Comparison of Lactose, Sodium Lauryl Sulphate (SLS) & Pluonic in Dissolution Profile of Ibuprofen Prepared by Crystallization Method

By

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

It is hereby declared that

1. The project submitted is my own original work while completing degree at Brac University.
2. The project 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 project 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 “Comparison of Lactose, Sodium Lauryl Sulphate (SLS) & Pluronic in Dissolution Profile of Ibuprofen prepared by Crystallization Method” submitted by Farhana Afrin Mow, ID: 14146009of Spring, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on 20/01/2020.

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Ethics Statement

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

Abstracts

Ibuprofen is widely used NSAID which deals with the treatment of mild to moderate pain formulated in various dosage forms. But poor water solubility and poor bioavailability is the drawback of this drug. So currently available marketed dosage forms are given with a high dose and it can cause adverse reactions in long term use. Lactose, Sodium Lauryl Sulphate (SLS) & Pluronic can enhance the dissolution rate of ibuprofen because all those excipients can enhance the solubility profile of ibuprofen in water. The comparison effect among these three excipients can be observed also. Precipitation crystallization technique is used to prepare ibuprofen particles to reduce the amount of dose. The experiment is done into two phase; particle preparation method (Crystallization) and dissolution method. The different dissolution time point indicates different dissolution rate for different excipients. All those contribute in lowering dose and increased the dissolution rate of ibuprofen in developed dosage forms like capsule.

Keywords: Ibuprofen, Excipient, Sodium Lauryl Sulphate, Pluronic, Dissolution rate, Crystallization method.

Dedication

This project work is dedicated to my parents for their love and constant support, my beloved husband and my respective supervisor who supported me in every spare of my work.

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Table of Contents

List of Tables

List of Figures

List of Acronyms

NSAIDs	Non-steroidal anti-inflammatory drugs
BCS	Biopharmaceutics Classification System
OTC	Over the Counter
AUC	Area under the curve
NCE	New Chemical Entities
SLS	Sodium Lauryl Sulphate
PG	Prostaglandin
CTAB	Cetyltrimethylammonium bromide
COX	Cyclooxygenase
CABG	Coronary Artery Bypass Graft
GIT	Gastrointestinal Tract
PEO	Polyethylene Oxide
PPO	Poly Propylene Oxide
BA	Bioavailability
TEN	Toxic Epidermal Necrolysis
NMDA	N-methyl-D-aspartate receptor

Chapter 1

Introduction

1.1 Background

Ibuprofen, a drug or medicine which is a non-steroidal anti-inflammatory drug belongs in (NSAID) class. Generally, it is used for managing pain, fever, and irritation as nicely as it also treats menstrual or period pain, migraines, as well as rheumatoid arthritis. It also additionally useful for enclose the patent ductusarteriosus in case of preterm infant. The route of administration of ibuprofen can be orally or intravenously. It typically starts working inside an hour after taking the medication. The chemical formulation of ibuprofen is $C_{13}H_{18}O_2$.

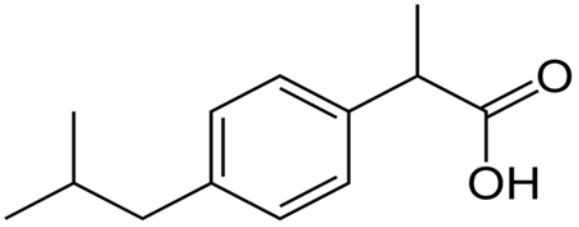

Figure 1: Ibuprofen

(UCLA Chemistry & Biochemistry, 2016)

Ibuprofen is derived from propionic acid which is a small molecule. It is also known as starting of the propionics. Ibuprofen has the chemical formula which is called- 2-(4-isobutylphenyl) propionic acid. There are some synonyms of ibuprofen which are:

- (±)-2-(p-isobutyl phenyl) propionic acid
- (±)-ibuprofen
- (±)-p-isobutyl hydra tropic acid
- (±)-α-methyl-4-(2-methylpropyl) benzene acetic acid

- (4-isobutylphenyl)-α-methylacetic acid
- (RS)-ibuprofen
- 2-(4-isobutylphenyl)propanoic acid
- 4-isobutylhydratropic acid etc (Brogna, 1986).

Ibuprofen contains a chiral carbon and has twice unique enantiomeric types of it which stay in distinct organic outcomes. The S-enantiomer is called the biologically active form of it, and the R-enantiomer is called having no biological activity or biologically inactive, are partly transformed to the S-enantiomer into human being (Afrose, 2017).

Initial development of ibuprofen had been in 1990. It is developed at some stage in gaining knowledge of for a better choice for aspirin. In 1961, ibuprofen was subsequently patented and the drug was once very firstly introduced to wards rheumatoid arthritis in UK in 1969 as well as USA in 1974 (Brogna, 1986).

Ibuprofen is poorly soluble in water and this drug is from the Class II of Biopharmaceutics Classification System (BCS) (Afrose, 2017). In this class, the drugs have high permeability and low solubility of drug. Ibuprofen is soluble in mostly in natural solvents for example ethanol (66.18 g/100mL at 40 °C for 90% EtOH), methanol, acetone and dichloromethane. It is recognized that the drugs which are water insoluble, are in the main hydrophobic in nature. They have a better affinity to penetrate extra unexpectedly towards the lipophilic intestinal membrane. So the absorption of those capsules in GI tract is now not up to the mark because the fact of insolubility of the drug in water (Nerurkar, Beach, Park, & Jun, 2005).

The inclusion of ibuprofen is performed rapidly as well as gets completed where as it is taken by mouth. The region beneath the plasma concentration-time curve (AUC) of ibuprofen is identified as dependent on doses. Ibuprofen considers the concentration-dependent manner with plasma albumin; the drug binds with it substantially. When the doses increased higher

than 600mg, the enlargement of the unknot fragment of the drug leads to an accelerated dispensation of ibuprofen and a diminished AUC of this complete drug. Considerable concentrations of ibuprofen which are accomplished in synovial fluid, that is a recommended site of motion for non-steroidal anti-inflammatory drugs (Davies, 1998).

Ibuprofen which can escalate the prospect of fatal heart attack or stroke, specifically if it is used for life long or clutch in a high amount, or if a patient is suffer from heart disease. It should be conscious about using the drug just before or after heart bypass surgery (coronary artery bypass graft, or CABG).

Ibuprofen can also originate stomach or intestinal bleeding, which can be deathly. These consequences can originate without knowing while taking of ibuprofen is in a large amount, especially for the adult persons. Ibuprofen overdose can also harm the condition of stomach or intestines. So only the smallest amount of medication is needed and can give relief from pain, swelling, or fever (Pain & Sense, 2019).

A learn about to decorate the dissolution rate of ibuprofen, a badly water insoluble drug which is used to be conveyed via combining particular formulations and approaches with the addition of a hydrophilic carrier for the preparation of micro particles. By the spray drying of ibuprofen micro suspensions which are formulated in the aqueous system in the presence of ethanol, micro particle production system used to be carried out. No change is performed in case of crystalinity and in case of chemical structure of ibuprofen. Dissolution performance of ibuprofen micro particles carried up to 100% in 3 minutes in contrast with much less than up to 10% for the ibuprofen which is not modified. The aid of the both modification of components and the spray drying method is ended up with the feasible extend to the dissolution rate of the examined model drug (Wikarsa, Durand, Delarbre, Baylac, & Bataille, 2008).

The word ‘excipient’ is acquired from the Latin word ‘excipere’ which means ‘to except’, that is simplified as the word called ‘other than’. Pharmaceutical excipients are generally everything without active pharmaceutical ingredient (API) of a drug. The descriptive definition of excipient is- “Pharmaceutical excipients are the materials or stuffs which are except than the active pharmaceutical ingredient (API) present in a drug, that have been conveniently examined for the protection harmlessness of the drug as well as that are willfully incorporated in the drug delivery system (Excipients, Excipients, & De, 2019).”

Main ideal properties of an excipient are given below:

- Stable and reproducible
- Cost effective
- Pharmacologically inert
- Desired functionality
- No interaction with drug or API

There are many roles of excipients in the formulation of drug. Some of them are mentioned below:

- During the manufacturing of an excipient, it encourages the process of the drug delivery system
- Excipients are utilized to enhance the patients’ acceptability of a drug. They also help to save, preserve and protect the drug formulations as well as enhance the stability and bioavailability of the drug
- Excipients help in case of product identification as well as enhance any quality of the overall safety

- The effectiveness and/or the delivery of the drug can be prolonged by using appropriate excipients
- Excipients also helps to keep the unification of the drug product during storage condition (Excipients et al., 2019).

In this research experiment, three different excipients are used to formulate three different capsule formulations of ibuprofen; the excipients are Lactose, Pluronic & Sodium Lauryl Sulphate (SLS).

Lactose as an excipient is the most oftentimes used in many pharmaceutical industries. Pharmaceutical dosage form contains a large portion of lactose as an excipient (About 60%–70% of pharmaceutical dosage forms). In case of volume, lactose is so called one of the biggest pharmaceutical excipient. Lactose can serve in many ways in the formulation of a drug like as a filler which gives bulk to the tablets for specify, gives the property for binding which gives the strength to form the structure along with maintain the formulation, gives the flow property to the formulation during production of the drug etc. Lactose can also assist to carry the drug molecule to the location of action in the body. A large number of industrial or pharmaceutical category lactose shows the different identification criteria for every identified drug formulation provocation. Different category of lactose shows the different properties during drug production. There are lots of special manufacturing strategies in the pharmaceutical companies which are used for making special categories of lactose. Lactose has multifaceted characteristics, for that reason it is impervious for utilization, tremendously has the low price as well as broadly accessible in different varieties (Access, 2019).

Sodium lauryl sulphate (SLS) is a surface-active agent which is called by the term of sodium dodecyl sulfate (Park & Choi, 2006). SLS is anionic surfactant. In accepted this migrates to the surface of liquids, the place its alignment and aggregation with different SLS molecules which

lowers the surface tension. This helps to make the spreading more easily and mixing of the liquid easily. The chemical formula of sodium lauryl sulphate (SLS) is $C_{12}H_{25}NaO_4S$ (Lee & Maibach, 2006).It has the quantity of purposeful uses which are counted as:

- It is utilized as an emulsifier agent
- It is used as modified-release agent
- It is used to enhance the penetration of drug molecule
- It is used as solubilizing agent in the formulation of tablet and capsule lubricant etc.

But now a day's SLS has no longer use of in the preparation of parenteral products (Medicines Agency, 2015).

Pluronic is a nonionic surfactant which is a polymer well suited with many different substances. It has micellar properties and its thermal gelation behavior render structures with first-rate solubility as nicely as offers appropriate delivery rate (Domínguez-Delgado et al., 2016). Pluronic has notable gel-forming capability, excessive adsorption capacity, and biocompatibility. It has been tested to be potential carriers for transport of distinct drug molecules for most routes of administration inclusive of oral, topical, intranasal, ocular, and parenteral. Moreover, these biomaterials are in a position to generate structures with predictable pore sizes and degradation rates for bone and cartilage regeneration. This entry summarizes latest developments in their properties and functions for biomedical and pharmaceutical uses. In the last 5 years, modified Pluronic has been significantly explored to develop successful systems with new physicochemical properties such as hydrophilicity, size, and surface charge. This method has improved the hydrophilic, vectorization, stability, mucoadhesivity as well as low protein adsorption and opsonization for the duration of circulation, ensuing in prolonged blood circulation for parenteral systems. Important benefits have been produced in the areas of mucosal transport of poorly absorbed drugs, particularly

peptides and proteins, which have extended their drug residence time (Domínguez-Delgado et al., 2016).

