the hydrophilic PEO block remain in contact with the surrounding water (Bodratti & Alexandridis, 2018). However, when the excess surfactants are present in the solution and the interface become

saturated with the surfactants, the remaining extra surfactants start to aggregate by themselves into a volume. No more ibuprofen is present in that volume of micelle.

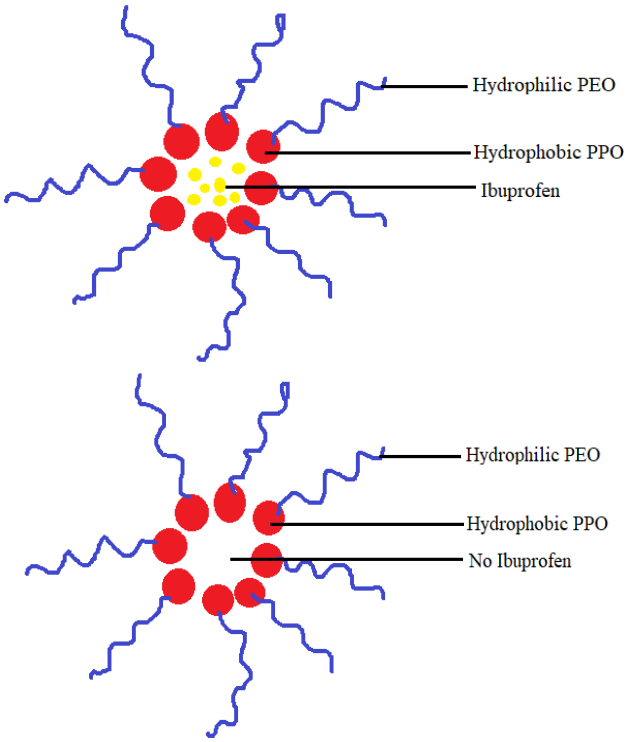

Figure 10 Solubility enhancement of ibuprofen by micellization

So, from our investigation it can be assumed that in the solution 2% poloxamer 407 concentration is the verge limit. Within the 2% concentration of poloxamer 407 the poloxamers enhance the ibuprofen solubility both as unimer and micelle (those are formed at low CMC value). Above it the CMC value increases and the excess poloxamer micelle started to aggregate by themselves and make a volume phase with no ibuprofen inside. Hence, not significant change in ibuprofen aqueous solubility seemed to happen with concentrations beyond 2%. Therefore, up to this concentration poloxamer 407 can be used in the formulation of ibuprofen to formulate a strong dosage form with better solubility and better bioavailability. Production cost can also be minimised since the extra formulation hassle of poor soluble ibuprofen can be avoided. Also, improvement in the ibuprofen

solubility will promote patient's satisfaction by lowering the dosing frequency and cost of the drug.

For L-leucine, ibuprofen shows an unpredictable pattern of increase in its aqueous solubility. From the Fig.9 it is clear that the ibuprofen solubility is varying with the L-leucine concentrations. It is not always increasing for all of the experimental L-leucine concentrations. The pattern of increase in ibuprofen solubility is erratic for L-leucine. Hence, the influence of L-leucine in uplifting the aqueous solubility of ibuprofen is not so noteworthy. However, it can act as an adjuvant in the formulation design of ibuprofen to potentiate its activity. It was found out that high leucine concentration is capable of improving particle morphology (Irvine et al., 2018). It can be used in the formulation as a carrier to deliver the drug in the targeted site of action. L-leucine can be used as performance modifier in DPI dosage form to improve the powder flow, particle deposition in lungs and particle agglomeration (Hazare & Menon, 2009). L-leucine was found to have an excellent aerosolization properties in ibuprofen particle technology, with the ability to enhance the secreted portions of powder by inducing particle formation and eliminating cohesion of spray dried particles (Irvine et al., 2018). Even though it doesn't seem to have any significant role in uplifting the ibuprofen solubility yet it can play a vital role in formulation design by modifying the activity.

