ENHANCEMENT OF SOLUBILITY & DISSOLUTION RATE OF NAPROXEN BY SOLID DISPERSION TECHNIQUE AND ITS COMPARISON WITH MARKETED FORMULATION

A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE

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SUBMITTED BY

SUBHANKAR SAHA

CLASS ROLL NUMBER: 001911402002

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UNDER THE GUIDANCE OF

DR. KETOUSETUO KUOTSU

DIVISION OF PHARMACEUTICS

DEPARTMENT OF PHARMACEUTICAL TECHNOLOGY

FACULTY OF ENGINEERING AND TECHNOLOGY JADAVPUR UNIVERSITY

KOLKATA – 700032

2022

DEDICATED TO MY NATION

CERTIFICATE

Department of Pharmaceutical Technology

Jadavpur University

Kolkata–700032

This is to certify that the dissertation entitled " **ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF NAPROXEN BY SOLID DISPERSION TECHNIQUE AND ITS COMPARISON WITH THE MARKETED FORMULATION**" submitted to Department of Pharmaceutical Technology, Jadavpur University in partial fulfillment of the requirements for completion of the degree of **Master of Pharmacy** is a record of original research work carried out by Mr. Subhankar Saha under my guidance & supervision in Department of Pharmaceutical Technology.

I further certify that neither this dissertation nor any part of it has been submitted to any other University or Institute for award of any degree or diploma. I am pleased to forward this dissertation for evaluation.

24/8/22

Dr. Ketousetuo Kuotsu

(Supervisor)

Associate Professor, Division of Pharmaceutics,

Department of Pharmaceutical Technology,

Jadavpur University, Kolkata-700032

Dr. Ketousetuo Kuotsu, M.Pham., PhD
Associate Professor
Department of Pharmaceutical Technology
Jadavpur University, Kolkata-700 032

24/8/22

Prof. (Dr.) Sanmoy Karmakar

Head of the Department,

Department of Pharmaceutical Technology

Jadavpur University, Kolkata-700032

Head
Dept. of Pharmaceutical Technology
Jadavpur University
Kolkata - 700 032, W.B. India

24/8/22

Prof. Chandan Mazumdar

(DEAN)

Faculty Council of Engineering & Technology

Jadavpur University, Kolkata-700032

DEAN
Faculty of Engineering & Technology
JADAVPUR UNIVERSITY
KOLKATA-700 032

DECLARATION OF ORIGINALITY AND COMPLIANCE OF ACADEMIC ETHICS

I hereby declare that the dissertation entitled "**ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF ATORVASTATIN CALCIUM TABLET BY SOLID DISPERSION TECHNIQUE: AN APPROACH TOWARDS DYSLIPIDEMIA**" is a bonafide and genuine research work carried out by me under the supervision of Dr. Ketousetuo Kuotsu, Associate Professor, Department of Pharmaceutical Technology, Jadavpur University. All information in this document have been obtained and presented in accordance with the academic rules & ethical conduct. I also declare that as required by these rules and conduct; I have fully cited and referenced all materials & results that are not original to this work.

NAME: Subhankar Saha

CLASS ROLL NUMBER: 002011402011

EXAMINATION ROLL NUMBER: M4PHP22006

REGISTRATION NUMBER: 154272 of 2020-21

Thesis Title

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Subhankar Saha
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PLACE:

KOLKATA

DATE: 22.08.2022

PREFACE

The dissertation is performed for the partial requirement of the degree of Master of Pharmacy. The present research work entitled *"**Enhancement of solubility & dissolution rate of naproxen by solid dispersion technique and its comparison with marketed formulation."*** was designed to enhance the solubility and dissolution rate of naproxen tablet by employing solid dispersion technique to improve its bioavailability.

Naproxen is a non-steroidal anti-inflammatory drug that inhibits both COX-1 and COX-2 reversibly to reduce the inflammation. It is used to treat symptoms of various types of arthritis, acute bursitis, muscle cramps, tendonitis etc. It belongs to Biopharmaceutics Classification System class-II drug and has lower solubility due to its very low aqueous solubility whereby bioavailability of the drug is often compromised. The objective of the study is to enhance the solubility and a dissolution profile of the Naproxen.

Solid dispersion(SD) is a technique which enhances the solubility and a dissolution profile of poorly soluble drug. Various methods are being used for SDs such as microwave irradiation fusion, kneading, solvent evaporation, fusion, and dropping method. In this project solvent evaporation technique has been employed by using common solvent ethanol along with the carrier to nullify the effect of temperature aided degradation during manufacture of the Solid dispersion. Various ratio of drug and carrier have been taken into consideration & evaluation to check the optimum concentration of the carrier showing desirable solubility & dissolution rate.

This thesis is divided into NINE chapters describing fundamentals, methodologies, results, discussion, conclusion & reference. Chapter 1 is the introductory chapter which deals with the solid dispersion technique. Chapter 2 is about literature review on various other works that had been done on this regard. After wards Chapter 3 discusses about the aim, objective and the plan of work of this research project. Chapter 4 contains the materials & methodologies used in this project. It describes the drug, polymer & the excipients profile, the development and evaluation method of the formulation. Chapter 5 contains the tables and graphs whereas Chapter 6 discusses the result obtained through various evaluations. Chapter 7 contains the conclusion section which gives a brief outline of results that obtained from the entire work. Chapter 8 includes the future scope about this research work. Chapter 9 consists of list of references that are being used to successfully complete the thesis work.

CONTENTS

CHAPTER 1

1. INTRODUCTION

Inflammation or pain is the most reported problem among the general human population over the world. It can be caused due to numerous reasons like, injuries, diseases due to internal or external stimulus. Pain can be acute, activated by specific disease or injury and it can be of chronic in nature due to any disease. On receiving the stimulus, a cascade of reactions takes place in the body that leads to the pain sensation which are targeted towards the injury site. This mechanism plays a protective role to alert the individual about the noxious stimulus and also to activate the immune system.

Disruption of this complex cascade of inflammation is the most preferred way to reduce pain or inflammation. This can be achieved by using four types of drugs. i.e. 1) Weak analgesics 2) Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) 3) Opioids 4) Adjuvant Drugs.[1],[2],[3]

NSAIDS are the first choice of drugs for management of pain. All the NSAIDS act through same mechanism of action, i.e., by blocking the synthesis of prostaglandins, main chemical responsible of inflammation. They block the cyclooxygenase (COX) isoenzymes in prostaglandin synthesis pathway, thus preventing prostaglandin formation. COX-1, a housekeeping enzyme expressed under basal conditions responsible for normal physiological conditions. Whereas, COX-2 enzyme produced during the inflammatory conditions, helps in prostaglandins, responsible for inflammations.

Naproxen (2-naphthaleneacetic acid), chemically a propionic acid derivative under non-steroidal anti-inflammatory drugs (NSAIDS) used in the treatment of pain management in various types of arthritis, ankylosing spondylosis, tendonitis, musculoskeletal disorders. Naproxen works by reversibly blocking both the COX-1 and COX-2 enzymes, preventing the prostaglandin synthesis thus reducing inflammation. Being a Biopharmaceutics Classification System (BCS) class II drug, it suffers from solubility issue (aqueous solubility = 0.036mg/ml) thus affecting the absorption process inside the body. This results in intake of high amount of drug, which leads to undesired side-effects. Efforts are being employed to improve the solubilities of BCS Class II drugs.[9]

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion, but it is problematic if the drug is poorly soluble or poor membrane penetrability. Almost more than 90% drugs are orally administered. Drug absorption, sufficient and reproducible bioavailability,

pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. More than 40% of new candidates entering drug development pipeline fail becauseof non-optimal biopharmaceutical properties.[15]

Various solubility improvement techniques have been developed to increase solubility and dissolution rates of poorly soluble drugs, like: - [7],[8]

1. Micronization 2. Complexation 3. Co-precipitation 4. Spray Drying

5. Freeze drying 6. Solid dispersion

Among these techniques solid dispersions is considered among the most successful techniques for enhancing the solubility of the poorly soluble drugs.

Solid dispersions (SD) are considered one of the most successful strategies to improve the dissolution profile of poorly soluble drugs.[8] It is a method to alter the solid state at the particle, or molecular level involves a physical change in the drug and is an attractive option for improving drug solubility. Solid dispersions is defined as the dispersion of one or more than one active ingredients into an inert carrier or matrix by various methods. The drug in solid dispersions can be dispersed as separate molecules, amorphous particles, or crystalline particles while the carrier can be in the crystalline or amorphous state. In aqueous medium the carrier gets dissolved and releases the drug with larger surface area, facilitating its solubility. Numerous studies on solid dispersions have been published and have showed many advantageous properties of solid dispersions in improving the solubility and dissolution rate of poorly soluble drugs. Numerous studies on solid dispersions have been published and have showed many advantageous properties of solid dispersions in improving the solubility and dissolution rate of poorly soluble drugs. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.[7]

NEED FOR SOLID DISPERSION TECHNIQUE IN VARIOUS DOSAGE FORM

The drugs which are having poor water solubility they often show poor oral bioavailability due to the low levels of absorption. Drugs that undergo dissolution rate limited absorption, their dissolution rate can be enhanced by micronisation or size reduction, but this leads to aggregation of particles which leads to poor wettability. Various other approaches for increasing the bioavailability of poorly water-soluble drugs include salt formation, solubilization using a co-solvent, complexation with cyclodextrin and particle size reduction; all these approaches have various limitations. Development of solid dispersions of poorly bioavailable drugs overcame the drawbacks of the previous approaches.[9] Solid dispersion is defined as dispersion of one or more active ingredients (hydrophobic) in an inert carrier (hydrophillic) at solid state prepared by melting (fusion) method, solvent, or melting solvent method. When the solid dispersion encounters the aqueous medium, the inert carrier dissolves and the drug is released, the increased surface area produces a higher dissolution rate thus increasing the bioavailability of the poorly soluble drug. The first drug whose rate and extent of absorption was significantly enhanced using solid dispersion was sulfathiazole by sekiguchi and obi[10] in which eutectic mixture of sulfathiazole with urea as the inert carrier was formed. Lyophilization is a molecular mixing technique where the drug and carrier were co-dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion. [10]

BENEFITS OF SOLID DISPERSIONS [11]

- Solid dispersions reduce particle size & increase wettability.
- It converts the crystallinity of drug into amorphous form.
- It improves the solubility of poorly soluble drugs.
- The taste of the drug can be masked by using solid dispersions
- Solid dispersions facilitate rapid disintegration oral tablets.
- Homogenous distribution of small amounts of drugs at solid state can be obtained through solid dispersions.