Permeability and dissolution rate of a drug can be accelerated by means of the use of a surfactant. Mechanism includes first of all moist capability and then inserting of solvent in the molecules of drug. Solubility of water insoluble tablets may be elevated via potential of utilize of surfactant. Surfactants are divided into three categories; anionic, cationic and non-ionic. Anionic surfactants and cationic surfactants are selected over the non-ionic surfactant. It works as pinnacle solubilizing agent (Solubility enhancement of poorly water soluble drugs: a reviewKesarwani, Rastogi, Bhalla, & Arora, 2014).

For the whole absorption and desirable bioavailability of orally administered drug, it must be disintegrating into the gastric juice. Dissolution rate of drug is called as the rate-controlling step which counts the rate and degree of absorption of that drug. Those have dissolution rates normally exhibit erratic and deficient absorption rate along with low bioavailability when it is administered by mouth. As long as the characteristics of low aqueous solubility and sluggish dissolution rate of BCS kind II and category IV drugs, it becomes the most essential challenge in improvement of drug and transportation procedures, improving water solubility and gradual dissolution rate of BCS Class II and Class IV drugs which have been scrutinized extensively (Saharan, Kukkar, Kataria, Gera, & Choudhury, 2009).

The experiment is established on the dissolution study of the distinctive formulations of ibuprofen capsules. Dissolution of a drug is the term which is imperative criterion of pharmaceutical dosage forms. This is nicely recognized that, inside the body condition dissolution testing, whether or not in enhancement or in motion, it is dependent on to display formulations of the drug considering some factors of enhancement and make certain each and every excellent control (Beyssac & Lavigne, 2005).

Oral dosage forms stay one of the most flexible and effective treatments accessible to patients. Dissolution testing is a requirement for all solid oral dosage types and is used at some point of the development life-cycle for product release and stability testing. It is a pivotal analytical test used for detecting physical adjustments in an API and developed product. At the beginning of the drug improvement process, in-vitro dissolution checking out underpins the optimization of drug-release from a given formulation.

The effectiveness of an oral dosage form relies upon the intrinsic capability of the drug to dissolve in the fluids of the gastrointestinal tract prior to being absorbed into the circulation. Therefore, the rate of dissolution of the capsule or tablet is pivotal to this technique (Alley, 2016).

Dissolution, the term is identified as the procedure through which solid components receives into solvent to produce a solution. In another word, this term is the manner via which a solid substance gets dissolved (Hamid, n.d.).

Dissolution rate would possibly additionally be described as extent of drug substance that moves in the solution per unit of time beneath quality stipulations of liquid or solid interface, temperature and solvent configuration. It might be also regarded as the specific kind of effective heterogeneous response by which a huge switch consequences as a total impact between get away and placement of solute molecules into the solid surface (Anonim, n.d.).

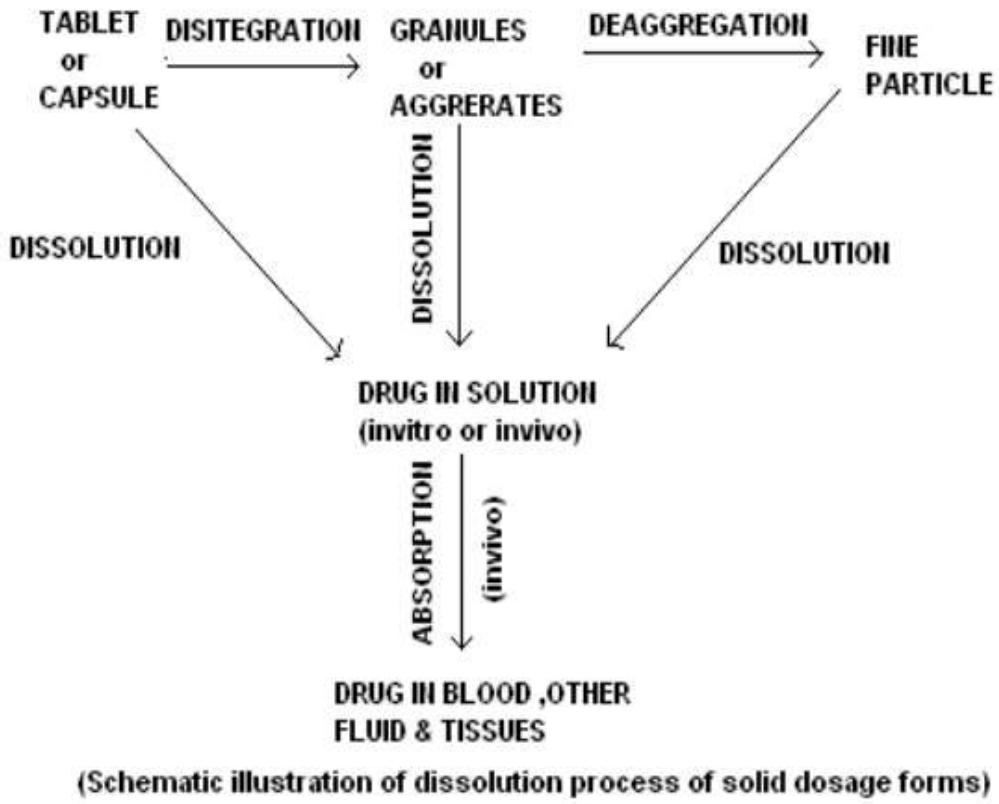

Figure 2: The approaches concerned in case of the dissolution rate of solid dosage forms

(Anonim, n.d.)

Dissolution rate testing is a vital phenomenon to identify the act of oral solid dosage forms. The magnitude of dissolution testing which depends upon the topic that is the drug has to be functional, it has to first be free from the drug and soluble in the gastric juice earlier than the absorption happens into the bloodstream in the body. On the other hand, the rate and extent of drug dissolution and absorption are recognized via the dissolution rate of the drug from its dosage form.

A dissolution rate checking calculates the quantity of drug which passes into solution over the duration of phase beneath the quality conditions. Features that have an effect on the dissolution rate of a drug product consist of the inherent characteristics of the active pharmaceutical ingredients (API) (e.g., solubility, moist ability, particle size, surface area, morphology, polymorphs), the components composition and traits (e.g., excipients, hardness, manufacturing

process), as well as the dissolution techniques which are utilized for theevaluation (e.g., apparatus, medium, test conditions, sampling, and sample analysis) (May, 2019).

Different elements can change the dissolution rates which are given below:

- Physical and chemical properties of drug
- Factors for drug product formulation
- Processing factors
- Aspects correlated with the dissolution instruments
- Aspects correlated with dissolution test parameters (Anonim, n.d.).

Crystallization the term is described as the solidification of atoms or molecules into a tremendously shaped referred to as crystals. It mentions to the gradual precipitation of crystals from the solution of a particular material. Though these crystals may have a structure from a pure soften or immediately from which is depositional from the gaseous phase. This procedure can moreover mention to the solid-liquid separation and purification technique that can make huge switch takes location into the liquid solution to the pure solid crystalline segment (Science, Helmenstine, & May, 2019).

Crystallization is the most important method for making particles in pharmaceutical companies as well as it performs an essential functional activity in defining the balance and the properties of drug release of the ultimate dosage forms (Shekunov & York, 2000).

The purposes of the crystallization technique into the pharmaceutical organizations are the removal of the contaminants and dissociation technique for the segregation as well as synthesis of uncontaminated active pharmaceutical components (API), co-crystals, con- trolled release pulmonary drug delivery system as well as severance of chiral isomers (Rohani, 2010).

Ibuprofen is crystallized from a δH≥8 liquid such as from C_1 to C_3, e.g., methanol; it assists to obtain ibuprofen crystals which are equant (cube, sphere or grain) in shape. Ibuprofen crystals which have highly large common particle size, higher bulk density, decrease bulk quantity and elevated glide properties in contrast to previously acknowledged bulk ibuprofen crystalline products (Documents, Pdfs, Free, & Easypdfcombine, 2019).

A new favorable formula of drug is synthesized chemically; it needs to transform it for getting expected formulation to show the proper action of drug in drug binding location. Pre-formulation learn is about is the section which is started as quickly as the developed molecular structure is seeded. The studies of physical, chemical, analytical, and pharmaceutical properties associated with molecule and provide the concept about suitable change in molecule is offered by that to exhibit a greater activity. Learning about the parameters and appropriate molecular change may be related with the technology of efficacious, secured, fixed as well as reliable pharmaceutical dosage form. Consequently, pre-formulation analyze about is an approach for technology of pharmaceutical technique which makes use of known- section and place utility of toxicology, biochemistry, medicinal chemistry, and analytical chemistry (Paridah et al., 2016). This helps to give a vision and knowledge about the improvement of pharmaceutical dosage forms.

The research work starts with the crystallization of ibuprofen (API) containing three different excipients (Lactose, Pluronic& Sodium Lauryl Sulphate). There are many edges of crystallization technique which are:

- Elevated decontamination of the sample can be gained in an individual step.
- Assemble a solid form that can become appropriate for straight to packaging and selling.

- Need beneath temperature and beneath energy that is required and it is corresponding to distillation step.
- It is cheap or cost effective than other separation techniques (Science et al., 2019).

After making the crystals, they are used to formulate three different capsule formulation of ibuprofen containing Lactose, Pluronic & Sodium Lauryl Sulphate individually. Dissolution of these three ibuprofen capsule formulations was monitored in given gastrointestinal track (GIT) media to find out which formulation was giving the better dissolution rate.

1.2 Aim

Basically the research paper is based on pre-formulation study. The aims of this research paper are mentioned below:

- It aims to determine the dissolution rate of ibuprofen in case of using three different excipients (Sodium Lauryl Sulphate, Lactose & Pluronic) which have numerous effects on the dissolution profile of ibuprofen.
- It aims to find out the effect of different excipients and make a comparison study among those excipients which are used in this experiment.
- It aims to study on the convenient dosage form of ibuprofen which is capsule dosage form prepared by precipitation crystallization method of ibuprofen.

1.3 Significance

The procedure of a suitable dissolution rate of pharmaceutical dosage form must take under the consideration depending on a number of parameters spanning the API, formulation and analytical method. In-vitro dissolution test ought to grant a robust body of data in order to guarantee the product performance and quality. Throughout the procedure, this is necessary to ensure that the in-vitro dissolution resembles in-vivo conditions. If the dissolution procedure

is designed effectively, it will accelerate the drug development, and ideally limit the need for human research too (Alley, 2016).

In the designing and development of drug products from available drug(s), some of the essential non-therapeutic supplies are essentially included. The products which do not have any therapeutic effects are commonly termed as excipients. Excipients are components of complicated medication items different than the dynamic pharmaceutical fixing (API) and are included in amid detailing for a precise reason. Excipients as like different dynamic pharmaceutical fixings need to be settled and institutionalized. They go about as defensive operators, building specialists and can likewise be utilized to enhance bioavailability of medicinal drugs in a few occurrences. Particular excipients are most fantastic for a particular dose frame (Y.Prasanna Raju, V. Jayasri, B. Rubia Yasmeen, V. Harini Chowdary & S. Satyanandam, 2011).

Dissolution study of ibuprofen capsules gives different the data about the rate of dissolution of the capsules containing different excipients. It shows different absorption and dissolution rate at different time point which provides the ideation about the pre-formulation quality of ibuprofen capsules. The performance of the capsules containing different excipients can also be determined by observing the dissolution data. If the in-vitro dissolution media is designed properly; the samples of the ibuprofen formulations will show the exact absorption and dissolution rate at different time point which will help to identify the most affective formulation of ibuprofen.