Chapter 6

Conclusion

Solubility is a very important criteria that should keep in mind when formulating a drug. Solubility exhibits a major influence in determining the bioavailability, efficacy, patient's acceptancy regarding a drug. Drugs with poor solubility tend to deliver nominal concentration of drug in the systemic circulation which is undesirable at any circumstances. Ibuprofen, a BCS class II drug exhibits low solubility and high permeability. The solubility problem of ibuprofen is a chief formulation concern for it. This work report solely concerns with improving the ibuprofen aqueous solubility with poloxamer 407 and L-leucine by dissolution method. The experiment was conducted in three types of solvent system (water, 10% ethanol and 20% ethanol). Form the conducted experiment; it can be concluded that poloxamer 407 significantly elevate the aqueous solubility of ibuprofen in all solvents up to a certain concentration (2%). Above that the change in the aqueous solubility is not momentous, since the existing poloxamer 407 are not capable of enhancing the ibuprofen solubility both as unimer or micelle beyond 2% of its concentration. For L-leucine, its effect on the aqueous solubility of ibuprofen is ambiguous, as the solubility seemed not to increase in a regular manner. Gradual irregularity was seen in the solubility of ibuprofen with L-leucine in all types of solvent. Therefore, L-leucine did not seem to have a significant influence in uplifting ibuprofen aqueous solubility. However, it can act as a modifier in the formulation design.

Chapter 7

Limitations

Even though poloxamer 407 seems to have significant role in enhancing ibuprofen solubility. However, it has some toxicological data in its record. Poloxamer 407 seemed to alter lipid metabolism and renal filtration with high dosage intraperitoneal administration (Dumortier et al., 2006a). In lipid metabolism intraperitoneal poloxamer 407 administration was found to induce hypertriglyceridemia and hypercholesterolemia (Dumortier et al., 2006a). Also, intraperitoneal injection containing poloxamer 407 was found to alter the filtration capacity of kidney reversibly in rat model (Li, Palmer, & Johnston, 1996).

Thus, when formulating or designing dosage form with poloxamer 407 these facts should be keep in mind and further investigations can be done to mitigate these unwanted occurrences.

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Appendices

Appendix A

Appendix A Shows the detailed data of ibuprofen including absorbance, concentration with poloxamer 407 in water from three trials at a wavelength of 264 nm.

Poloxamer 407 Conc.	Absorbance	Ibuprofen Conc.	Ibuprofen Conc. average	STDEV of Ibuprofen conc.	% of Error
	0.153	117.6923077			
0.0%	0.141	108.4615385	111.7948718	5.12179086	1.844269
	0.142	109.2307692			
	0.874	672.3076923			
0.5%	0.813	625.3846154	645.1282051	24.3292666	1.518124
	0.829	637.6923077			
	1.464	1126.153846			
1.0%	1.485	1142.307692	1135.128205	8.22513586	0.291691
	1.478	1136.923077			
	1.956	1504.615385			
1.5%	2.044	1572.307692	1505.641026	66.1598089	1.768875
	1.872	1440			
	2.324	1787.692308			
2.0%	2.451	1885.384615	1808.717949	68.6140623	1.527097
	2.279	1753.076923			
	2.731	2100.76923			
2.5%	2.664	2049.230769	2058.717949	38.2016863	0.746982
	2.634	2026.153846			
	2.676	2058.461538			
3.0%	2.680	2061.538462	2073.589744	23.58835	0.45793
	2.731	2100.769231			

Appendix B

Appendix B Shows the detailed data of ibuprofen including absorbance, concentration with poloxamer 407 in 10% ethanol from three trials at a wavelength of 264 nm.

Poloxamer 407 Conc.	Absorbance	Ibuprofen Conc.	Ibuprofen Conc. average	STDEV of Ibuprofen Conc.	% of Error
	0.271	208.4615385			
0.0%	0.288	221.5384615	209.2307692	11.94167284	2.297545
	0.257	197.6923077			
	0.624	480			
0.5%	0.622	478.4615385	486.4102564	12.45900576	1.03111
	0.651	500.7692308			
	1.133	871.5384615			
1.0%	1.148	883.0769231	875.1282051	6.894528031	0.317145
	1.132	870.7692308			
	1.702	1309.230769			
1.5%	1.651	1270	1282.564103	23.10681824	0.725246
	1.649	1268.461538			
	2.779	2137.692308			
2.0%	2.816	2166.153846	2140.769231	23.99457532	0.451198
	2.754	2118.461538			
	3.121	2400.769231			
2.5%	3.172	2440	2427.179487	22.87518659	0.379391
	3.173	2440.769231			
	3.269	2514.615385			
3.0%	3.324	2556.923077	2557.948718	43.85514977	0.690165
	3.383	2602.307692			

Appendix C

Appendix C Shows the detailed data of ibuprofen including absorbance, concentration with poloxamer 407 in 20% ethanol from three trials at a wavelength of 264 nm.