- Solid dispersions stabilize the unstable drugs.
- Solid dispersions can dispense liquid or gaseous compounds.
- Solid dispersions formulate a faster release priming dose in a sustained release dosage form.
- It can used to formulate sustained release dosage or prolonged release regimens of soluble drugs using poorly soluble or insoluble carriers.

LIMITATIONS OF SOLID DISPERSIONS [11]

- Hygroscopicity and temperature sensitivity causes stability issues.
- Reproducibility of solid dispersions is less.
- Product quality may be low.
- Temperature and moisture have degrading effect on solid dispersions.

APPLICATIONS [11],[12]

1. To increase the solubility of poorly soluble drugs, thus increasing the dissolution rate, absorption and bioavailability.
2. To mask the unpleasant taste and smell of the drugs.
3. To stabilize the unstable drugs against hydrolysis oxidation, reduction, isomerization, photo oxidation, racemization etc.
4. To reduce some side effects of the drug.
5. To avoid undesired incompatibilities.
6. To formulate a fast release primary dose in a sustained released dosage form.
7. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
8. To obtain a homogeneous distribution of a small amount of drug in solid state.
9. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
10. To reduce presystemic inactivation of drugs like morphine and progesterone.
11. To prevent any change in chemical properties of the drug.

CLASSIFICATION OF SOLID DISPERSION [13]

According to Chiou and Reigalman, solid dispersions are classified into 4 major types, i.e.,

- Simple eutectic mixtures
- Solid solutions
- Glass solution and suspension
- Amorphous precipitation in a crystalline carrier

Simple eutectic mixture

These are prepared by rapid solidification of the fused melt of two components that show complete liquid miscibility and negligible solid solubility. Thermodynamically, such a system is an intimately blended physical mixture of its two crystalline components. Thus, the X-ray diffraction pattern of a eutectic constitutes an additive composite of two components. Ex. Chloramphenicol -urea; Paracetamol-urea; Griseofulvin & Tolbutamide-PEG 2000.

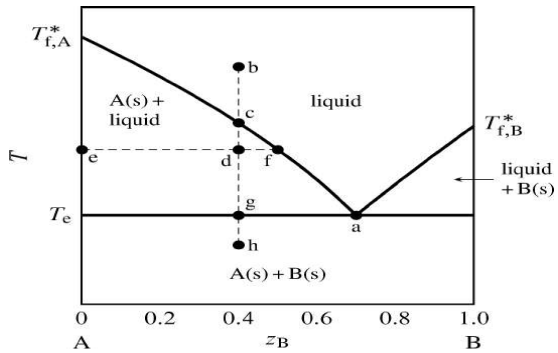


Figure 1: Schematic Phase diagram for simple eutectic mixture.

Solid solution

In a solid solution the two components crystallize together in a homogeneous one phase system. The particle size of the drug in the solid solution is reduced to its molecular size. Thus, a solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture. Solid solutions can be classified by two methods. According to the extent of miscibility of the two components, they may be classified as continuous or discontinuous.

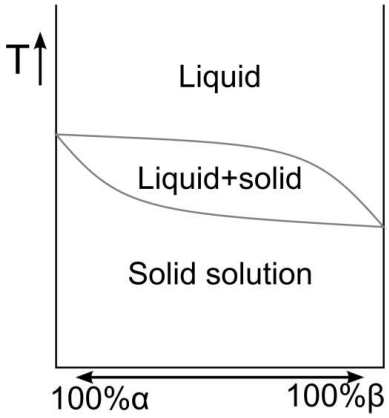


Figure 2: Continuous solid solution phase diagram

i. Continuous Solid Solutions

The two components are miscible in the solid state in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components. Till date no solid solutions of this type has been reported in pharmaceutical industry.

ii. Discontinuous Solid Solutions

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram, show the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Below a certain temperature, the mutual solubilities of the two components start to decrease.
According to the way in which the solvate molecules are distributed in the solvent. The two types of solid solutions are:

- **Substitutional Crystalline Solutions**

A substitutional crystalline solid dispersion is a type of solid solutions which have a crystalline structure, in which the solute molecules substitute for solvent molecules in the crystal lattice. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.

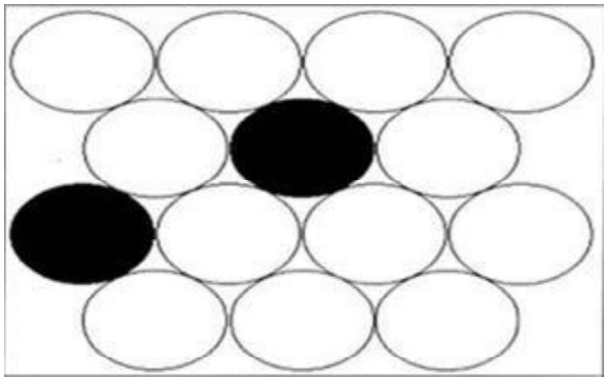


Figure 3: Substitutional Crystalline solid solution.

- **Interstitial Crystalline Solid Solutions**

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. In the case of interstitial crystalline solid solutions, the solute molecules should have a molecular diameter

that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

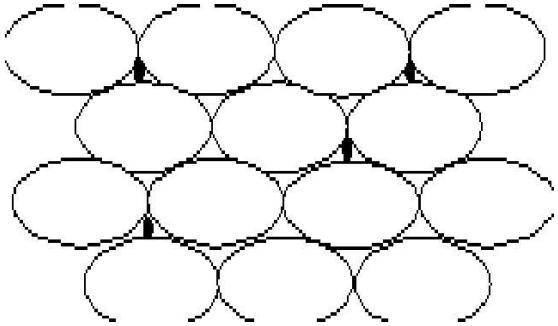


Figure 4: Interstitial Crystalline solid solution.

- **Amorphous Solid Solutions**

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, Chiou and Riegelman were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carrier's urea and sugars such as sucrose, dextrose and galactose, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol and various cellulose derivatives have been utilized for this purpose.

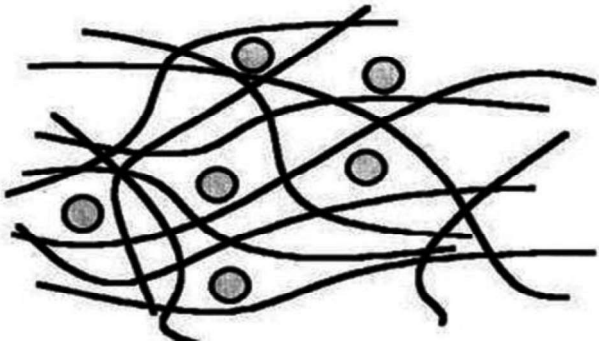


Figure 5: Amorphous solid solution

- **Glass solution and suspensions**

These are homogeneous glassy system in which solute dissolves in glass carrier. Glass suspensions are mixture in which precipitated particles are suspended in

glass solvent. Lattice energy is much lower in glass solution and suspension. Different Characteristics of glassy state are transparency, brittleness below the glass transition temperature. e.g., Carriers for glass solution and suspension – citric acid, sugars (dextrose, sucrose, galactose), PVP, PEG, urea.

- **Amorphous precipitations in a crystalline carrier**

The difference between this group of solid dispersions and the simple eutectic mixture is that the drug is precipitated out in an amorphous form in the former as opposed to a crystalline form in the latter. e.g., Sulfathiazole was precipitated in the amorphous form in crystalline urea.

COMMONLY METHODS USED FOR PREPARATION OF SOLID DISPERSION[14],[15]

- Fusion method
- Solvent method
- Melting solvent method
- Supercritical fluid method
- Electro spinning method.
- Solvent evaporation method
- Melt agglomeration method
- Lyophilization Techniques
- Spray-Drying method
- Dropping method solution
- Melt extrusion method
- Gel entrapment technique
- Kneading technique
- Co-precipitation method
- Co-grinding method

- **FUSION METHOD**

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. The first solid dispersions are created for pharmaceuticalapplications were prepared by the fusion method. In this

method, both the drug and carrier are melted at high temperature, mixed well and cooled to get solid dispersion.

ADVANTAGES

The main advantage of direct melting method is its simplicity and economy. In addition, melting under vacuum or blanket of an inert gas such as nitrogen may be employed to prevent oxidation of drug or carrier.

DISADVANTAGES

Firstly, a major disadvantage is that the method can only be applied when drug and matrix are compatible when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture which results in an inhomogeneous solid dispersion. In this case phase separation can occur. Slow cooling yielded crystalline drug, whereas, fast cooling produced amorphous solid dispersions.

- **SOLVENT METHOD**

The first step in the solvent method is the preparation of a solution containing both matrix and material and drug. The second step involves the removal of solvent resulting in the formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties. Using the solvent method, the pharmaceutical engineer faces two challenges. First challenge is to mix both drug and matrix in one solution, which is difficult when they differ significantly in polarity. To minimize the drug particle size in the solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible, preferably drug and matrix material are in the dissolved state in one solution and solid dispersions are obtained.

ADVANTAGES

The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for evaporation of organic solvents.

DISADVANTAGES

The disadvantages include the higher cost of preparation, the difficulty in completely removing liquid solvent and possible adverse effect of the supposed negligible amount of the solvent on the chemical stability of the drug are some of the disadvantages of this method.

- **MELTING SOLVENT METHOD[16]**

In this method drug is first dissolved in a suitable liquid solvent solution is then incorporated directly into the melt of polyethylene glycol obtainable below 700˚C without removing the liquid solvent. It has been shown that 5- 10% (w/w) of liquid compound could be incorporated into polyethylene glycol 6000 without significant loss of its solid property.

ADVANTAGES

Thermal decomposition of drugs or carriers is prevented due to application of the low temperature for removal of organic solvents.

DISADVANTAGES

As the practical point of view, the melting-solvent method is limited to drugs with a lowtherapeutic dose, e.g., Below 50 mg.

Moreover, it is impossible that the selected solvent or dissolved drug may not be miscible with the melt of polyethylene glycol.

The feasibility of the method has been demonstrated on spironolactone polyethylene glycol 6000 systems.