As the samples of ibuprofen are formulated by using different excipients, mostly appropriate excipient can be chosen among all the excipients by analyzing the dissolution rate of the samples. The dissolution data will show the bioavailability of the drug formulation. By this procedure we can formulate a perfect ibuprofen capsule formulation using the appropriate excipient and that will give proper and enhanced drug activity in our body.

Chapter 2

Literature review

2.1 Introduction

This chapter is basically primarily based on the background of research topic, highlight the development in the field, assessment and distinction of specific studies involving the topic, discussing the controversial components which helps to identify the predominant gaps about the topic as well as highlighting the magnitude of the research work (Engelbrecht, 2015). Based on that, this chapter begins with the discussion about the API (Ibuprofen) and dissolution profile of it in details as the background and why the sample has been chosen as API of the research experiment. Besides that, this chapter will also focus on pre-formulation study as well as different formulations of ibuprofen and compare and contrast among the formulations of ibuprofen. There are three different types of excipients have been used in different formulations. Why these particular excipients have been chosen in the experiment will be discussed in this chapter. In this research experiment capsule formulation of ibuprofen has been chosen. Why this particular formulation has been chosen here also will be focused on this chapter. As it is a pre-formulation study, during formulation of capsule fillers (crystallization of ibuprofen using different excipients) crystallization method is used. In this chapter, why crystallization method has been chosen will be described also.

2.2 Therapeutic application of ibuprofen

Ibuprofen [(+/-) 2-(p-isobutyl phenyl propanoic acid $(CH_3)_2CHCH_2$-$C_6H_4CH_3CHCO_2H$] is properly acknowledged as a non-steroidal anti-inflammatory (NSAID), analgesic as well as antipyretic agent. This drug is weakly acidic drug which having excessive permeability via stomach due to the fact it stays 99.9 % unionized in stomach (pKa of Ibuprofen – 4.43, pH of

gastric fluid – 1.2). This drug generally permeable via stomach however it is due to the solubility imitate ion that cannot penetrate into the systemic circulation and gastric empting time which is from 30 min to 2 hr (Mission, 2011).

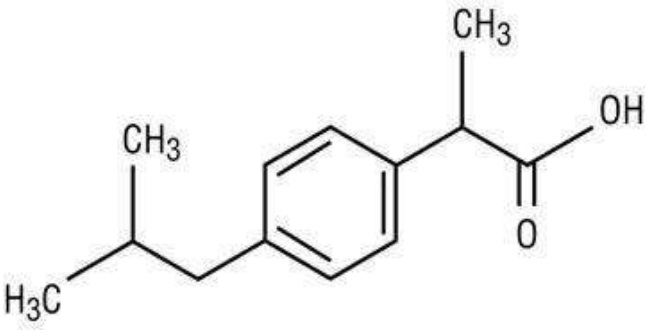

Figure 3: Structure of ibuprofen

(Designs & Weissman, 2011)

The lower amount dose of ibuprofen is highly admirable as aspirin and paracetamol for treating various symptoms of particular diseases and these medications are counted as the over the counter medicines (OTC Drugs). Ibuprofen is extensively utilized as an analgesic, an anti-inflammatory and an antipyretic agent. Recemic ibuprofen and S(+) enantiomers of ibuprofen are typically utilized in the remedy of average to reasonable pain associated to dysmenorrheal or menstrual pain, headache, migraine, postoperative dental pain, administration of spondylitis, osteoarthritis, rheumatoid arthritis as well as smooth tissue disorder. A wide variety of distinctive movements of non-steroidal anti-inflammatory drugs (NSAIDs)might moreover be allocated for the prevention of prostaglandins (PGs) or thromboxane synthesis, such as in case of adjustment into the platelet attribute (PGI2 and Thromboxane), prolongation of gestation and labor (PGE2, PGF2A), gastrointestinal mucosal destruction (PGI2 and PGE2), fluid and electrolyte disparity (renal PGs), untimely discontinuation of ductusarteriosus (PGE2) and bronchial asthma (PGs) (Bushra & Aslam, 2010).

2.3 Pharmacodynamics of ibuprofen

There are distinctive inflammatory passages regarding with long term and short term inflammation where ibuprofen has several movements. The most important consequences mentioned in case of ibuprofen which are associated with management of pain, fever and short term inflammation with aid of the impediment of the synthesis of pro-steroids on the way of COX-1 and COX-2. Comfort from pain is ascribed to fringe influenced territories as well as focal sensory system outcomes in torment transmission interceded through the dorsal horn and upper spinothalamic tract. A few surveys have attempted to interface the agony guideline with a doable improvement on the combination of endogenous cannabinoids, activity on the NMDA receptors. Effects on agony have been demonstrated which is connected with the cortically excited possibilities.

The antipyretic effect is referenced by the connection to the effect on the prostanoid amalgamation because of the way that the prostanoids have lots of significances flagging go between of pyresis in the hypothalamic-preoptic area.

Ibuprofen administration in different patient having rheumatic illnesses has demonstrated to oversee joint manifestations. Ibuprofen is to a great extent utilized in OTC items, for example, a specialist for the administration of dysmenorrheal.

In case of analytical utilization of ibuprofen, it has been expressed to limit neuro-degeneration when given in low dosages over quite a while. Then again, its utilization in Parkinson malady is related to the essentialness of aggravation and oxidative worry in the pathology of this condition. The utilization of ibuprofen for breast malignant growth is related to an investigation that demonstrates a lesson of half in the pace of breast cancer disease (Brogna, 1986).

2.4 Mechanism of action of ibuprofen

The careful instrument of activity of ibuprofen is obscure. Be that as it may, ibuprofen is respected a NSAID and henceforth it is a non-specific inhibitor of cyclooxygenase, that is a protein stressed in prostaglandin (arbiters of agony and fever) and thromboxane (triggers of blood coagulating) combination by utilizing the arachidonic corrosive pathway.

Ibuprofen is a non-selective COX inhibitor and consequently, it hinders the action of both COX-1 and COX-2. The hindrance of COX-2 exercise diminishes the amalgamation of prostaglandins engaged with intervening aggravation, agony, fever, and growing while the restraint of COX-1 is thought to reason a portion of the reactions of ibuprofen which incorporates GI ulceration (Brogna, 1986).

2.5 Metabolism of ibuprofen

Ibuprofen is quickly used and bio transformed into liver for the development of basic metabolites which are mentioned as hydroxylated and carboxylated subordinates. It is consumed as soon as the R-enantiomer experiences colossal enantiomeric transformation (53-65%) to the greater dynamic S-enantiomer in vivo by utilizing the movement of alpha-methyl acyl-CoA racemes.

Ibuprofen digestion may be partitioned in stage I which is identified to by means of the hydroxylation of the isobutyl chains for the development of 2 or 3-hydroxy subsidiaries saw through oxidation to 2-carboxy-ibuprofen and p-carboxy-2-propionate. These oxidative responses are completed by means of the action of the cytochrome P450 isoforms CYP 2C9, CYP 2C19 and CYP 2C8. Consequently, these proteins partake in the oxidation of the alkyl side chain to hydroxyl and carboxyl subsidiaries. From this chemicals, the significant impetus in the arrangement of oxidative metabolites is the isoform CYP 2C9.

The metabolic stage I went with through a stage II where the oxidative metabolites can furthermore be conjugated to glucuronide before discharge. This movement structures phenolic and acyl glucuronides (Brogna, 1986).

2.6 Solubility of ibuprofen

Medication substances are grouped into four significant classes dependent on their dissolvability parameters just as permeability to bio-layers, and this sort of characterization framework is mentioned as a Biopharmaceutical Classification System (BCS). The BCS framework is isolated into four significant classes and the medications are arranged dependent on three main considerations administering bioavailability, in particular, disintegration, solvency, and permeability (Sachan, Bhattacharya, Pushkar, & Mishra, 2009).

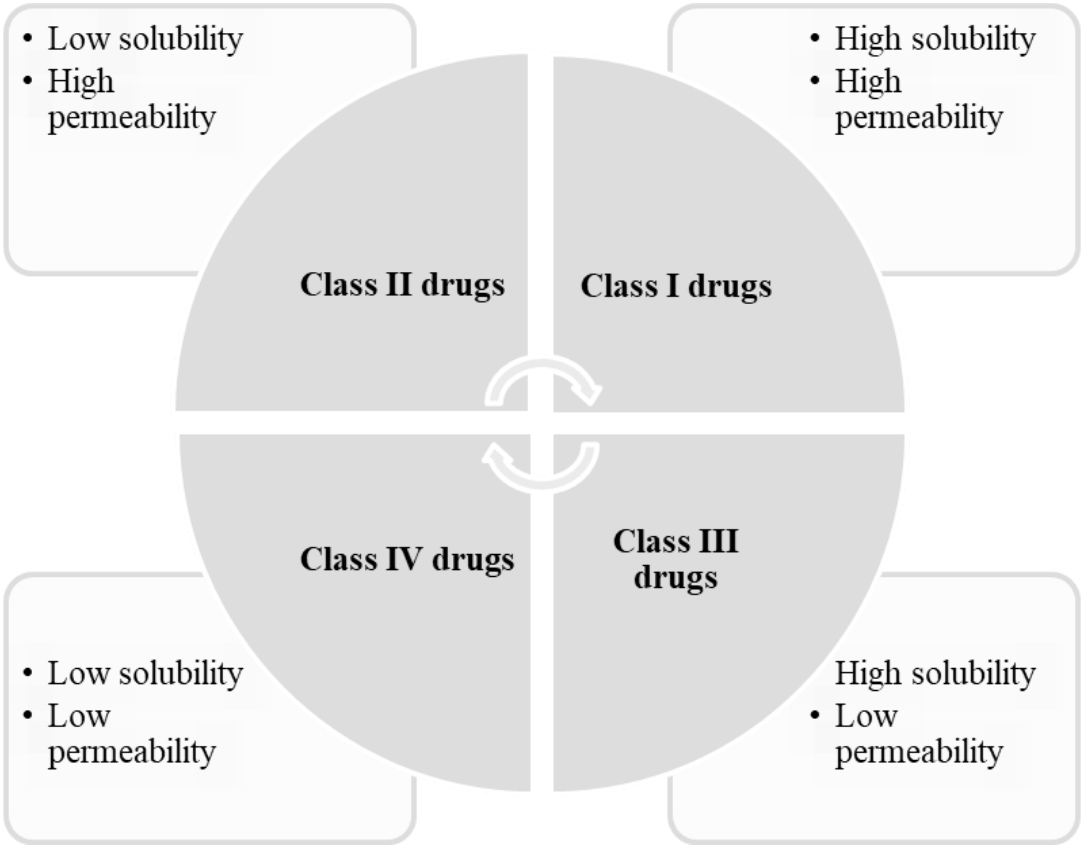

Figure 4: Biopharmaceutical Classification System (BCS)

Ibuprofen is an inadequately water-dissolvable medication which is described by disintegration restricted oral bioavailability and it has a place with Class II classification order of Biopharmaceutical Classification System (BCS) (Stoyanova, Vinarov, & Tcholakova, 2016). It is recognized that inadequately water dissolvable medications are normally hydrophobic in character, which have a superior liking to enter all the more quickly towards the lipophilic intestinal film. The poor fluid solvency qualities of ibuprofen makes troubles decide its exact dissolvability esteem in water, for example, softening point modification and temperature change because of the long haul fiery unsettling in disintegration strategy (Afrose, 2017).