Poloxamer 407 Conc.	Absorbance	Ibuprofen Conc.	Ibuprofen Conc. average	STDEV of Ibuprofen Conc.	% of Error
	0.343	263.8461538			
0.0%	0.363	279.2307692	270	8.140773265	1.213742
	0.347	266.9230769			
	1.202	924.6153846			
0.50%	1.198	921.5384615	922.0512821	2.350038818	0.102599
	1.196	920			
	1.921	1477.692308			
1.0%	2.014	1549.230769	1505.384615	38.40765456	1.027057
	1.936	1489.230769			
	2.602	2001.538462			
1.50%	2.682	2063.076923	2044.871795	37.68707447	0.741909
	2.691	2070			
	3.136	2412.307692			
2.0%	3.127	2405.384615	2418.974359	17.88082397	0.297564
	3.171	2439.230769			
	3.296	2535.384615			
2.5%	3.361	2585.384615	2555.128205	26.60619376	0.419174
	3.308	2544.615385			
	3.405	2619.230769			
3.0%	3.419	2630	2615.128205	17.29201569	0.266181
	3.375	2596.153846			

Appendix D

Appendix D Shows the detailed data of ibuprofen including absorbance, concentration with L-leucine in water from three trials at a wavelength of 264 nm.

L-leucine Conc.	Absorbance	Ibuprofen Conc.	Ibuprofen Conc. average	STDEV of Ibuprofen Conc.	% of Error
	0.137	105.3846154			
0.10%	0.193	148.4615385	133.5897436	24.4384668	7.364193
	0.191	146.9230769			
	0.216	166.1538462			
0.20%	0.183	140.7692308	160.3091168	17.3091168	4.347943
	0.226	173.8461538			
	0.313	240.7692308			
0.40%	0.280	215.3846154	228.4615385	12.7097782	2.23949
	0.298	229.2307692			
	0.235	180.7692308			
0.80%	0.273	210	193.0769231	15.1520889	3.159123
	0.245	188.4615385			
	0.265	203.8461538			
1.20%	0.291	223.8461538	215.3846154	10.3489416	1.934219
	0.284	218.4615385			
	0.225	173.0769231			
1.50%	0.245	188.4615385	182.0512821	8.00640769	1.770387
	0.240	184.6153846			

Appendix E

Appendix E Shows the detailed data of ibuprofen including absorbance, concentration with L-leucine in 10% ethanol from three trials at a wavelength of 264 nm.

L-leucine Conc.	Absorbance	Ibuprofen Conc.	Ibuprofen Conc. average	STDEV of Ibuprofen Conc.	% of Error
	0.280	215.3846154			
0.10%	0.220	169.2307692	198.7179487	25.6089543	5.187751
	0.275	211.5384615			
	0.510	392.3076923			
0.20%	0.249	191.5384615	280.5128205	102.311548	14.68237
	0.335	257.6923077			
	0.276	212.3076923			
0.40%	0.251	193.0769231	194.1025641	17.7145902	3.673873
	0.230	176.9230769			
	0.372	286.1538462			
0.80%	0.306	235.3846154	244.1025641	38.44102017	6.339382
	0.274	210.7692308			
	0.404	310.7692308			
1.20%	0.397	305.3846154	300.5128205	13.37518088	1.791682
	0.371	285.3846154			
	0.419	322.3076923			
1.50%	0.415	319.2307692	320.2564103	1.776462367	0.223297
	0.415	319.2307692			

Appendix F

Appendix F Shows the detailed data of ibuprofen including absorbance, concentration with L-leucine in 20% ethanol from three trials at a wavelength of 264 nm.

L-leucine Conc.	Absorbance	Ibuprofen Conc.	Ibuprofen Conc. average	STDEV of Ibuprofen Conc.	% of Error
	0.407	313.0769231			
0.10%	0.387	297.6923077	300.5128205	11.4181765	1.5295303
	0.378	290.7692308			
	0.511	393.0769231			
0.20%	0.417	320.7692308	353.8461538	36.5445339	4.1575002
	0.452	347.6923077			
	0.650	500			
0.40%	0.688	529.2307692	482.3076923	57.8357192	4.827211
	0.543	417.6923077			
	0.674	518.4615385			
0.80%	0.559	430	455.3846154	54.9717518	4.8594325
	0.543	417.6923077			
	0.569	437.6923077			
1.20%	0.569	437.6923077	437.1794872	0.88823118	0.0817882
	0.567	436.1538462			
	0.563	433.0769231			
1.50%	0.578	444.6153846	440	6.10557995	0.558597
	0.575	442.3076923			