- **SUPERCRITICAL FLUID METHODS [16]**

Supercritical fluid methods are mostly applied with carbon dioxide, which h is used as either a solvent for drug and matrix or as an ant solvent. When supercritical C02 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not

require the use of organic solvents and since CO_2 is considered environmentally friendly, this technique is referred to as "solvent free". The technique is known as Rapid Expansion of Supercritical Solution[31,32].

ADVANTAGES

The supercritical anti solvent rapidly penetrates into the droplets, in which drug and matrix become supersaturated, crystallize and form particles.

The general term for this process is precipitation with compressed anti oven. More specific examples of PCA are Supercritical Anti Solvent when supercritical CO2 is used or Aerosol Solvent Extraction System, and solution Enhanced Dispersion by supercritical fluids[33].

DISADVANTAGES

Usually, organic solvents like dichloromethane or methanol have to be applied to dissolve both drug and matrix which are more expensive.

- **ELECTROSPINNING METHOD [16]**

Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through millimeter scale nozzles. This process involves the application of a strong electrostatic field over a conductive capillary attaching to reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape. Beyond the critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape. Beyond the critical Value, a charged polymer jet is ejected from the apex of cone. The ejected charge jet is then carried to the collection screen via the electrostatic force. The Columbic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited by the viscosity increase, as the charged jet is dried.

ADVANTAGES

This technique has tremendous potential for the preparation of Nano fibers and controllingthe release of biomedicine. Process is simplest, the cheapest. This technique can be utilized for the preparation of solid dispersions in future.

DISADVANTAGES

This is a very expensive method to develop solid dispersions

- **SOLVENT EVAPORATION METHOD [17]**

Solvent evaporation method consists of the solubilizing of the drug and carrier in a volatile solvent that is latter evaporated. In this method, the thermal decomposition of drugs or carriers can be prevented since organic solvent evaporation occurs at low temperature. A basic process of preparing solid dispersions of this type consists of dissolving the drug and thy polymeric carrier in a common solvent, such as ethanol, chloroform mixture of ethanol and dichloromethane .Normally, the resulting films are pulverized and milled.

ADVANTAGES

The main advantage of the solvent method is that thermal decomposition of drugs or carrierscan be prevented because of the low temperature required for evaporation of organic solvents.

DISADVANTAGES

The disadvantages include the higher cost of preparation, the difficulty in completely removing liquid solvent and possible adverse effect of the supposed negligible amount of the solvent on the chemical stability of the drug are some of the disadvantages of this method.

- **MELT AGGLOMERATION METHOD [18]**

The technique has been usually used to prepare where, the binder acts as a carrier. In addition, it is prepared either by heating binder, drug and excipient to a temperature

above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipient by using a high shear mixer. A rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a high binder content can be incorporated in the agglomerates. In addition, the melt in procedure also results in homogenous distribution of drug agglomerate. Larger particles result in densification of agglomerates while fine particle cause complete adhesion. The mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles.

- **LYOPHILLIZATION TECHNIQUES [18]**

Lyophilization has been thought of a molecular mixing technique. The drug and carrier are co dissolved in a common solvent, Frozen and sublimed to obtain a lyophilized molecular dispersion.

- **SPRAY-DRYING METHOD [19]**

Drug is dissolved in suitable solvent and required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is evaporated under vacuum. Solid dispersions are reduced in size by mortar and sieved.

- **DROPPING METHOD SOLUTION**

The dropping method, developed by Ulrich *et al*., to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods. For laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipette and then dropped onto a plate, where it solidifies into round particles. The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate. It does not use organic solvent and,

therefore, has none of the problems associated with solvent evaporation.

- **MELT EXTRUSION METHOD** [20],[21]

Solid dispersion by this method is composed of active ingredient and carrier and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. Melt extrusion technique is used in the preparation of diverse dosage forms in the pharmaceutical industry e.g., sustained- release pellets.

- **GEL ENTRAPMENT TECHNIQUE** [21]

Modified polymers like hydroxyl propyl methyl cellulose, carboxymethyl cellulose etc. are dissolved in organic solvent to form a clear and transparent gel. Then drug for example is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by mortar and sieved.

- **KNEADING TECHNIQUE**

In this method, carrier is admixed with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary.

- **CO-PRECIPITATION METHOD** [24]

Required amount of drug is added to the solution of carrier. The system is kept under magnetic agitation and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex.

- **CO-GRINDING METHOD** [24]

Physical mixture of drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball

mill steel balls are added. The powder mixture is pulverized. Then the sample is collected and kept at room temperature in a screw capped glass vial until use. Ex. Chlordiazepoxide solid dispersion was prepared by this method.

Selection of method for preparation of solid dispersion of naproxen and maltodextrin: The limitation of the above-mentioned methods (hot-melt method, spray-dried method etc.) is that these methods require extra instruments and a large amount of drugs or carriers. The spray-dried method includes interaction of the machine configuration and formulation variables, which could affect drying efficiency and therefore impact the solid states property of SD. However, the hot-melt method commonly operates at high temperatures (more than 100 °C), which could affect the stability of drugs. By comparison, the conventional solvent evaporation method has the advantages of low cost, operating and reproducing conveniently. The solvent evaporation method consists of the solubilization of the drug and carrier in a volatile solvent that is later evaporated. In this method, the thermal decomposition of drugs or carriers can be prevented since organic solvent evaporation occurs at low temperature.

THE RATIONALE BEHIND FAVOURING SOLVENT EVAPORATION METHOD: [29],[33]

In the preparation of solid dispersions, hot melt extrusion and solvent evaporation are the two main process solutions with large scale production possibilities. The main advantages of solvent evaporation methods compared with hot melt extrusion include the possibility to incorporate a heat labile drug into the polymer matrix, and the ability to form solid dispersionusing polymers with high melting points or glass transition temperatures. Many studies canbe found utilizing the solvent evaporation approach using different evaporation methods including rotary evaporation) slow evaporation on a hot plate (Desai *et al.*,), evaporation under a stream of nitrogen[62] (Prabhu *et al.*), spin evaporation (Van Eerdenbrugh and Taylor), spray drying

(Thybo *et al.*) and the precipitation of solid dispersions using a super critical fluid (Wu et al.). Despite the variety of methods available, the role of the solvent evaporation rate as a potentially important process parameter on the initial drug solid state and the physical stability of solid dispersions have not been fully explored.

MECHANISM OF INCREASED DISSOLUTION RATE BY SOLID DISPERSION [35]

Solid dispersion increases the dissolution rate of poorly water-soluble drugs by one of the following mechanisms:

- Reduction in particle size.
- Solubilization effect (use of carriers).
- Increased wettability and dispensability by carriers
- Changing crystalline form of drug to amorphous form: Formation of metastable dispersion with reduced lattice energy for faster dissolution.
- Reduction in aggregation and agglomeration of drug particles.

• SELECTION OF CARRIER [37]

For a suitable carrier with increasing rate of dissolution of drug requires the following characteristics:

• The carrier should be freely soluble in water with a high rate of dissolution.

• It should be nontoxic in nature.

• It should be pharmacologically inert.

• It should possess heat stability with a low melting point.

• It should be able to enhance aqueous solubility of the drug.

• It should possess chemical compatibility with the drug and should not form strongly bonded complexes with the drug.

• Economical.

The selection of the carrier has the influence on the dissolution characteristics of the dispersed drugs, since the dissolution rate of one component from the surface is affected by the other component in a multiple component mixture. Therefore, a water-soluble carrier results in a faster release of the drug from the matrix. A poorly soluble or insoluble carrier leads to slower release of a drug from the matrix. If the active drug present is a minor component in the dispersion, faster release of a drug can be achieved from matrix.

MALTODEXTRIN

General structure of maltodextrin consists of D-glucose chain of variable length of 3-20 glucose chains. The molecular weight ranges from 504.5 gm/mol to 2774 gm/mol. Maltodextrins are classifies according to the Maltodextrins also have high aqueous solubility and melting point well within the acceptable range of 240˚C. This solubility and temperature help in using the solvent evaporation method, melting method, fusion method for solid dispersion preparations. Dissolution rate of relatively poor soluble drug can be prepared by solid dispersions using maltodextrins. Allergenicity of maltodextrins is very low. Though its, glycemic index is high, yet it can be administered at therapeutic level, without any side effects.

POLYVINYLPYRROLIDONE(PVP)

GENERAL CHARACTERISTICS OF PVP: Polymerization of vinylpyrrolidone leads to polyvinylpyrrolidone (PVP) of molecular weights ranging from 2500 to 3000000. These can be classified according to the K value, which is calculated using Fikentscher's equation. The glass transition temperature of a given PVP is dependent not only on its MW but also on the moisture content. In general, the glass transition temperature (TG) is high; for example, PVP K25 has a TG of 1550˚C. For this reason, PVPs have only limited application for the preparation of solid dispersions by the hot melt method. PVP is suitable for the preparation of solid dispersions by

the solvent method. Similarly, like the PEGs, PVPs have good water solubility and can improve the wettability of the dispersed compound in many cases. Improved wetting and thereby an improved dissolution rate from a solid dispersion in PVP has been demonstrated for flufenamic acid . Increasing chain length of PVP reduces aqueous solubility and increases viscosity leading to less usage of high molecular weight PVPs.

POLYVINYLALCOHOL(PVA),CROSPOVIDONE(PVP-CL), POLYVINYLPYRROLIDONE-POLYVINYLACETATE COPOLYMER(PVPPVA)

These three polymers belong to the polyvinyl group. Whereas polyvinyl alcohol (PVA) and vinylpyrrolidone/vinylacetate (PVP-PVA) copolymers are both water soluble, crospovidone swells when dispersed in water. The use of PVA/PVP copolymers as carriers in solid dispersions has been shown to lead to enormous increases in the drug release rate. Studies with the cytostatic drug HO-221 showed that the PVA/PVP solid dispersed not only dissolved 25 times faster than the drug powder, but also enhanced the bioavailability in beagles by a factor of 3.540. Even though crospovidone does not dissolve in water, it can also be used as a carrier to improve drug release rates. For example, a 1:2 ratio of furosemide to crospovidone led to an increase in the dissolution rate by a factor of 5.841, in comparison with either the drug powder or a physical mixture of furosemide with crospovidone.