2.7 Dissolution profile of ibuprofen

In vitro disintegration reads for strong oral measurements structures have right now extended the extension to a scope of particular dose structures, for example, suspensions. For class II medications, similar to Ibuprofen, it is extremely basic to have discriminative strategies for unmistakable details at physiological states for gastrointestinal tract, which will recognize particular issues that bargain the medication bioavailability. The dissolution studies are used to simulate in vitro conduct of the pharmaceutical dosage form therefore, the technique validation is required to asses' reproducibility test. These characteristics will assist to predict the in vitro overall performance (Rajpurohit, Sharma, Sharma, & Bhandari, 2015).

2.8 API (Ibuprofen) of the experiment

Ibuprofen is used as the API (active pharmaceutical ingredient) of the research experiment. There are many worthy reasons behind why ibuprofen has been chosen as an API of this research experiment.

Ibuprofen is for the most part regularly and generally utilized medication around the globe as a non-steroidal anti-inflammatory drug (NSAID). It performs by lessening hormones that reason aggravation and torment in the body. Ibuprofen is utilized to lessen fever and treat

torment or aggravation brought about by numerous conditions, for example, cerebral pain, toothache, back torment, joint pain, dysmenorrheal, or a less damage. It is an inadequately water dissolvable medication. The measure of portion of ibuprofen is given in various sums as per illness, for example,

- Normal dose for adults in case of dysmenorrhea:

200-400 mg orally given every 4 to 6 hours or as needed.

- Normal dose for adults in case of osteoarthritis:

Initial dose: 400 to 800 mg orally given at every 6 to 8 hours.

Maintenance dose: It can be increased to a maximum level, daily dose can be 3200 mg based on patient response and tolerance.

- Normal dose for adults in case of rheumatoid arthritis:

Initial dose: 400 to 800 mg is orally given at every 6 to 8 hours.

Maintenance dose: It can be increased to a maximum level, daily dose can be 3200 mg based on patient response and tolerance.

- Normal dose for adults in case of pain or fever:

Oral: For mild to moderate pain: 200 to 400 mg is given orally at every 4 to 6 hours as needed for the patient. Amount of doses greater than 400 mg do not give any higher efficacy.

IV: ⁽Patients should be hydrated properly before IV ibuprofen administration⁾

Pain: 400 to 800 mg is given intravenously over 30 minutes in every 6 hours as needed.

Initial: 400 mg is given intravenously over 30 minutes

Maintenance: 400 mg is given in every 4 to 6 hours or 100 to 200 mg is given in every 4 hours as needed.

- Normal dose for adolescents in case of Fever or Pain:

Greater than 6 months to 12 years: 5 mg/kg/dose for temperature less than 102.5 degrees F (39.2 degrees C) orally given in every 6 to 8 hours as needed. 10 mg/kg/dose for temperature greater than or equal to 102.5 degrees F (39.2 degrees C) orally given in every 6 to 8 hours as needed. The recommended maximum daily dose is 40 mg/kg.

- OTC pediatric labeling (analgesic, antipyretic):

6 months to 11 years: 7.5 mg/kg/dose is given in every 6 to 8 hours;

Maximum daily dose: 30 mg/kg is given (Pain & Sense, 2019).

From the mentioned dosing information of ibuprofen, it is clear that a large amount of ibuprofen is given to the patients. But it is harmful for the patients as it can cause many short term and long term effects to the patients. There are some common short terms and long terms side effects of ibuprofen are:

Short term side effects:

- Decreased appetite
- Nervousness
- Swelling or rapid weight gain
- Bloating, gas, diarrhea (Pain & Sense, 2019)
- Dizziness
- Rash
- Vomiting
- Constipation
- Ringing in the ears

- Drowsiness
- Nausea
- Stomachache
- Heartburn

Long term reactions:

- It makes differences in normal visions
- Shortness of breath ⟨even with gentle exertion⟩
- Swelling or quickly weight gaining (Pain & Sense, 2019)
- Liver despondency or aggravation of the liver
- Lower platelet check
- Blood present intourine
- Urinary tract contamination
- A situationwhen the bone marrow can’t make enough white platelets, known as agranulocytosis
- Lower amount of red blood cell or anemia
- Serious and conceivably perilous skin responses, for example, Stevens-Johnson Syndrome or poisonous epidermal necrolysis (TEN)
- Stroke
- Heart attack
- High blood pressure (in general a more serious hazard with long haul utilization and keep in mind that taking certain different drugs)

- Harmful kidney problem (Sense, 2017).

Bioavailability (BA) is a term utilized in pharmacology and nutritional and ecological sciences. In pharmacology, it alludes to the degree and rate at which a regulated medication is consumed by utilizing the body's circulatory framework, the foundational dissemination. Bioavailability is an essential estimation instrument considering the way that it decides the right measurement for non-intravenous organization of a medication (Industry, Glossary, & Stone, 2019). Ibuprofen is an active potential drug; smaller dose of ibuprofen can be effective for treating the particular disease in our body. As ibuprofen is an active potential drug, smaller amount of ibuprofen can show the desired bioavailability in our body. But higher amount of doses is given to the patients (10-20 times higher than the required amount of dose in our body) who are causing those serious short term and long term side effects which are not expected at all. This following research experiment deals with the smaller amount of dose of ibuprofen which gives the desired bioavailability as well as which can reduce the harmful side effects of larger dose of ibuprofen. It also shows the effectiveness of smaller dose of ibuprofen.

2.9 Different formulations of ibuprofen

There are various formulations of ibuprofen drug which have different route of administration like topical, oral, intravenous, inhalation etc. Different dosage forms of ibuprofen are:

- Tablets (film coated, sugar coated, chewable)
- Capsules (coated, liquid filled, solid filled)
- Gels
- Dry powder inhalers
- Creams
- Injection solutions

- Kits
- Suspensions
- Solutions/ Suspension drops

Among all the dosage forms of ibuprofen the research experiment is carried out with capsule formulation of ibuprofen. There are some advantages and reasons behind using capsule formulation of ibuprofen which is used for running the experiment. The advantages and reason are:

- The capsule form of dosages is more appropriate form of drugs which having unpleasant odor and taste. If those drugs are capsulated in a polymer capsule, it assists to prevent the unpleasant characteristics of the drug molecules.
- Every single capsule can contain a perfect unit dose of drugs. It helps to prevent taking increased amount of drugs too. In the research work, decreasing the amount of ibuprofen taking is one of the main targets. So capsule dosage form is the ideal formulation for the experiment. In the case of liquid or suspension based dosage forms, these types of advantages are not seen at all.
- In general capsule dosage forms require minimum numbers of excipients because the active drug molecules are safely placed inside the capsule shell, so the drug stability is maintained properly. But in case of tablets, there are required many number of excipients to maintain the stability of the tablet dosage forms (Textbook, 2019).
- As produced in large quantities capsule dosage forms are economic, attractive and available in wide range of colors. It requires little pressure to compact the material.
- The surface area of the capsule dosage forms are increased so the dissolution rate of the drug gets increased (By, 2019).

By considering all the reasons mentioned above, capsule dosage form is used to continue the experiment.

2.10 Excipients (Lactose, Sodium Lauryl Sulphate & Pluronic)

In this research experiment three different excipients are used in three different samples of capsule dosage form of ibuprofen which are Lactose, Sodium Lauryl Sulphate (SLS) & Pluronic. There are some reasons and advantages of using these excipients which are mentioned below:

Lactose:

Lactose with the chemical formula of $C_{12}H_{22}O_{11}$ is called as milk sugar. This compound is disaccharide which is made out of one galactose and one glucose particle. In different pharmaceutical business, lactose is utilized in assembling tablets because of the reality it has sublime compressibility criteria's. On the other hand, this compound also used to shape a diluent powder for dry-powder inward breaths. This compound may furthermore be recorded as lactose hydrous, lactose anhydrous, lactose monohydrate, or lactose spray-dried (Monohydrate, Ingredient, et al., 2019).

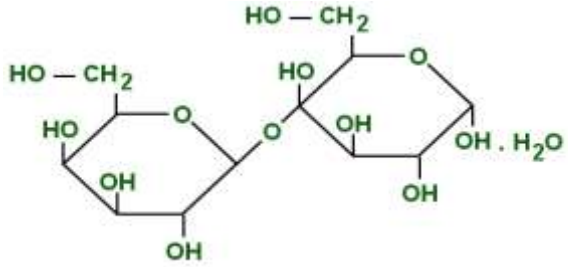

Figure 5: Chemical structure of Lactose

(Monohydrate, Of, & Intolerance, 2019)

There are several advantages of using lactose as excipients which are mentioned below:

- Its aldehyde levels are very low. Aldehydes have been embroiled in the cross connecting responses that reason no solubility of hard gelatin container shells that outcomes in expanded disintegration times. A broad diagram of the effect of aldehydes on gelatin cases can be seen in given table.

Table 1: Measured aldehyde content of certain excipients

(Use of lactose in hard gelatin capsules, 2013)

Excipients	Formaldehyde	Acetaldehyde	Other Aldehydes
Lactose	0.1ppm	ND	ND
Microcrystalline Cellulose	0.4ppm	0.1ppm	ND
Partly pregelatinised corn starch	2.5ppm	0.1ppm	ND
Mannitol	0.2ppm	ND	ND
Dibasic Calcium Phosphate	ND	ND	ND

- Lactose monohydrate and anhydrous lactose the two shows extremely lower hygroscopicity. Lactose monohydrate ingests just about 0.2% water at 90% RH, and anhydrous lactose retains around 1%. The hysteresis in anhydrous lactose plot is inferable from crystallization of the anhydrous lactose part to lactose monohydrate.
- Lactose is soluble in water and doesn't add to the blockage of certain sinkers utilized in case disintegration testing (*Use of lactose in hard gelatin capsules,* 2013).
- Lactose is cost effective as well as it is available.

- Lactose has a bland taste and low hygroscopicity.
- Lactose has good compatibility activity with the active pharmaceutical ingredients (APIs) and other excipients.
- Lactose has superb physical and chemical stability and water solubility activity (Guo, 2004).

Ibuprofen is low soluble drug and lactose can make higher the solubility and dissolution rate of the drug. Considering all these criteria mentioned above, Lactose has been chosen as an excipient in this research experiment.

Sodium Lauryl Sulphate (SLS):

Sodium lauryl sulfate ($C_{12}H_{25}SO_4Na$), a surface-active agent or surfactant which is utilized in cleaning and restorative items. It is additionally known as sodium dodecyl sulfate (SDS).In the pharmaceutical industry, it has been used as an excipient in dissolvable dosage forms (Lee & Maibach, 2006).

Figure 6: Sodium Lauryl Sulphate (SLS)

(Lee & Maibach, 2006)

SLS has various useful uses; it goes about as an emulsifying specialist, modified release agent, and entrance enhancer, solubilizing operator, tablet and capsule lubricator. It isn't prescribed for the parenteral route of administration. Approved restorative items contain SLS going from 0.15% (for example creams) to 25% (cured shampoos) (European Medicines Agency,

2017).The improvement in the dissolution rate of ibuprofen from its strong scatterings with the SLS utilized in this examination could be ascribed to a few factors, for example, improved wet capacity, nearby solubilization, and medication molecule size decrease (Tapan Kumar Giri, 2010).

Pluronic:

Poloxamers, otherwise called Pluronics , are square copolymers of polyethylene oxide (PEO) as well as polypropylene oxide (PPO), which have an amphiphilic characteristics and helpful affiliation and adsorption properties exuding from that(Bodratti & Alexandridis, 2018). Pluronic has biocompatibility, degradation behavior, and non-toxic nature on administration to human tissues. These characteristics make it acceptable for use in the administration of drugs through different parenteral and oral routes (Domínguez-Delgado et al., 2016).

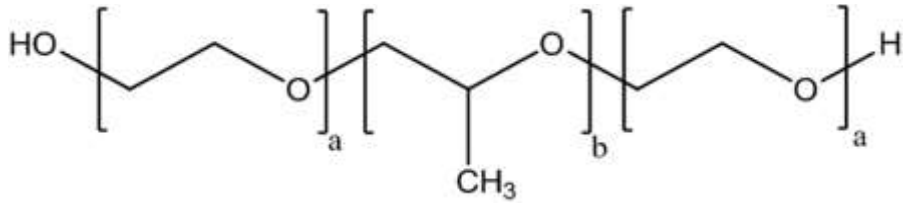

Figure 7: Structure of Pluronic

(Heuser, Schmitt, Gussone, & Wombacher, 2016)

Pluronic are polymers utilized for medication conveyance as detailing excipients. They are utilized in pharmaceutical production as surfactants, emulsifying operators, solubilizing agents, dispersing agent, and as in vivo absorbance enhancers. They are likewise utilized in topical dosage form and rectal suppositories. The regular accessible evaluations are poloxamer 68, 88, 98, 108, 124, 188, 237, 338, and 407 (Cart, 2014). Pluronics discover use in numerous applications that require solubilization or adjustment of mixes and furthermore have remarkable physiological properties, including low danger. In like manner, pluronics work well for as excipients for pharmaceutical industries. Ebb and flow difficulties confronting

nanomedicine rotate around the vehicle of regularly water insoluble medications all through the body, trailed by focused conveyance. Prudent structure of medication conveyance frameworks prompts improved bioavailability, persistent consistence and remedial results. The rich stage conduct (micelles, hydrogels, lyotropic fluid precious stones, and so on.) of pluronics makes them manageable to different sorts of preparing and different item shapes (Bodratti & Alexandridis, 2018). All these criteria of Pluronic make it capable to be an appropriate excipient for the formulation of ibuprofen.

2.11 Technology used in drug formulation

Crystallization is the technique for shaping strong material from a fluid arrangement or soften, where the solid material framed has crystalline (as adversarial to formless) structure. The feed material is both in arrangement or is a fluid over the dissolving purpose of the solid stage. On the off chance that in arrangement, there might likewise be more than one dissolvable present. There may also be broken down or strong contaminations existing in arrangement. A few polluting influences may furthermore have entirely practically identical properties to the solute (particularly for side-items from natural responses). During crystallization, pollutions can likewise remain in arrangement, take shape independently, or consolidate somehow or another into the product crystals. The item material is solid, and existing as particles in a scope of sizes. The item is normally encompassed by method for mother liquor. The waste stream from the technique is fluid, containing every remaining broke down item and polluting influences (Hallas, 2019).

In this research experiment, precipitation crystallization technique is used to formulate ibuprofen capsule fillers because there are various advantages using this technique. The reason behind using crystallization technique in this experiment is given below:

- High purging can be purchased in a solitary advance.

- Produces a solid stage which may likewise be fitting for direct bundling and deal.
- Generates at a reduction temperature and causes low vitality necessities than relating refining partitions.
- Plant may be simple and helpful to gather and keep up.
- May be more monetary than elective partition procedures (Hallas, 2019).
- This technique helps to get powder formulation of ibuprofen drug which is desired to use as capsule filler in a little amount.

2.12 Conclusion

The research paper proposes a new detain to develop the solubility and dissolution rate of ibuprofen by using three excipients; Sodium Lauryl Sulphate (SLS), Lactose & Pluronic. This chapter gives the basic information about the excipients, techniques and API which is used in the experiment. Beside this, it contains much informative information that assists to make the comparative study between the excipients and their activity on solubility, bioavailability and dissolution rate of ibuprofen.

Chapter 3

Methodology

3.1 Introduction

This following chapter, firstly shows details about primary products are mentioned which have been used in this proposed research experiment. As well as the sources and specifications of the materials are mentioned in this chapter. Beside these, all the equipment or apparatus which are used to do this research experiment; are also mentioned in details in this chapter. Lastly the details about the process how the experiment is done (methodology) are outlined and described here.

3.2 Chemicals

1.Model drug

Ibuprofen (BP)

Lot No: W010011898

Source: Beximco Pharmaceuticals Ltd

2.Lactose

L-lactose (USP)

Source: Beximco Pharmaceuticals Ltd

3.Sodium Lauryl Sulphate (SLS)

Sodium Lauryl Sulphate (Needle shape)

Lot No: L188381603

Source: Loba Chemie, Bangladesh

4.Pluronic

Kolliphor® P 407 micro Geismar

Lot No: GNB28621CT

Source: BSF Bangladesh

3.3 Solvents

1.Ethanol

Ethanol (Merck KgaA; GR grade)

Lot No: K45600783

2.Water

Distilled water

Source: Prepared in Pharmaceutical Technology Lab, BRAC University

3.4 Apparatus and Instruments

1.Weight Balance

Digital Analytical Balance 3-Digit

Model: PA2/3, Ohaus, Corp, USA

2.Magnetic Stirrer

Hot plate with stirrer

Model: LMS 1003

3.Oven

Drying Oven

Model: Eco cell 55

4.Dissolution Machine

Universal Dissolution Tester (LOGAN)

Model: UDT 804

5.UV Spectrometer

Ultra violet spectrophotometer machine

Model: UV 1280

6.Micro syringe Filter (China)

Pore size: 0.45μm

Diameter: 25mm

The whole experiment was divided into two methods; one was particle preparation method and another was dissolution study of the pre-formulated drug. Before doing these methods, preparation of stock solution and standard curve of ibuprofen were done properly.

3.5 Preparation of stock solution

To preparation of stock solution first of all, a 100ml volumetric flask was taken. 10mg or 0.01g ibuprofen was measured by Digital Analytical Balance or Weight Balance. To prepare 35% of ethanol solution, 35g of ethanol was measured by weight balance and 10mg or 0.01g ibuprofen was taken into it. Ibuprofen dissolved in ethanol properly and this solution was made up to 100% or 100ml by using distilled water.

3.6 Dilution of stock solution

The stock solution of ibuprofen was made in the laboratory by using ibuprofen active drug powder in 35% aqueous ethanol. For making the dilution of stock solution, the given concentrations were taken theoretically which are: 4µg/ml, 6µg/ml, 8µg/ml, 12µg/ml, 14µg/ml, 18µg/ml &20µg/ml in total volume of 50ml. To prepare a riveted amount of dilute solution for the stock solution, the principle which was used is given below:

$S_1V_1 = S_2V_2$, where:

V_1 = Volume of stock solution

S_1 = Concentration of stock solution

V_2 = Final volume of new solution

S_2 = Final concentration of new solution

For preparing the dilute solution 500ml of solution was needed in total. For preparing this solution, 35% or 35g of ethanol was taken to 100ml of distilled water. By calculating in this way 500ml of dilute solution was prepared.

3.7 Calibration curve preparation

For the preparation of calibration curve, different concentrated ibuprofen solutions were prepared in different volumetric flasks up to 50ml. The solutions were diluted by using dilute solution. The concentrations of different solutions were 4µg/ml, 6µg/ml, 8µg/ml, 12µg/ml, 14µg/ml, 18µg/ml &20µg/ml in total volume of 50ml. In UV Spectrophotometer Machine, the absorbencies of different solution samples were taken at 221nm. Data for the standard curve of ibuprofen drug in 35% ethanol solution is given below:

Table 2: Absorbance of ibuprofen in different concentrations for standard curve

Ibuprofen concentration (µg/ml)	Absorbance at 221nm
0	0.000
4	0.013
6	0.019
8	0.026
12	0.039
14	0.045
18	0.058
20	0.067

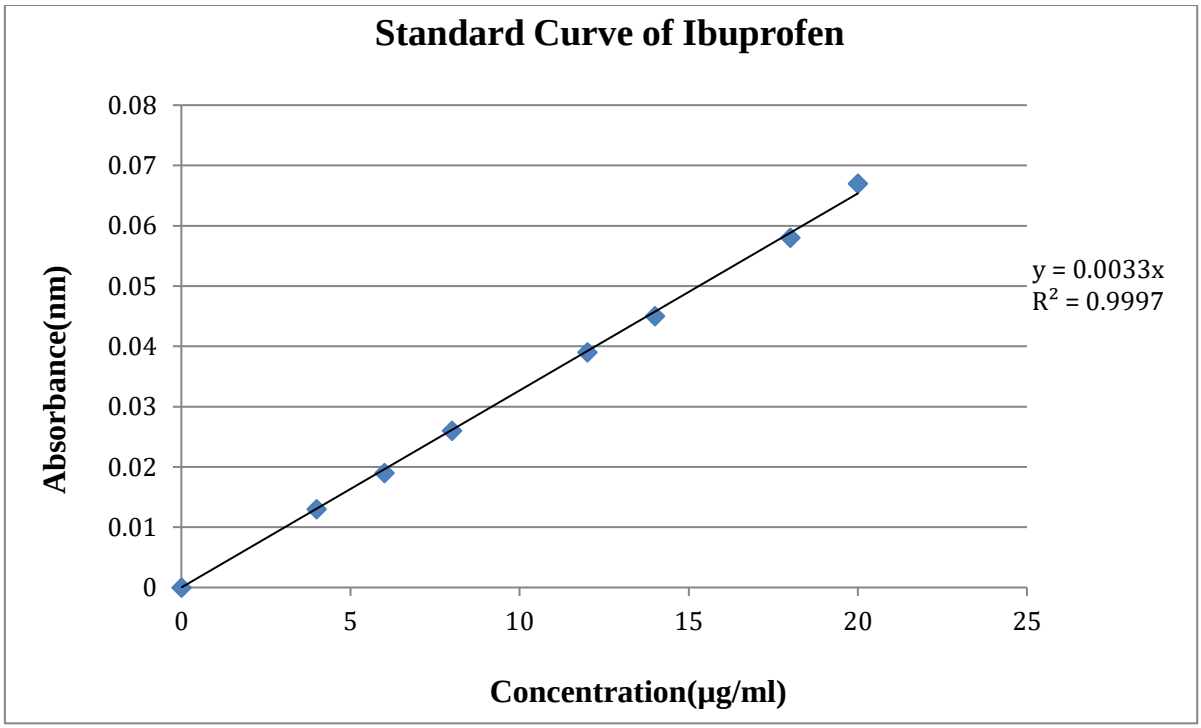

Figure 8: Standard curve of Ibuprofen

So, the standard curve of ibuprofen which is shown above gives the graphical presentation of the absorbance of ibuprofen in different concentrations obtains a straight line of regression value of 0.998 which follows the Beer-Lamberts law.

3.8 Particle preparation method

In this method, crystal particles of ibuprofen were prepared by using precipitation crystallization method using different excipients (Lactose, Sodium Lauryl Sulphate & Pluronic). This method was anti-solvent crystallization method which was involved in two different phases. The first phase was the ibuprofen was dissolved in ethanol which was called solvent phase. The second phase was the insoluble containing dissolved excipients which was called the anti-solvent phase. The ratio of solvent and anti-solvent was taken 1:9 (Afrose, 2017).