CELLULOSE DERIVATIVES

Celluloses are naturally occurring polysaccharides that are ubiquitous in the plant kingdom. They consist of high molecular weight unbranched chains, in which the saccharide units are linked by ß-1, 4- glycoside bonds. By appropriate alkylation, the cellulose can be derivatized to form methyl- cellulose (MC), hydroxypropyl-cellulose (HPC), hydroxypropyl methyl- cellulose (HPMC) and many other semisynthetic types of cellulose. Since each glucose unit has three hydroxyl groups

that can be derivatized, the average substitution grade (SG). A further possibility for derivatization is the esterification of the cellulose to form compounds such as cellulose acetate phthalate (CAP) and Hydroxypropyl methylcellulose phthalate (HPMCP).

HYDROXYPROPYLMETHYLCELLULOSE(HPMC)

HPMCs are mixed ethers of cellulose, in which 16.5-30% of the hydroxyl groups are methylated and 4- 32% are derivatized with hydroxypropyl groups. The molecular weight of the HPMCs ranges from about 10000 to 1500000 and they are soluble in water and mixtures of ethanol with dichloromethane and methanol with dichloromethane43. A poorly soluble weak base with incomplete bioavailability showed that the release rate and the bioavailability in beagles could be improved through preparation of a solid dispersion in HPMC44. Other drugs which exhibit faster release from solid dispersion in HPMC include the poorly soluble weak acids and benidipine.

HYDROXYPROPYLCELLULOSE(HPC)

Hydroxypropyl methylcellulose exhibits good solubility in a range of solvents, including water (up till 400C), ethanol, methanol and chloroform. The average MW of the HPCs ranges from 37000 (Type SSL) to 1150000 (Type H) 46. The release rate improved as the proportion of HPC was increased and when lower MW HPCs were used as the carrier.

CARBOXYMETHYL CELLULOSE(CMC)

CMEC also belongs to the cellulose ethers, but unlike many of the others it is resistant to dissolution under gastric (acidic) conditions. It dissolves readily at pH values above 5-6, with lowest dissolution pH being dependent on the grade of the CMEC. Amorphous solid dispersions of nifedipine and spironolactone show enormous increases in the dissolution rate of the drug at pH values of 6.8.

HYDROXYPROPYLMETHYLCELLULOSE PHTHALATE (HPMCP)

HPMCPs are cellulose esters which are often used as enteric coatings. Depending on the grade, they dissolve first at pH 5 (HP 50) or pH 5.5 (HP 55). Their solubility in organic solvents is also type-dependent. Their MWs range from 20000 to 2000000.

POLYACRYLATES AND POLYMETHACRYLATES

Polyacrylates and polymethacrylates are glassy substances that are produced by the polymerization of acrylic and methacrylic acid, and derivatives of these polymers such as esters amides and nitriles. Commonly they are referred today the trade name Eudragit49. Eudragit E is often used to improve the release rate since it is soluble in buffer solutions at pH values up to 5 and swells at higher pH, while Eudragit L can be used when it is desirable to avoid release in the stomach. When benipidine was formulated as a evaporate with Eudragit E, the rate of dissolution was much higher than from the pure drug powder.

UREA

In one of the first bioavailability studies of solid dispersions, it was shown that sulphathiazole was better absorbed in rabbits when given as a eutectic with urea10. Although urea is not often used as a carrier these days. In the case of ursodeoxycholic acid the release rate from urea dispersions prepared by the hot melt method was faster than from other carriers studied, including PEG 6000.

SUGAR, POLYOLS AND THEIR POLYMERS

Chitosan a derivative of the polysaccharide chitin which is formed by deacetylation at the N position has also been used as a carrier in solid dispersions. Both chitosan and its salt form, chitosan glutamate, were able to improve the release of nifedipine by a factor of two to three compared to the drug powder.

EMULSIFIERS

Two mechanisms are possible here for release behavior of drug: improvement of wetting characteristics and solubilization of the drug. Bile salts and their derivatives are natural surfactants that are built from a steroidal skeleton in the liver and which are important to the emulsification of fats and oils in the diet. As with other surfactants, they can enhance the wetting and solubility of many lipophilic substances, leading to an increase in the dissolution rate.

ORGANIC ACIDS AND THEIR DERIVATIVES

Organic acids such as succinic acid and citric acid have also been used as carriers in solid dispersions, originally to enhance the release rate of griseofulvin.

2. LITERATURE REVIEW

Sonal V. Bhujbal *et al.* explained about the various preparation strategies of solid dispersions. There are various factors responsible for stability of the solid dispersions prepared through various methods. If the boiling point of the solvent is <50 ºC, then solvent cast method can be applied. For solvents with higher boiling points, rotavapour or spray drying can be applied for preparation. If the drug can melt at <150 ºC without degradation, the melting methods can be used.

Kim Hakyeong *et. al.* prepared naproxen solid dispersions with pyridinecarboxamide using cocrystallization and eutectic methods. It showed improved dissolution profile of naproxen (<30 minutes) through *in-vitro* dissolution studies. The eutectic mixtures showed improved dissolution in both the acidic and alkaline pH, while the co-crystallines showed good results only in pH >5.

Nagabandi *et. al* aimed to improve the dissolution rate of naproxen by preparing lipid based solid dispersions. Gelucire 44/14, a hydrophilic lipid-based carrier was used. Pearlitol SD 200 was used as inert carrier. Solvents evaporation technique was applied and micromeritic evalutions, *in-vitro* and *ex-vivo* studies were carried out. In-vitro dissolution studies were carried out along with marketed product (Inspra). The prepared solid dispersions released much more drug than the marketed product within the 2 hours of dissolution time.

Ramadhani *et. al* reviewed the various solid dispersions of NSAIDS and their preparation methods. Dissolution profiles and *in-vivo* studies indicated that the NSAIDS in the solid dispersion forms were therapeutically better than their pure forms.

Peng Zhang *et al.* studied the preparation, characterization, and in vitro/vivo evaluation of polymer-assisting formulation of atorvastatin calcium based on solid dispersion technique. Due to low solubility and bioavailability, atorvastatin calcium isconfronted with challenge in conceiving appropriate formulation. Solid dispersion of atorvastatin calcium was prepared through the solvent evaporation method, with Poloxamer 188 as hydrophilic carriers. This formulation was then characterized by scanning electron microscopy, differential scanning calorimetry, powder X-ray diffraction and fourier transform infrared spectroscopy. In addition, the drug solubility studies as well as dissolution rates compared with bulk drug and market tablets Lipitor were also examined. Furthermore, the study investigated thepharmacokinetics after oral administration of Lipitor and solid dispersion. And the AUC 0–8 h and C max increased after taking Atorvastatin-P188 solid dispersion orally compared with that of Lipitor. All these could be demonstrated that Atorvastatin -P188 solid dispersions would be prospective means for enhancing higher oral bioavailability of Atorvastatin.

CHAPTER 3

3.1. AIM & OBJECTIVE

The aim of this research work is to apply the solid dispersion technique for improving the bioavailability by improving the solubility and dissolution rate by using the maltodextrin as its carrier and its effect on the solubility and dissolution rate of the drug.

The objective of this work is to

i. Improve the solubility and dissolution rate and bioavailability of the naproxen, which is a BCS Class II drug.
ii. Use of solvent evaporation method of solid dispersion techniques, with maltodextrin as carrier.
iii. To optimize the formulation and characterisation, solubility study and dissolution profile study of the formulations.
iv. Comparison with the commercially available product.

3.2. PLAN OF WORK

1. Determination of absorbance maxima & development of calibration curve of naproxen at ph 1.2 in aqueous medium using JASCO V-550 double beam UV spectrophotometer.
2. Preparation of solid dispersion of Naproxen-Maltodextrin at 1:1, 1:1.5,1:2, 1:2.5, 1:3 & 1:4 ratio using solvent evaporation technique, where ethanol was being used as solvent for naproxen and water for maltodextrin.
3. Identification of crystallinity of pure drug and slid dispersion using X-Ray diffraction (XRD) technique.
4. Drug excipient compatibility study using Fourier transforms infrared spectroscopy (FTIR) after keeping the formulation under 40ºC, 75% RH for at least 3 months.
5. All pre-compression parameters like Angle of Repose, Bulk Density, Tapped Density, Carr's index, Haussner ratio etc. must be checked.
6. Preparation of tablets by direct compression method using 10 station compression machine. (Rimek mini press-1 Karnavati Engineering Ltd, Mehsana, Gujrat)
7. Evaluation of post compression parameters such as thickness, hardness, friability, uniformity of drug content, weight variation, disintegration time.
8. Stability study of the optimized formulation.
9. *In vitro* dissolution study of prepared tablet and commercially available immediate release tablet.
10. Comparison of the solubility analysis.

4.1. MATERIALS AND METHODS

4.1.1 DRUG INFORMATION [9],10],[70]

Naproxen is an anti- inflammatory drug of non-steroidal class (NSAIDS) which reduces pain by reversibly inhibiting the both the cyclooxygenase isoenzymes, i.e., COX-1 & COX-2. The It prevents the formation of inflammatory substances like prostaglandins, thus reducing the pain. Specifically, naproxen prevents the conversion of arachidonic acid, a poly unsaturated omega-6 fatty acid to various prostaglandins, which s responsible for the inflammation. It is prescribed mainly for pain relieving different symptoms in various types of arthritis like osteoarthritis, rheumatoid arthritis, or juvenile arthritis, like pain, swelling, stiffness, joint pain etc.

IUPAC name of naproxen is (S)-6-methoxy-α methyl-2-naphthaleneacetic acid. Naproxen has a molecular weight of 230.26 and a molecular formula of $C_{14}H_{14}O_3$. Naproxen is an odourless, white to off-white crystalline substance. It is lipid soluble, practically insoluble in water at low pH(<4) and freely soluble in water at high pH(>7.5). Naproxen is rapidly absorbed after oral administration, with a T_{max} of 2-4 hours. It has a moderate bioavailability owing to the poor solubility. It also has low volume of distribution of 0.16L/Kg. This results in the increased doses and may lead to undesired side effects like myocardial infarctions, stroke, etc and gastrointestinal adverse effects like ulceration, bleeding, and perforation of GI tract. There are many existing factors limiting the successful use of orally administered naproxen, including problems with drug formulation due to poor aqueous solubility and more importantly, insufficient, and fluctuating bioavailability obtained after oral administration.

PHARMACOKINETICS

Absorption

Naproxen undergoes quick absorption when taken orally, with a T_{max} time of 2-4 hours. The bioavailability of the drug is about 95%. Food intake does not affect the rate of absorption.