The anti-solvent was prepared individually using Lactose, Sodium Lauryl Sulphate & Pluronic and they were dissolved individually in distilled water. Lactose, Sodium Lauryl Sulphate & Pluronic all these excipients dissolve in water. On the other hand, in solvent phase ibuprofen was taken into ethanol and got dissolved. The % of ibuprofen and ethanol (Solvent) and the % of excipients (Lactose, Sodium Lauryl Sulphate & Pluronic) and distilled water (anti-solvent) was calculated by using the solvent and anti-solvent ratio. The % of ibuprofen and for different % of excipients is mentioned below:

Table 3: % Amount of ibuprofen for different amount of excipients

% of Ibuprofen	% of Excipients
2%	2% Lactose
5%	2% Sodium Lauryl Sulphate (SLS)
8%	2% Pluronic

After preparing the solvent and anti-solvent solution for each excipient, three samples of containing each excipient (45ml of anti-solvent solution) were taken in three individual conical flasks. The conical flasks were placed on the magnetic stirrer machine and the solutions were stirred with three magnets. On the other hand, 5ml of solvent was taken for each sample and infused into the anti-solvent solution by using syringe when the anti-solvent solutions were rotating. The stirring rotation speed was 600rpm and the stirring was continued for 1hour.

After stirring for 1hour, crystals of ibuprofen were formed. The crystals were taken by filtration method and after getting the crystals of ibuprofen using different excipients (Lactose, Sodium Lauryl Sulphate & Pluronic) they were dried out into the hot oven. These procedures were same for three excipients- Lactose, Sodium Lauryl Sulphate & Pluronic.

3.9 Formulation of ibuprofen capsules

After getting the dried crystal samples of ibuprofen containing different excipients (Lactose, Sodium Lauryl Sulphate & Pluronic), capsules of ibuprofen were formulated. 20mg of crystal ibuprofen containing each excipient were filled into the capsule shells and the different samples containing different excipients were formulated for testing the dissolution profile.

3.10 Test for the dissolution profile of ibuprofen

After preparing the samples containing different excipients, the samples were taken for the dissolution test. Two samples containing each excipient were taken for the dissolution test. Firstly, phosphate buffer saline solution was prepared maintaining the pH 7.4. In dissolution machine, phosphate buffer saline was given as media and the temperature risen at 37˚C and the rotation of the buffer saline was 100rmp. Two samples containing each excipient were given to the media and 5ml of the dissolution sample was taken at the time point of 2min, 6min, 10min, 15min, 20min, 30min, 60min, 90min & 120min. These samples collected from different time point were taken by a 5ml pipette and stored in different test tubes. Total 18 samples were collected at different time point for each excipient containing ibuprofen capsules. Total 54 sample were collected totally all ibuprofen capsules containing different excipients (Lactose, Sodium Lauryl Sulphate & Pluronic).

After collecting all the samples, they are filtered by the micro disc syringe filters. The pore size of the disc filters is 0.22-micron meter. After filtering the samples, they were taken to the UV spectrophotometer machine for collecting the absorbance data. Collecting the absorbance data for each formulation containing different excipients, the effects of those excipients and the comparison among those excipients can be examined properly.

3.11 Conclusion

The whole chapter is based on the description of all products and procedures which are used in the research experiment that helps to give a clear vision about the whole method of the experiment.

Chapter 4

Result and Discussion

4.1 Introduction

The chapter begins with a graphical presentation of % release of different ibuprofen formulations containing different excipients. It highlights the effects of those excipients by presenting graphs in different time point and the comparison data too. Finally, it mentions the discussion about dissolution profile of ibuprofen of different formulations.

4.2 Dissolution study of ibuprofen containing Lactose

Table 4: % release of ibuprofen containing Lactose

Time (min)	%Release of Ibuprofen	STDV	% Error
0	0	0	0
2	19.1667	3.535534	18.44626
6	25	2.357023	9.42809
10	120	2.357023	1.964186
15	135.8333	5.892557	4.338078
20	140	11.78511	8.417938
30	187.5	5.892557	3.142697
60	210	0	0
90	237.5	8.249579	3.473507
120	233.3333	9.42809	4.04061

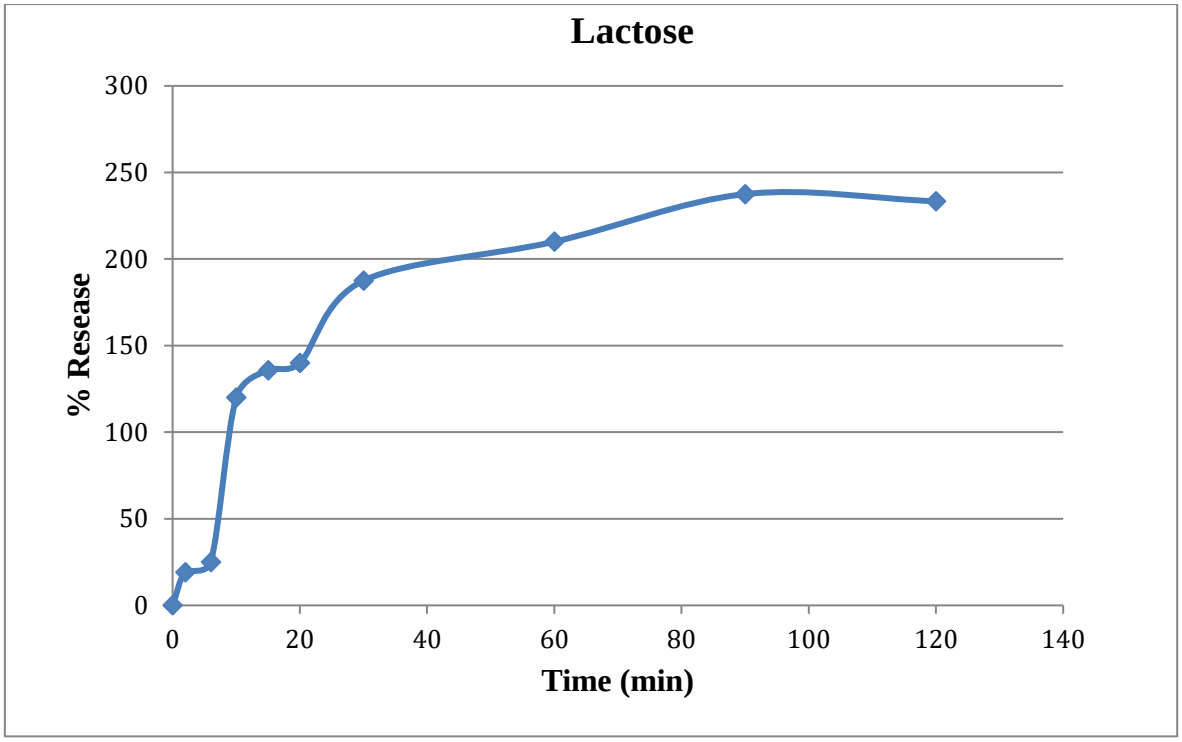

Figure 9: % Release Vs. Time curve of ibuprofen containing Lactose

4.3 Dissolution study of ibuprofen containing Pluronic

Table 5: % release of ibuprofen containing Pluronic

Time (min)	% Release of Ibuprofen	STDV	%Error
0	0	0	0
2	33.33333	0	0
6	57.5	5.892557	10.24792
10	60.83333	1.178511	1.937279
15	63.33333	2.357023	3.721615
20	78.33333	7.071068	9.026895
30	93.33333	0	0
60	95	23.57023	24.81076
90	111.667	2.357023	2.110767
120	125	0	0

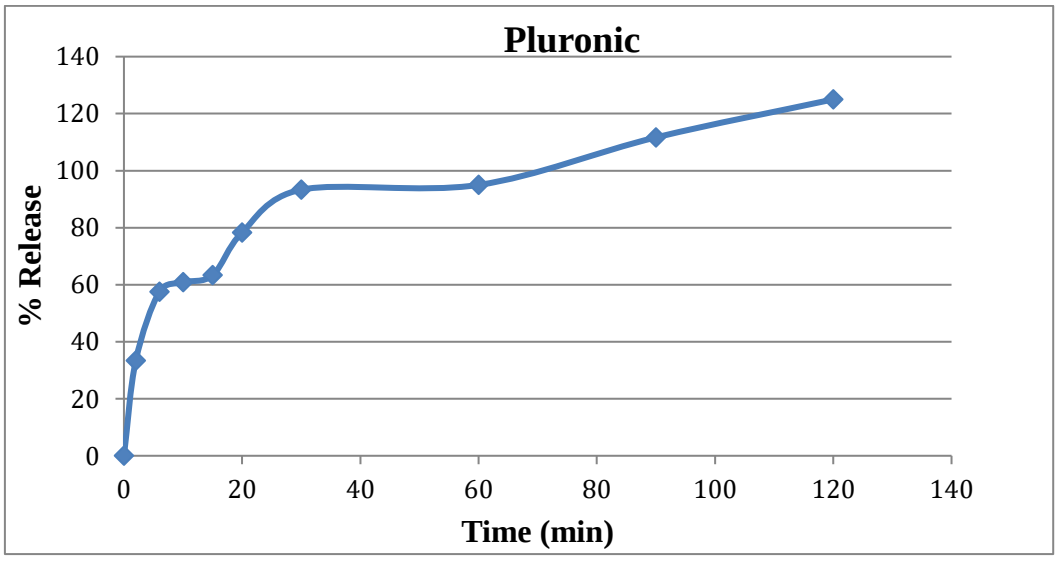

Figure 10: % Release Vs. Time curve of ibuprofen containing Pluronic

4.4 Dissolution study of ibuprofen containing Sodium Lauryl Sulphate (SLS)

Table 6: % release of ibuprofen containing Sodium Lauryl Sulphate (SLS)

Time (min)	% Release of Ibuprofen	STDV	% Error
0	0	0	0
2	37.5	5.892557	15.71348
6	54.16667	8.249579	15.22999
10	91.66667	2.357023	2.571297
15	93.33333	2.357023	2.525381
20	110.8333	1.178511	1.063318
30	94.16667	45.96194	48.80914
60	140	4.714045	3.367175
90	155.8333	3.535534	2.268792
120	188.3333	7.071068	3.754549

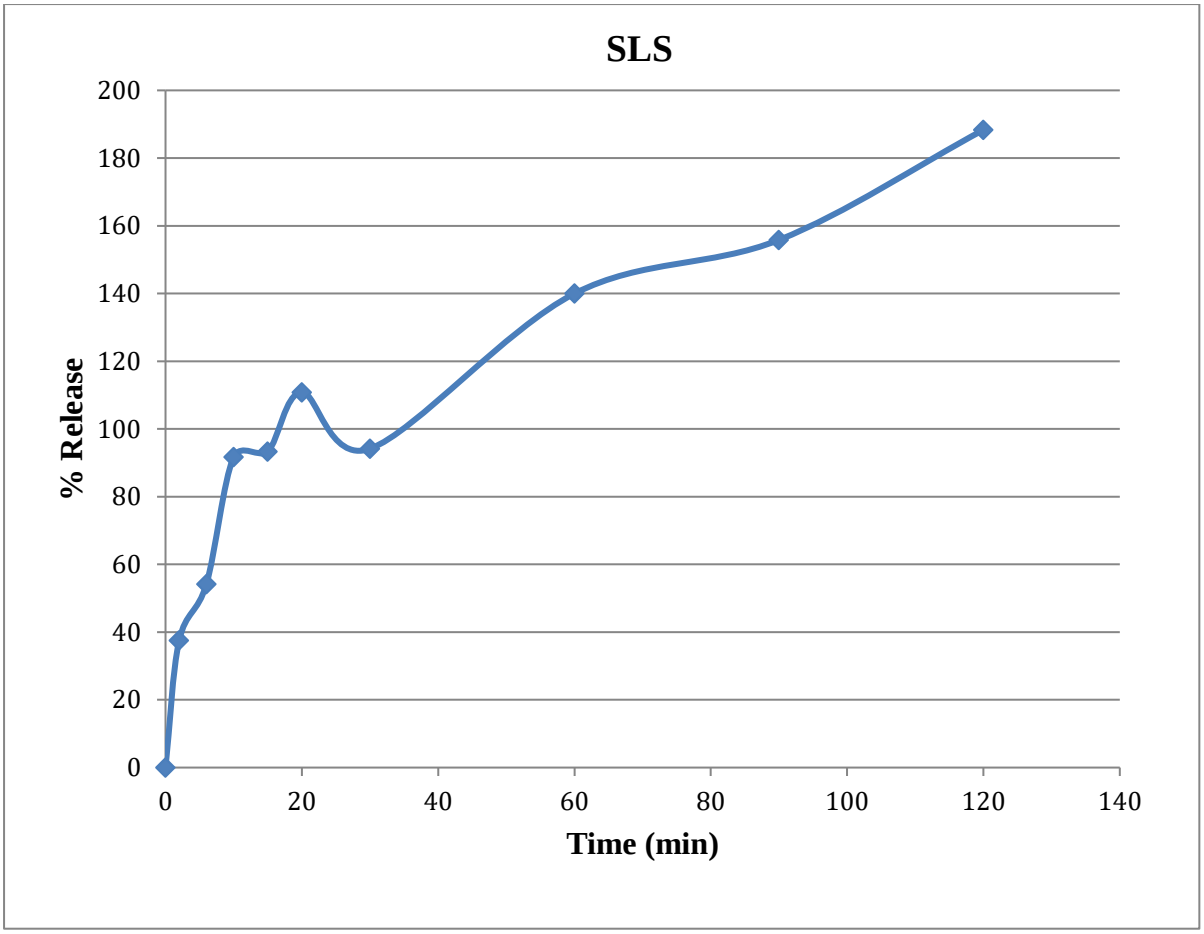

Figure 11: % Release Vs. Time curve of ibuprofen containing SLS

4.5 Comparison study among Lactose, Sodium Lauryl Sulphate (SLS) & Pluronic

Date profile:

Table 7: % release of ibuprofen drug containing different excipients

Time (min)	Lactose (% drug release)	Pluronic (% drug release)	SLS (% drug release)
0	0	0	0
2	19.17	33.3	37.5
6	25	57.5	54.2
10	120	60.8	91.7
15	135.83	63.3	93.3
20	140	78.3	110.8
30	187.5	93.3	94.2
60	210	95	140
90	237.5	111.7	155.8
120	233.3	125	188.3

4.6 Dissolution profile of ibuprofen

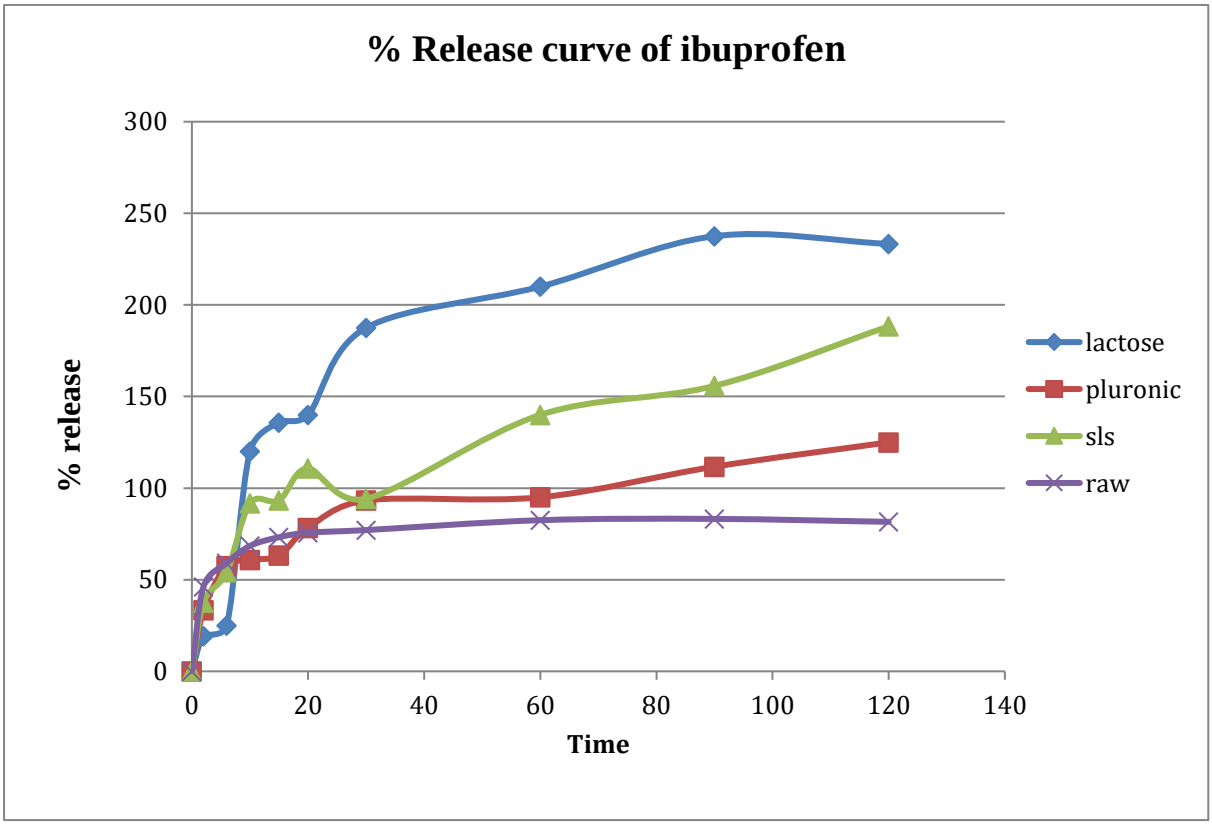

Figure 12: % Release of ibuprofen drug containing different excipients and raw powder

(Afrose, 2017)

4.7 Discussion

Ibuprofen is water insoluble drug as mentioned before; the solubility of the drug can be enhanced by adding different excipients. In this experiment Lactose, Pluronic & Sodium Lauryl Sulphate (SLS) are taken as excipients to enhance the bioavailability and dissolution rate of ibuprofen. Among these three excipients Pluronic & Sodium Lauryl Sulphate (SLS) are called surfactants. On the other hand, Lactose works as a diluent. In this discussion part the effect of these three excipients will be discussed as well as which excipient gave the better effect among them will be discussed by analyzing the graphs.

4.8 Ibuprofen and Lactose

Lactose has a good solubility property in water without any saturation. The calibration curve (Figure 9) shows the rapid dissolution profile of ibuprofen in the presence of lactose excipient. The curves also show the dissolution rate gets 100% after 5-6min of dissolution. It means ibuprofen capsule gets fully dissolved in the given media and shows the higher dissolution rate considering the % release of raw ibuprofen powder at the same time point.

4.9 Ibuprofen and Pluronic

Pluronic has the biocompatibility, degradation behavior, and non-toxic nature on administration to human tissues. It is a nonionic surfactant which is a polymer compatible with many different substances (Domínguez-Delgado et al., 2016). It is also used as solubilizing agent. Considering all the properties pluronic is used as an excipient. It additionally goes about as a surfactant. Surfactants are ordered by their polar head gathering, the charged head alluded as ionic surfactants and uncharged surfactants are by and large alluded to as nonionic surfactant. Due to their one of single kind practical properties, surfactants locate a wide scope of employments in pharmaceutical arrangements. These incorporate improvements of the dissolvability or dependability of a medication in a fluid arrangement, adjustment and change of the surface of a semisolid readiness, or modify the stream properties of crush. Notwithstanding their utilization as excipients to improve the physical and substance attributes of the definition, surfactants might be incorporated to improve the viability or bio-execution of the item (Dhananjay S Jadhav, 2004). The calibration curve (Figure 12) shows that the dissolution rate after 10min of dissolution starts faster. The % drug release gets 100% after 70min of dissolution of capsule starts. The dissolution rate of ibuprofen with the excipient pluronic is kind of similar to the % release of raw ibuprofen powder at the same time point.

4.10 Ibuprofen and Sodium Lauryl Sulphate (SLS)

Sodium Lauryl Sulfate (SLS), another surfactant which is utilized as an excipient in this exploration try. The impacts of surfactants on the solubilization and dissolution rate of ineffectively dissolvable acidic medications are huge, which helps to distinguish mostly appropriate surfactant for directing an acidic medication disintegration test. Sodium lauryl sulfate (SLS) is an anionic surfactant which is utilized in this investigation. The disintegration pace of ibuprofen was generously upgraded in medium containing SLS. For acidic medications, the capacity of medium which contains an anionic surfactant for upgrading paces for disintegration of acidic medications (Park & Choi, 2006). Considering the advantageous activities of surfactants mentioned in 4.8, Sodium Lauryl Sulphate (SLS) also selected as an excipient for the research experiment. The calibration curve (Figure 11) shows the higher dissolution rate after 10-15min of dissolution starts. The % drug release gets 100% after 18-19min of dissolution of capsule starts.

4.11 Conclusion

Considering Figure 9, 10 & 11 along with the calibration curve (Figure 12) mentioned in this chapter (Comparison study of % release of ibuprofen containing excipients Lactose, Sodium Lauryl Sulphate & Pluronic), it can be said that among these three excipients, lactose helps to give the better dissolution rate of ibuprofen capsules considering the % release of raw ibuprofen powder at the same time point.

Chapter 5

Conclusion

From the discussions mentioned in different chapters from this research paper, it can be said that use of different excipients can improve the solubility property of poorly insoluble ibuprofen drug. This experiment analysis proved that among all the excipients; Lactose, Sodium Lauryl Sulphate & Pluronic have a better impact on the improvement of solubility, bioavailability and dissolution rate of ibuprofen. This experimental data also proves that Lactose has the better activity among all these three excipients. This method can be used for future DPI formulation and lactose can be an excipient as well as can be worked as a carrier for DPI formulation. It is also shown that, surfactants have a great impact on solubility enhancement. As this experiment used the crystallization method to formulate the ibuprofen capsules, it may help to reduce the amount of dose of ibuprofen which was one of the purposes of this experiment. Thus helps to reduce the long term and short term side effects of ibuprofen with a higher amount of dose. Finally, this capsule formula can give the better bioavailability and better dissolution profile with a reduced amount of dose which is expected at all.

References

Access, G. (2019). *Start tracking your Reading History × Start tracking your Reading History*

×. 3–5.

Afrose, A. (2017). *Crystallization engineering techniques for developing a novel dry powder inhaler formulation for ibuprofen*. https://doi.org/10.5204/thesis.eprints.107550

Alley, S. (2016). *The role of dissolution in drug development*. 1–5. Retrieved from https://www.outsourcing-pharma.com/Headlines/Promotional-Features/The-role-of-dissolution-in-drug-development

Anonim. (n.d.). *Importance , Objectives & Factors Affecting Dissolution Rate , Theories of Dissolution And Official Dissolution Tests (Equipments of Dissolution Study)*.