Distribution

Naproxen has very low volume of distribution of approximately 0.16L/Kg. The protein binding rate is very high (99%). Primarily it binds to the albumins, to a certain extent it binds to the globulins. It also binds significantly to the salivary proteins but to a lesser extent (≈66%).

Metabolism

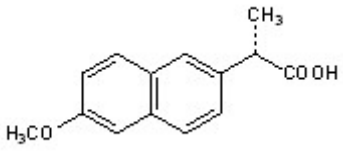
Naproxen is extensively metabolised in liver by Cytochrome P450 system. 2 phase metabolism takes place i.e., Phase I dealkylation leads to 6-O-Desmethylnaproxen and then phase II acylglucoronidation to 6-0-desmethylnaproxen acyl gluconoride. All the metabolites are therapeutically inactive.

Excretion

Naproxen is excreted mainly through urine. Little amount is excreted through faeces (<5%). Majority of excreted products are gluconoride or other conjugates of the 6-O-Desmethyl naproxen (66-92%). Other forms are pure naproxen (1%), 6-O-Desmethylnaproxen (1%). Naproxen has an approximate half life of 15 hours. Elimination of naproxen is decreased in patients with severe renal impairment. Naproxen is not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance <30mL/Min).

MECHANISM OF ACTION

Naproxen reversibly binds with the COX-1 and COX-2 isoenzymes and inhibits prostaglandin synthesis. The pain is induced by the PGs synthesized by the COX-2 enzymes, which is effectively reduced by the naproxen. It has been shown to reduce the inflammation in patients with various arthritis, ankylosing spondylitis, muscle cramps, acute tendinitis, bursitis etc.



4.1.2. EXCIPIENTS

1. Maltodextrin [34]

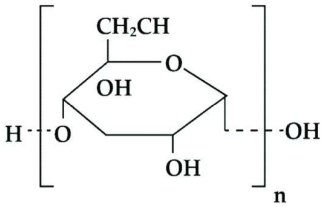
Synonyms: Maltodextrins

Procured from: Sigma Aldrich

Empirical Formula: $C_{6n}H_{(10n+2)}O_{(5n+1)}$

Molecular weight: Variable, between 504.5(n=3) and 2774.7(n=17) gm/mol

Chemical Structure:



pH: 4.0-7.0

Melting Point: 240˚C

Density: 1.6 gm/cm^3

Solubility: 1.2kg/L

Description

Maltodextrin is a white to off white coloured solid polysaccharide compound, which is derived by partial hydrolysis of the starch. It is found in variable chain of $2<n<20$ units. It consists of mainly D-Glucose linked with α -1,6 bonds. Maltodextrins are classified by the dextrose equivalent (DE). They have a DE value between 3 to 20. Higher the value of DE of maltodextrin, lower the glucose chain and higher the solubility.

Maltodextrins are very faint in sweetness, almost 0-5% of sucrose's sweetness, depending on the length of the polysaccharide chain. It is a fully bio- compatible material which can be used for various biological applications.

Applications

Maltodextrins mainly finds its use as thickener, filler in food and food processing industries. It is also used as dietary supplement for humans.

In pharmaceuticals too, it is found use as filler and/or thickeners. In this research work, it has been used as a carrier for naproxen in increasing its solubility.

Due to its high solubility in water and organic solvents like alcohol.

2. Ethanol[36]

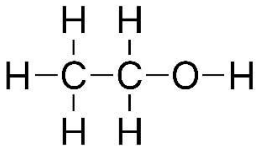
Synonyms: Ethyl alcohol, Fermentation alcohol, Methyl carbinol

Procured from: Alpha chemika, Mumbai.

Molecular weight: 46.07

Empirical formula: C_2H_6O or CH_3CH_2OH

Chemical Structure:



Boiling point: 78°C

Density: 0.789 g/mL at 25°C

Description: The product is a 190-proof ethanol. Ethanol, a primary alcohol, is an important raw material for the synthesis of various compounds. It can be synthesized either from molasses by fermentation or by hydration of ethylene. It acts as a hydrogen source and reaction medium during the transfer hydrogenation of carbonyl compounds in the presence of sodium hydroxide. The impact of ethanol/water fumigation on the performance of dieselengines has been studied.

Application: as a common solvent. Both the drug Atorvastatin calcium and carrier PEG 6000 dissolved in ethanol.

Stability & storage conditions: Ethanol can be stored at room temperature. It is highly inflammable, hence should be kept separate from fire.

Incompatibility: alkali metal, oxidizing agents, peroxides.

3. Lactose

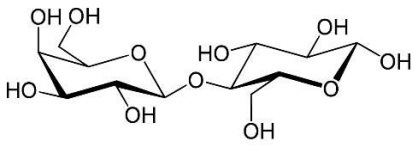
Synonyms: Milk sugar, Lactobiose

Procured from: Sigma- Aldrich

Molecular weight: 342.3 gm/mol

Emperical formula: $C_6H_{22}O_{11}$

Chemical Structure:



Melting point: 203°C

Density: 1.52 gm/cm^3

Solubility: 195 gm/L

Description: Lactose is a white to off-white coloured powder, disaccharide compound composed of 1 D-galactose and D-glucose molecules bonded through a β-1,4 glycosidic bond. It a water soluble, non-hygroscopic, slightly sweet taste. Glycemic index of lactose is 46. Industrially it is manufactured from whey concentrate.

Application: Used as diluent and binder for tablet compression, granulation, capsule filing etc.

Stability and Incompatibility: Generally stable. Incompatible with amine drugs, causing mailard reaction.

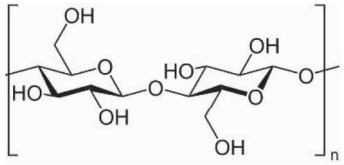
4. Microcrystalline cellulose (MCC)

Synonyms: Avicel, cellulose microcrystalline, A-cellulose, cellulose gel etc.
Procured from: Sigma-Aldrich

Molecular weight: 370.35

Molecular formula: $C_{14}H_{26}O_{11}$

Chemical Structure:



pH: The pH of the supernatant liquid is between 5.0 and 7.5 (10% suspension in water)

Melting point: 76-78°C

Density: 1.5 g/cm3 at 20°C

Flash point: 164°C

Solubility: Practically insoluble in water, in acetone, in anhydrous ethanol, in Toluene, indilute acids and in a 50g/L solution of sodium hydroxide

5. Hydroxypropylmethyl cellulose (HPMC)[37]

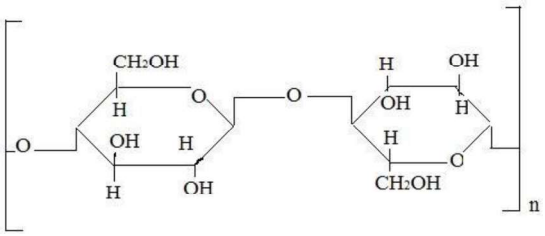
Synonyms: Benecel MHPC, E464, Methocel, methyl cellulose propylene glycol ether, metolose, Tylopur, Hypromellose.

Procured from: Loba chemie.

Molecular weight: 1261.4

Description: HPMC is an odorless and tasteless, white or creamy- white fibrous or granular powder.

Chemical Structure:



Solubility: soluble in cold water , forming a viscous colloidal solution, practically insoluble in chloroform ,ethanol (95%) and ether.

Functional categories: Coating agent, film former, rate controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity enhancer.

pH: 5.5-8.0

Melting point: Browns at 190-200°C, Chars at 225-230°C, Glass transition temperature is 170-180°C

Moisture content: It absorbs moisture from the atmosphere, the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

Density (bulk): 0.341 g/cm^3

Density (tapped): 0.557 g/cm^3

Applications: It is widely used in oral, ophthalmic, and topical pharmaceutical formulations.

Incompatibilities: It is incompatible with some oxidizing agents. Since it is non-ionic, Hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Stability and storage: HPMC powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3-11. Hypromellose powder should be stored in a well closed container, in a cool, dry place.

6. Talc[39]

Synonyms: Talcum powder, soapstone, steatite, Mussolinite, trimagnesium dioxido(oxo)silane; hydroxy-oxido-oxosilane, Agalite, Asbestine, Snowgoose.

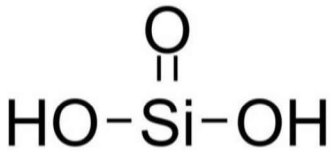
Procured from: Sigma-Aldrich

Molecular weight: 379.27

Molecular formula: $H_2Mg_3O_{12}Si_4$

Description: Finely powdered native hydrous magnesium silicate. It is used as a dusting powder, either alone or with starch or boric acid, for medicinal and toilet preparations. It is also an excipient and filler for pills, tablets, and for dusting tablet molds.

Chemical Structure:



Density: 2.78 g/cm3

Crystal system: Triclinic

Application: It is primarily used as a glidant to improve powder flow in tablet compression. Also used as adsorbent.

Solubility: not soluble in water and is slightly soluble in dilute mineral acids.

Storage Conditions: can be kept at room temperature, dry, ventilated place.

Combustible innature.

7. Magnesium Stearate[39],[40]

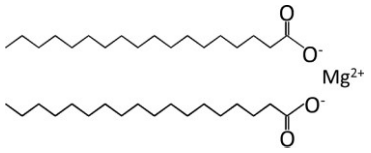
Synonyms: Stearic acid magnesium salt, magnesium salt, magnesium octadecanoate

Procured from: Sigma-Aldrich

Description: It's a fine, white, precipitated of milled, impalpable powder of low bulk densityhaving a faint odour of stearic acid & a characteristic taste.

Structural formula: $[CH_3(CH_2)_{16}COO]_2Mg$

Chemical Structure:



Molecular weight: 591.34

Solubility: It is insoluble in water, ethanol and ether, slightly soluble in warm benzene andwarm ethanol.

Functional categories: Tablet and capsule lubricant

Melting point:117-150°C

Density (Bulk): 0.159 gm/cm3

Density (tapped): 0.286 gm/cm3

Stability and storage conditions: It should be stored in well-closed container in a cool, dryplace.

4.1.3. EQUIPMENTS

1. Weighing Balance

Manufacturer: Precisa

Description: A scale or balance is a device to measure weight or mass. These are also known as mass scales, weight scales, mass balances, weight balances. The traditional scale consists of two plates or bowls suspended at equal distances from a fulcrum. One plate holds an object of unknown mass (or weight), while known masses are added to the other plate until static equilibrium is achieved and the plates level off, which happens when the masses on the two plates are equal. The perfect scale rests at neutral. A spring scale will make use of a spring of known stiffness to determine mass (or weight). Suspending a certain mass will extend the spring by a certain amount depending on the spring's stiffness (or spring constant). The heavier the object, the more the spring stretches, as described in Hooke's law. Other types of scales making use of different physical principles also exist. Some scales can be calibrated to read in units of force (weight) such as newtons instead of units of mass such as kilograms. Scales and balances are widely used in commerce, as many products are sold and packaged by mass.

2. UV Spectroscopy

Manufacturer: Model: Jasco V-550

Description: Ultraviolet visible spectroscopy or ultraviolet visible spectrophotometry (UV–Vis or UV/Vis) refers to absorption spectroscopy or reflectance spectroscopy in part of the ultraviolet and the full, adjacent visible regions of the electromagnetic spectrum. This means it uses light in the visible and adjacent ranges. The absorption or reflectance in the visible range directly affects the perceived color of the chemicals involved. In this region of the spectrum, atoms and molecules undergo electronic transitions. Absorption spectroscopy is complementary to fluorescence spectroscopy, in that fluorescence deals with transitions of electrons from the excited state to the ground state, while absorption measures transitions from the ground state to the excited state. It works on the

principles of Beer-Lambart law.

3. Magnetic Stirrer

Description: A magnetic stirrer or magnetic mixer is a laboratory device that employs a rotating magnetic field to cause a stir bar (typically coated with PTFE) immersed in a liquid to spin very quickly, thus stirring it. The rotating field may be created either by a rotating magnet or a set of stationary electromagnets, placed beneath the vessel with the liquid. It is used in the fields where other forms of stirring, such as motorized stirrers and stirring rods, may not be viable for use.

4. Lyophilizer

Manufacturer: Scanvac

Description: A lyophilizer executes a water removal process typically used to preserve perishable materials, to extend shelf life or make the material more convenient for transport. Lyophilizers work by freezing the material, then reducing the pressure and adding heat to allow the frozen water in the material to sublimate.

5. Tablet Compression Machine

Manufacturer: REMIK

Description: A tablet press is a mechanical device that compresses powder into tablets of uniform size and weight. A tablet press can be used to manufacture tablets of a wide variety of materials, including pharmaceuticals, nutraceuticals, cleaning products, industrial pellets and cosmetics. To form a tablet, the granulated powder material must be metered into a cavity formed by two punches and a die, and then the punches must be pressed together with great force to fuse the material together. A tablet is formed by the combined pressing action of two punches and a die. In the first step of a typical operation, the bottom punch is lowered in the die creating a cavity into which the granulated feedstock is fed. The exact depth of the

lower punch can be precisely controlled to meter the amount of powder that fills the cavity. The excess is scraped from the top of the die, and the lower punch is drawn down and temporarily covered to prevent spillage. Then, the upper punch is brought down into contact with the powder as the cover is removed. The force of compression is delivered by high pressure compression rolls which fuse the granulated material together into a hard tablet. After compression, the lower punch is raised to eject the tablet. Tablet tooling design is critical to ensuring a robust tablet compression process. Considerations when designing pharmaceutical tablet compression tool design include tooling set, head flat, top head angle, top head radius, head back angle, and punch shank. As well as ensuring a single dose of drug, the tablet tooling is also critical in ensuring the size, shape, embossing and other physical characteristics of the tablet that are required for identification.

There are 2 types of tablet presses: single-punch and rotary tablet presses. Most high- speed tablet presses take the form of a rotating turret that holds any number of punches. As they rotate around the turret, the punches come into contact with cams which control the punch's vertical position. Punches and dies are usually custom made for each application and can be made in a wide variety of sizes, shapes, and can be customized with manufacturer codes and scoring lines to make tablets easier to break. Depending on tablet size, shape, material, and press configuration, a typical modern press can produce from 250,000 to over 1,700,000 tablets an hour.

6. Hardness Tester

Description: Hardness tester is a device that indicates the hardness of a material, usually by measuring the effect on its surface of a localized penetration by a standardized rounded or pointed indenter of diamond, carbide, or hard steel. Based on the principles of Young's law.

Example: Monsanto hardness tester, Pfizer hardness tester, Digital Hardness tester.

7. Friabilator

Manufacturer: Electrolab Roche's friabilator.

Description: Tablet friability can be used to measure efficiency of tabletting equipment or as an indicator of formulation suitability as well as routine QC functions. It can also be thought of as measuring “dusting”. Tablets are rotated in a plastic drum for a specified period of time. A gravimetric determination is then made to quantitate the amount of surface material that has worn off.

8. Tapped Density Tester

Description: The tapped density is an increased bulk density attained after mechanically tapping a container containing the powder sample. Tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel (initially 500 times) containing a powder sample.

9. Vernier Caliper

Description: A vernier scale is a visual aid to take an accurate measurement reading between two graduation markings on a linear scale by using mechanical interpolation; thereby increasing resolution and reducing measurement uncertainty by using vernier acuity to reduce human estimation error.

10. Disintegration Apparatus

Manufacturer: LABINDIA

Description: Disintegration testers are used to test how a drug in pellet form will disintegrate in solution. Like dissolution testers, they permit researchers and medical practitioners to analyze the in vitro breakdown of powdered compounds for quality control purposes.

11. Dissolution Apparatus

Manufacturer: LABINDIA

Description: In the pharmaceutical industry, drug dissolution testing is routinely usedto provide critical in vitro drug release information for both quality control

purposes, i.e., to assess batch-to-batch consistency of solid oral dosage forms such as tablets,and drug development, i.e., to predict in vivo drug release profiles. There are three typical situations where dissolution testing plays a vital role: (i) formulation and optimization decisions: during product development, for products where dissolution performance is a critical quality attribute, both the product formulation and the manufacturing process are optimized based on achieving specific dissolution targets.

(ii) Equivalence decisions: during generic product development, and also when implementing post-approval process or formulation changes, similarity of in vitro dissolution profiles between the reference product and its generic or modified version are one of the key requirements for regulatory approval decisions. (iii) Product compliance and release decisions: during routine manufacturing, dissolution outcomesare very often one of the criteria used to make product release decisions.

Example: USP Type II Dissolution Apparatus

12. Fourier Transform Infrared Spectrometer

Manufacturer: Perkin Elmer

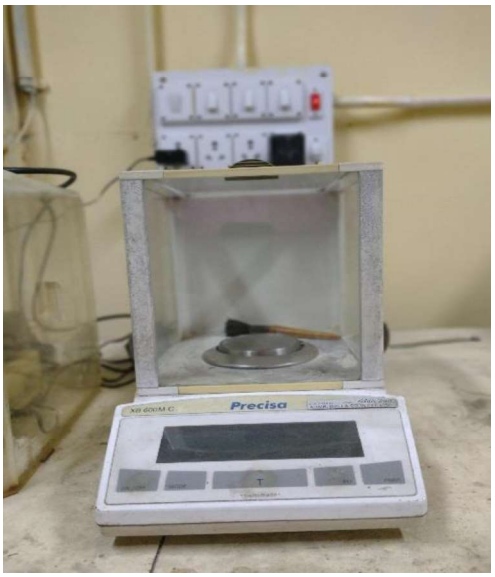
Description: An FTIR spectrometer simultaneously collects high-resolution spectral data over a wide spectral range. This confers a significant advantage over a dispersive spectrometer, which measures intensity over a narrow range of wavelengths at a time.

13. X-Ray Diffraction Analyzer

Manufacturer: Rigaku Corporation

Description: X-ray diffraction analysis (**XRD**) is a technique used in materials science to determine the crystallographic structure of a material. **XRD** works by irradiating a material with incident X-rays and then measuring the intensities and scattering angles of the X-rays that leave the material.

Some Instruments That Were Used During The Experiment



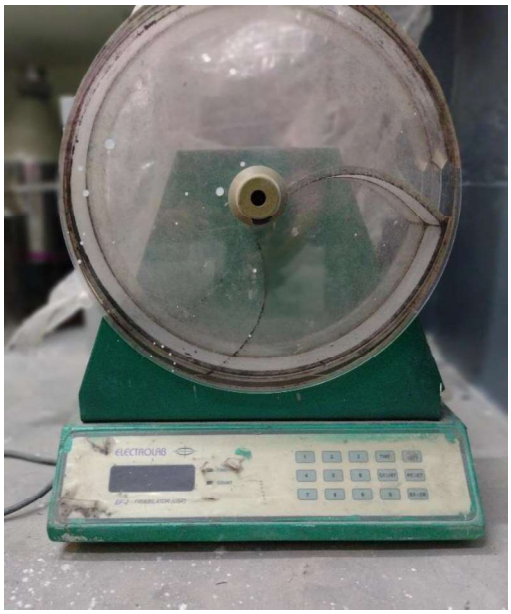
WEIGHING MACHINE: PRECISA

UV/VISIBLE SPECTROPHOTOMETER

JASCO V-550 DOUBLE BEAM SPECTROPHOTOMETER

TABLET PUNCHING MACHINE: REMIK 10

LYOPHILLIZER: SCANVAC



FRIABILATOR: ELECTROLAB

DISINTEGRATION TEST APPARATUS: VEEGO

DIGITAL HARDNESS TESTER: VEEGO

DISSOLUTION APPARATUS, USP TYPE-II

4.2. METHODS

1. Determination of λmax and development of calibration curve of Naproxen:

Maximum absorbance (λmax) of naproxen was measured by dissolving 10 mg of drug in 100 ml deionized water and was scanned using UV-VIS Spectrophotometer (JASSCO V-550) at 200-400 nm.[43],[44]

2. Preparation of pH 1.2 buffer

8.5 ml of concentrated hydrochloric acid was diluted with distilled water and volume was made up to 1000 ml with distilled water. pH (1.2) was adjusted with dilute hydrochloric acid.[43]

3. Development of Standard Calibration Curve in pH 1.2:

Stock solution was prepared by dissolving naproxen in 100ml of pH 1.2 buffer solution to get a concentration of 100 µg/ml.

This stock solution was further diluted to get solutions of various concentration ranging from 0.5 µg/ml to 5 µg/ml.