Beyssac, E., & Lavigne, J. (2005). Dissolution study of active pharmaceutical ingredients using the flow through apparatus Usp 4. *Dissolution Technologies*, *12*(2), 23–25. https://doi.org/10.14227/DT120205P23

Bodratti, A. M., & Alexandridis, P. (2018). Formulation of poloxamers for drug delivery. *Journal of Functional Biomaterials*, *9*(1), 1–32. https://doi.org/10.3390/jfb9010011

Brogna, L. (1986). Product ingredients. *Journal of Wound, Ostomy and Continence Nursing*, *13*(3), 123. https://doi.org/10.1097/00152192-198605000-00048

Bushra, R., & Aslam, N. (2010). An overview of clinical pharmacology of ibuprofen. *Oman Medical Journal*, *25*(3), 155–161. https://doi.org/10.5001/omj.2010.49

By, A. S. (2019). *What are the Advantages and Disadvantages of Capsules ? Page not found Page not found Page not found*. 1–5.

Cart, A. D. D. T. O. (2014). *Poloxamer 188 solution*. *188*, 2018–2019.

Davies, N. M. (1998). Clinical pharmacokinetics of ibuprofen. The first 30 years. *Clinical Pharmacokinetics*, *34*(2), 101–154. https://doi.org/10.2165/00003088-199834020-00002

Dhananjay S Jadhav. (2004). Surfactants and Its Application in Pharmaceuticals: an Overview. *PharmaTutor Pharmacy Infopedia*, 1.

Documents, C., Pdfs, I., Free, F., & Easypdfcombine, G. (2019). *Free PDF Converter ComTekk SINAD Software*. 1–10.

Domínguez-Delgado, C. L., Fuentes-Prado, E., Escobar-Chávez, J. J., Vidal-Romero, G., Rodríguez-Cruz, I. M., & Díaz-Torres, R. (2016). Chitosan and Pluronic ® F-127: Pharmaceutical Applications . *Encyclopedia of Biomedical Polymers and Polymeric Biomaterials*, (January), 1513–1535. https://doi.org/10.1081/e-ebpp-120050057

Engelbrecht, S. (2015). How to write the literature review. *Hertie*, (February 2007), 2015.

European Medicines Agency. (2017). Questions and answers on benzalkonium chloride used as an excipient in medicinal products for human use. *Ema/Chmp/704195/2013*, *44*(828), 1–10.

Excipients, P., Excipients, P., & De, S. (2019). *Ideal Excipient Properties Roles of Excipients*. 1–8.

Guo, J.-H. (2004). Lactose in Pharmaceutical Applications. *Drug Development & Delivery*, *4*(5), 1–10. Retrieved from http://www.drug-dev.com/ME2/dirmod.asp?sid=&nm=&type=Publishing&mod=Publications%3A%3AArticle&mid=8F3A7027421841978F18BE895F87F791&tier=4&id=B77205DCDDA246CCB4B55DF48B264A4B

Hallas, N. J. (2019). *used for crystallization are dealt with in a separate article on Crystallizers .2019*, 2019.

Hamid, P. G. (n.d.). *Pharmacist Ghada Hamid*. 1–14.

Heuser, A., Schmitt, A. D., Gussone, N., & Wombacher, F. (2016). Analytical methods.

Advances in Isotope Geochemistry, (13), 23–73. https://doi.org/10.1007/978-3-540-68953-9_2

Industry, B., Glossary, B., & Stone, B. Y. K. (2019). *What Is Bioavailability ? Learn about bioavailability , or the rate at which a drug is absorbed*. 1–6.

Lee, C. H., & Maibach, H. I. (2006). Sodium lauryl sulfate. *Irritant Dermatitis*, 257–267. https://doi.org/10.1007/3-540-31294-3_30

May, Y. (2019). *affect the*. (1), 2–5.

Medicines Agency, E. (2015). Background review for sodium laurilsulfate used as an excipient. *Committee for Human Medicinal Products (CHMP)*, *44*(July).

Mission, V. (2011). *I NTERNATIONAL J OURNAL OF P HARMACY & L IFE S CIENCES*. *2*(2), 542–545.

Monohydrate, L., Ingredient, I., Rh, D., Topics, D., Intolerance, L., Diseases, K., … Publication, N. I. H. (2019). *Lactose Monohydrate*. 2018–2019.

Monohydrate, L., Of, S., & Intolerance, L. (2019). *10/8/2019*. *2019*, 8–11.

Nerurkar, J., Beach, J. W., Park, M. O., & Jun, H. W. (2005). Solubility of (±)-ibuprofen and S (+)-ibuprofen in the presence of cosolvents and cyclodextrins. *Pharmaceutical Development and Technology*, *10*(3), 413–421. https://doi.org/10.1081/PDT-54446

Pain, M. M., & Sense, S. (2019). *What is ibuprofen?* 1–6.

Paridah, M. ., Moradbak, A., Mohamed, A. ., Owolabi, F. abdulwahab taiwo, Asniza, M., & Abdul Khalid, S. H. . (2016). We are IntechOpen , the world ’ s leading publisher of Open Access books Built by scientists , for scientists TOP 1 %. *Intech*, *i*(tourism), 13. https://doi.org/http://dx.doi.org/10.5772/57353

Park, S. H., & Choi, H. K. (2006). The effects of surfactants on the dissolution profiles of poorly water-soluble acidic drugs. *International Journal of Pharmaceutics*, *321*(1–2), 35–41. https://doi.org/10.1016/j.ijpharm.2006.05.004

Rajpurohit, H., Sharma, P., Sharma, S., & Bhandari, A. (2015). *Polymers for Colon Targeted Drug Delivery*. *72*(6), 689–696. https://doi.org/10.4103/0250

Rohani, S. (2010). Applications of the crystallization process in the pharmaceutical industry. *Frontiers of Chemical Engineering in China*, *4*(1), 2–9. https://doi.org/10.1007/s11705-009-0297-z

Sachan, N. K., Bhattacharya, A., Pushkar, S., & Mishra, A. (2009). Biopharmaceutical classification system: A strategic tool for oral drug delivery technology. *Asian Journal of Pharmaceutics*, *3*(2), 76–81. https://doi.org/10.4103/0973-8398.55042

Saharan, V., Kukkar, V., Kataria, M., Gera, M., & Choudhury, P. (2009). Dissolution enhancement of drugs. part i: technologies and effect of carriers. *International Journal of Health Research*, *2*(2), 105–124. Retrieved from http://www.ajol.info/index.php/ijhr/article/view/55401

Science, C. D., Helmenstine, A. M., & May, U. (2019). *Crystallization De nition*. 1–5.

Sense, S. (2017). *What is ibuprofen?* 1–5.

Shekunov, B. Y., & York, P. (2000). Crystallization processes in pharmaceutical technology and drug delivery design. *Journal of Crystal Growth*, *211*(1), 122–136. https://doi.org/10.1016/S0022-0248(99)00819-2

Solubility enhancement of poorly water soluble drugs: a reviewKesarwani, P., Rastogi, S., Bhalla, V., & Arora, V. (2014). Solubility enhancement of poorly water soluble drugs: a review. *International Journal of Pharmaceutical Sciences and Research*, *5*(8), 3123.

https://doi.org/10.13040/IJPSR.0975-8232.5(8).3123-27

Stoyanova, K., Vinarov, Z., & Tcholakova, S. (2016). Improving Ibuprofen solubility by surfactant-facilitated self-assembly into mixed micelles. *Journal of Drug Delivery Science and Technology*, *36*, 208–215. https://doi.org/10.1016/j.jddst.2016.10.011

Tapan Kumar Giri, H. (2010). Solubility Enhancement of Ibuprofen in the Presence of Hydrophilic Polymer and Surfactant. *International Journal of Applied Biology and P...*, (2).

Textbook, C. (2019). *We have solutions for your book !* 1–2.

UCLA Chemistry & Biochemistry. (2016). Illustrated Glossary of Organic Chemistry. *UCLA Chemistry & Biochemistry*, 2016. Retrieved from http://www.chem.ucla.edu/harding/IGOC/B/beers_law.html

Use of lactose in hard gelatin capsules. (2013). Retrieved from http://www.dfepharma.com/en/downloads.aspx?id=%7B31927851-1682-44BB-A385-790BEBBC7586%7D

Wikarsa, S., Durand, D., Delarbre, J. L., Baylac, G., & Bataille, B. (2008). The improvement of ibuprofen dissolution rate through microparticles spray drying processed in an aqueous system. *Drug Development and Industrial Pharmacy*, *34*(5), 485–491. https://doi.org/10.1080/03639040701743949

Y.Prasanna Raju, V. Jayasri, B. Rubia Yasmeen, V. Harini Chowdary, & S. Satyanandam. (2011). Significance of Pharmaceutical Excipients – A Review. *Jitps*, *2*(6), 191–201.

Appendix 1

Ibuprofen capsule containing lactose:

Serial No.	Sample No.	Time (min)	Absorbance (nm)	Drug conc. (µg/ml)
1	0	0	0	0
2	Run 1	2	0.01	3.333333
3	Run 2	2	0.013	4.333333
4	Run 1	6	0.014	4.666667
5	Run 2	6	0.016	5.333333
6	Run 1	10	0.071	23.66667
7	Run 2	10	0.073	24.33333
8	Run 1	15	0.079	26.33333
9	Run 2	15	0.084	28
10	Run 1	20	0.079	26.33333
11	Run 2	20	0.089	29.66667
12	Run 1	30	0.115	38.33333
13	Run 2	30	0.11	36.66667
14	Run 1	60	0.126	42
15	Run 2	60	0.126	42
16	Run 1	90	0.139	46.33333
17	Run 2	90	0.146	48.66667
18	Run 1	120	0.144	48
19	Run 2	120	0.136	45.33333

Appendix 2

Ibuprofen capsule containing pluronic:

Serial No.	Sample No.	Time (min)	Absorbance (nm)	Drug conc. (µg/ml)
1	0	0	0	0
2	Run 1	2	0.02	6.666667
3	Run 2	2	0.02	6.666667
4	Run 1	6	0.037	12.33333
5	Run 2	6	0.032	10.66667
6	Run 1	10	0.037	12.33333
7	Run 2	10	0.036	12
8	Run 1	15	0.039	13
9	Run 2	15	0.037	12.33333
10	Run 1	20	0.044	14.66667
11	Run 2	20	0.05	16.66667
12	Run 1	30	0.056	18.66667
13	Run 2	30	0.056	18.66667

14	Run 1	60	0.047	15.66667
15	Run 2	60	0.067	22.33333
16	Run 1	90	0.066	22
17	Run 2	90	0.068	22.66667
18	Run 1	120	0.075	25
19	Run 2	120	0.075	25

Appendix 3

Ibuprofen capsule containing SLS:

Serial No.	Sample No.	Time (min)	Absorbance (nm)	Drug conc. (µg/ml)
1	0	0	0	0
2	Run 1	2	0.02	6.666667
3	Run 2	2	0.025	8.333333
4	Run 1	6	0.029	9.666667
5	Run 2	6	0.036	12
6	Run 1	10	0.054	18
7	Run 2	10	0.056	18.66667
8	Run 1	15	0.055	18.33333
9	Run 2	15	0.057	19
10	Run 1	20	0.067	22.33333
11	Run 2	20	0.066	22
12	Run 1	30	0.037	12.33333
13	Run 2	30	0.076	25.33333
14	Run 1	60	0.086	28.66667
15	Run 2	60	0.082	27.33333
16	Run 1	90	0.092	30.66667
17	Run 2	90	0.095	31.66667
18	Run 1	120	0.116	38.66667
19	Run 2	120	0.11	36.66667