All the samples were scanned at 232nm wavelength, which was its λmax.[45]

4. Preparation of Solid dispersion[9],[10]

To prepare the SD of naproxen and maltodextrin, solvent evaporation by using lyophilization technique. Different weight ratios of naproxen bulk drug: carrier (Maltodextrin) combinations (1:1, 1:2, 1:3, 1:4, 1:5 w/w) were dissolved in their respective solvents, i.e. Naproxen in ethanol and maltodextrin in water, ultrasonicated for 5 mins and stirred in magnetic stirrer for 10 hours at 55ºC, 500 rpm. Then the mixture was lyophilized at -50ºC for 24 hours for complete removal of the residual solvent (ethanol) from the sample. Lyophilizer uses deep vacuum (<.200mbar) and heat to remove moisture from a sample. The drying process, or phase change, in lyophillization is unique and is called sublimation. In sublimation, molecules go directly from the solid phase (ice) to a gaseous phase (vapour) without passing through the liquid phase. The resultant

was pulverized, filtered through 80 mesh sieve and stored in a desiccator at about 25ºC until further use.

5. Solubility studies

After the preparation of Solid dispersion of the drug naproxen & carrier maltodextrin in varied ratios, solubility profile of the formulations was calculated. Calculated amount of the pure drug & solid dispersion from each formulation has been taken into the screw cap vials and was dissolved in 5 ml of acidic buffer of pH 1.2 by ultra-sonication (3 times) for 15 minutes. Samples were then filtered through a 0.45 micrometer filter paper and subjected to UV-VIS spectrophotometer (JASC0 V-550) at a specific wavelength of 232 nm (previously calibrated). This was performed in triplicate.[46]

6. Drug-Excipient Compatibility Studies

Stability studies were carried out as per the International Conference on Harmonization(ICH) Guidelines. Samples (physical mixture of drug and carrier) were placed inside sealed 40 ml HDPE container with child resistant cap under controlled temperature environment inside stability chamber (Thermo Lab, India) at 40ºC± 0.5ºC / 75±5 % RH for 3 months. The sample were withdrawn and evaluated for its content and at pre-determined time intervals (after 2 weeks, 4 weeks, 6 weeks, …., 12 weeks). The variations were analyzed and compared with the freshly prepared formulations. The process gets repeated for the formulation containing pure drug, SD1, SD2, SD3 etc.[47]

7. Characterization of solid dispersions

- **Fourier-Transform Infrared Spectroscopy (FTIR)**

Infrared spectroscopy was conducted employing Perkin Elmer (Massachusetts, USA) Spectrophotometer, and the spectrum was recorded in the wavelength region of 5000-500cm^{-1}. The procedure consisted of dispersing a sample (drug alone or mixture of drug and excipients) in KBr & compressing into discs by applying pressure. The pellet was placed in the light path, and the spectrum was obtained. It is used for conferring any interaction of the drug Naproxen with the carrier maltodextrin.

- **Powder X-Ray diffraction(PXRD)**

The powder X-ray diffraction patterns of the samples were recorded using Rigaku Miniflex Diffractmeter (Rigaku Corporation, Tokyo, Japan), a voltage of 40kV and a 30 mA current. The sample were analyzed over a 20 range of 5-80º, with a scanning rate of 2º/min and a Cu Ka radiation source. X-ray diffraction is based on constructive interference of monochromatic X-rays and a crystalline sample. These X-rays are generated by a cathode ray tube, filtered to produce monochromatic radiation, collimated to concentrate, and directed toward the sample. Pure ATC drug generally can be found in crystalline state, whereas after formation of SD, it gets transformed into amorphous form. Hence X-ray powder diffraction is most widely used for the identification of unknown crystalline materials.

8. Preparation of tablet by direct compression

i.Preformulation[51]

- **Bulk Density($D_{b)}$**

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this bulk density was calculated according to the formula mentioned below. It is expressed in gm/ml and is given by

$D_b = M/V_b$

Where, M and V_b are mass of powder and bulk volume of the powder respectively.

- **Tapped Density(D_t)**

It is the ratio of total mass of powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2% (in a bulk density apparatus). It is expressed in gm/ml and is given by,

$D_t = M/V_t$

Where, M and V_t are mass of powder and tapped volume of the powder respectively.

- **Hausner's Ratio**

Hausner's Ratio is an ease of index of powder flow. It is calculated by using the following formula :

Hausner's Ratio= Tapped Density/ Bulk Density .

Table 1: Hausner ratio and Flow character of powder.

HAUSNER RATIO	FLOW CHARACTER
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very, very poor

•Compressibility Index

The Compressibility Index of the powder is determined by Carr's Compressibility Index:

Carr's Index(%) = $\{(D_t-D_b)/D_t\}$x 100

Table 2: Compressibility Index or Carr's Index and Flow character of powder

COMPRESSIBILITY	INDEX PROPERTIES
≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very very poor

•Angle of repose

Funnel method was used to measure the angle of repose of powder. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder (2.0 cm above the hard surface)[106]. The powder cone was measured & angle of repose wascalculated using the following equation:

Angle of repose (θ) = $\tan^{-1}$ H/R

Where, H= Height of the powder cone.

R= Radius of the powder cone.

Table 3: Angle of repose and Flow character of powder.

Flow Ability	Angle of Repose
Excellent	<25
Good	25-30
Moderate flow	30-40
Poor flow	>40

ii.Stability Studies

Stability studies were carried out as per the International Conference on Harmonization Guidelines. The excipient to be used were placed inside sealed 40 ml HDPE container with child resistant cap under controlled temperature environment inside stability chamber (Thermo Lab, India) at 40ºC± 0.5ºC / 75±5% RH for 3 months. The sample were withdrawn and evaluated for the content and *in vitro* release at pre-determined time intervals (1 month, 2 month and 3 month). The variations are analyzed and compared with the freshly prepared formulations.

iii.Preparation of the tablet

The tablet containing SD of naproxen and maltodextrin were prepared by direct compression method. The Solid dispersions containing various ratios of the drug and the hydrophilic carrier along with other excipient were passed through sieve # 80 before their use in the formulation.

125 mg of naproxen was taken as reference dose for checking the extent of solubility in pH 1.2 buffer. So, in each formulation amount of SD should be equivalent to 125 mg of naproxen.

The excipients to be used with the formulation of Atorvastatin calcium-SD tablets are:
Microcrystalline cellulose (MCC), HPMC 5LV, Lactose, Talc, Magnesium stearate.

The excipients were accurately weighed and added into the blender in ascending order. The powder mixture was blended for 20 minutes to obtain uniform distribution of the drug in formulation. The blend was mixed with talc and magnesium stearate fortwo minutes and kept in desiccators until further used.

Compression Of Tablet: In the present study, the tablet was prepared manually using ten station compression machine (Rimek mini press-1, Karnavati Engineering Ltd. Mehsana, Gujrat). Accurately weighed amount of ingredient mixture was fed manually into die cavity and compressed using 12-mm circular punches with compression force of about 5-6kg/cm^2.

The process gets repeated for the formulation containing Pure drug, SD1, SD2, SD3.

iv.Post-compression parameter of tablet [51],[55]

- **Hardness test**

Automatic digital tablet hardness tester (8M, Dr Schleuniger, and Switzerland) was used to determine the crushing strength. 6 tablets were randomly selected from each formulation and the pressure at which each tablet crushed was recorded.

- **Friability test**

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (w_0 initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (w).

The % friability was then calculated by Percentage of Friability= 100 (1-w/w_0)

Percentage friability of tablets less than 1% is considered acceptable.

- **Thickness**

The thickness of a tablet was the only dimensional variable related to the process. At a constant compressive load, tablet thickness varies with changes of die fill,

particle size distribution, mixing, size of granules and the tablet weight. Tablet thickness was evaluated for batch-to-batch consistency. Six tablets were selected in a batch for the determination of thickness variation with vernier caliper. All readings should be taken in triplicate and determine its average.

- **Weight Variation**

Twenty tablets from each of the formulation were weighed individually with an analytical weighing balance (Model: AY-200, SHIMADZU Corporation, Japan). The average weights for each batch as well as a percentage deviation from the mean value were calculated.

Thirty tablets were randomly selected for the test. Every tablet in each batch should have uniform weight. Twenty tablets were weighted individually. Average weight was calculated from the total weight of all the tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits.

% weight variation=[(individual weight-average weight)/individual weight]x100

Out of twenty tablets, if two tablets deviate the limit, perform test for other ten tablets. Out of thirty tablets if not more than two tablets deviate, the batch passes test.

Table 4: Tablet weight variation limit.

Tablet weight(IP/BP)	limit	Tablet weight (USP)
80 mg or less	±10%	130 mg or less
More than 80 mg & less than 250 mg	±7.5%	130-324 mg
250mg or more	±5%	More than 324 mg

- **Drug content variation**

10 tablets where finely powdered and an amount equivalent to 100 mg of atorvastatin calcium was accurately weighed and transferred to 100 ml volumetric flask, then 70 ml of buffer pH 1.2 (0.01N HCl) was added. The flask was shaken

for 10 minutes. Finally, the volume was made up to the mark with the same buffer solution. The resultant solution was then filtered through Whatman filter paper (No. 41) and 1ml of the filtrate was suitably diluted up to 100 ml with same buffer solution and analyzed for Atorvastatin calcium content at 244 nm using a double beam UV visible spectrophotometer (JASCO V-550) and 0.01 N HCL as blank.

- **Disintegration Test**

Disintegration test is a method to evaluate the rate of disintegration of tablets. It is also defined as break down of solid dosage form into smaller particles when it is disintegrated.Place one tablet in each of the six tubes and added a disc to each tube. Maintain the temperature of the disintegration media at 37± 2ºC as specified in the monographs. At the end of time limit specified, left the basket from fluid and observe the tablets. If one or two tablets failed to disintegrate completely, repeat the test on 12 additional tablets. Not less than 16 out of 18 tablets tested disintegrate completely.

Table 5: Various tablet dosage forms and their given disintegration time

Tablets	Disintegration time
Uncoated tablets	15 min
Plain coated tablets	60 min
Enteric coated tablets	3 hours
Dispersible tablets	3 min
Effervescent tablets	Less than 3 min
Buccal tablets	4 hours
Chewable tablets	Not required

.

• *In-vitro* Dissolution Studies [67]

Dissolution is defined as "the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition" . Dissolution is conducted to know the minimum time taken by the drug to dissolve itself in the systemic circulation and starts its action in the body. There are 2 methods of to know the dissolution rate,

1. In vitro studies
2. In vivo studies.

In the pharmaceutical industry, drug dissolution testing is routinely used to provide analytical in vitro drug release erudition for both quality control scheme, i.e., to compute batch-to-batch consistency of solid oral dosage forms such as tablets and drug reinforcement, i.e., to anticipate in vivo drug release profiles. It serves as presentative factor for bioavailability and bioequivalence.

The dissolution method is a kinetic method .i.e., periodical samples were withdrawn for the determination. The in vitro dissolution was carried out using USP Dissolution testing apparatus type-II (ELECTROLAB, INDIA)

1) 0.1 N HCl buffer solution pH 1.2(900ml) was measured and transferred into the dissolution flask.
2) The temperature was maintained at 37±0.50 C.
3) Prepared tablets and marketed tablets were placed at the bottom of the jar.
4) The paddle was rotated at 50 rpm.
5) 5 ml of sample was withdrawn at the starting and transferred into the test tube appropriately labelled. Immediately 5ml of 0.1 N HCl buffer solution pH 1.2 was replaced into the dissolution flask.
6) Similarly, samples were collected at 5,10,15,20,30 min intervals. A 5 ml of fresh dissolution medium was replaced in the flask whenever the sample is withdrawn.
7) All samples were filtered by using durapore filter paper.
8) The absorbance at 241 nm was measured in uv/visible spectrophotometer

(JASCO V-550) using the 0.1 N HCl buffer solutions as a blank.

9) The absorbance was recorded in the table and further calculations are done
10) A graph was plotted by taking cumulative percent of drug dissolved on y-axis andtime on x-axis.

- **Drug Release Kinetics Model** [70]

Different kinetic models can be applied to evaluate the different release pattern of thedrug from the oral dosage form. These models are utilized in the prediction of drug behavior and release kinetics. These are given as

Zero order:

Zero-order model Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$Qt = Q0 + K0\ t$

Rearrangement of the above equation yields:

$Qt = Q0 + K0t$

Where, Qt is the amount of drug dissolved in time t,

Q0 is the initial amount of drug in the solution (most times, Q0 = 0) and

K0 is the zero-order release constant expressed in units of concentration/time.

To study the release kinetics, data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time.

Application: This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms,osmotic systems, etc.

First order:

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis.The release of the drug which followed first order kinetics can be expressed by the equation:

$dC/dt = -Kc$

where K is first order rate constant n units of $time^{-1}$.The above equation can be

expressed as:

$\log C = \log C_0 - (Kt / 2.303)$

where C_0 is the initial concentration of drug, k is the first order rate constant, and t is the time[28]. The data obtained are plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of -K/2.303. Application: This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms suchas those containing water-soluble drugs in porous matrices.

Higuchi

In 1963 Higuchi developed several theoretical models to study the release of water-soluble & poorly water-soluble drugs incorporated in semi solid/ in solid matrices.

Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. It is used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms.

$Q = K_h t^{1/2}$

Where, K_h is release rate constant for Higuchi model.

Korsmeyer Pappas[78]

In 1983, Korsemeyer *et al.* developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time (t) which can be describes as,

$\ln (Qt/Q\infty) = \ln K + n \ln t$

Where, $Qt/Q\infty$ is the fraction of drug release at time t & K is the rate constant comprising the structural & geometric characteristics of the formulation & n is the release exponent. For the determination of exponent n, the portion of the release curve where $Qt/Q\infty < 0.6$ should only be used. This model can be used to analyze the release of pharmaceutical dosage forms when the release mechanism is not well known or when more than one type of release phenomena could be involved.

n= 0.45 indicates Fickian diffusion, $0.45<n<1$ indicates Anomalous transport or non Fickian diffusion (both diffusion & erosion), n= or > 1 indicates Case – II transport (erosion of the polymeric chain).

5. TABLES & GRAPHS

- **Maximum Absorbance of Naproxen in distilled water using UV Spectrophotometer**

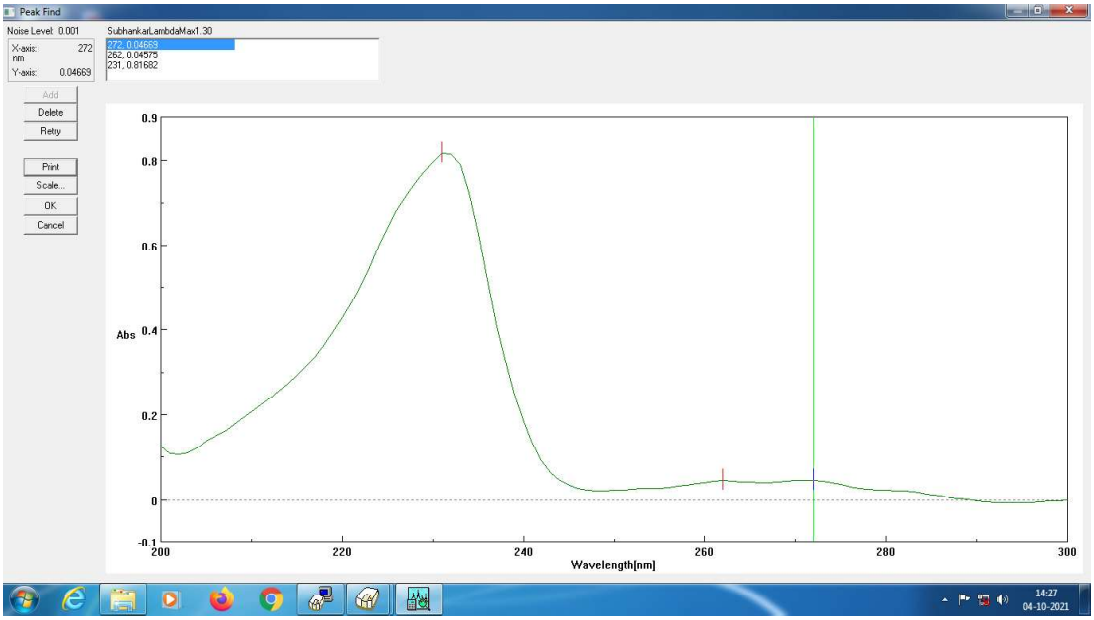


Figure 6: λmax of Naproxen in distilled water

- **Table 6: Determination of standard calibration curve of Naproxen at pH 1.2**

No.	Concentration(mcg/ml)	Absorbance
1	0.5	0.1224
2	1	0.2487
3	1.5	0.3743
4	2	0.484
5	2.5	0.5984

- **Standard calibration curve of Naproxen at pH 1.2**

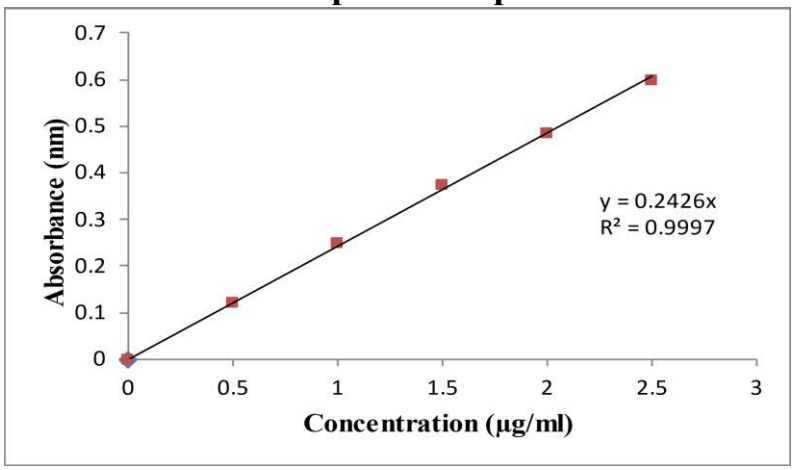


Figure 7: Calibration curve of naproxen at pH 1.2

•Table 7: Solubility Profile of the pure drug and the solid dispersion in various ratios (1:1, 1:2, 1:3, 1:4 etc) (n=3)

Formulation Code	Pure drug: Carrier	Solubility in mg/ml in acidic buffer of pH 1.2
Pure drug		0.2550
SD1	1:1	0.3129
SD2	1:2	0.3845
SD3	1:3	0.5674
SD4	1:4	0.7758
SD5	1:5	0.8124

•Solubility profile of the pure drug and drug: carrier solid dispersion in different ratios [(1:1), (1:2), (1:3), (1:4), (1:5)]

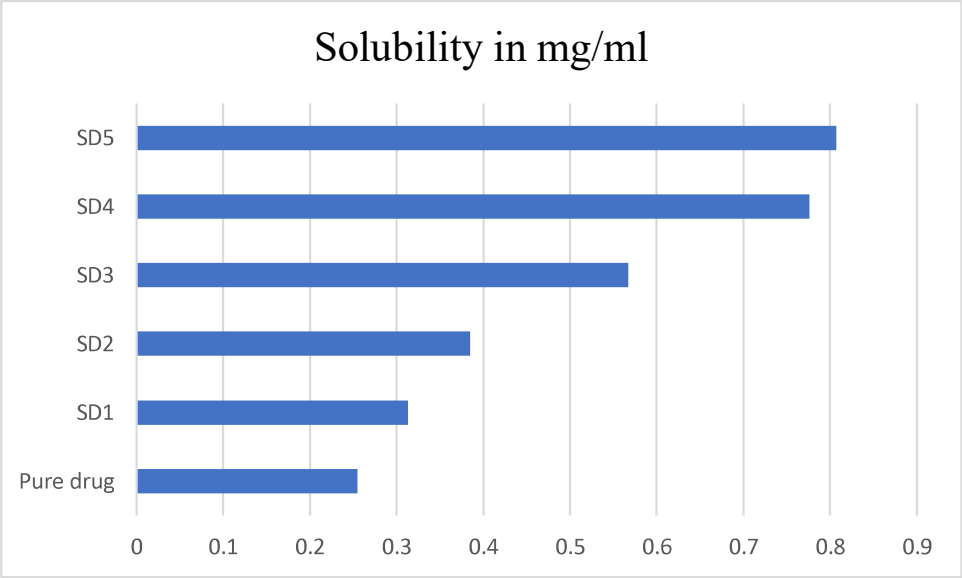


Figure 8: Solubility profile of various prepared solid dispersions

- **Table 8: Formulation details during preparation of Solid Dispersion of Naproxen and Maltodextrin:**

SL NO.	FORMULATION CODE	Ratio of Drug to carrier	Amount of Drug (mg)	Amount of maltodextrin (mg)	Total amount of SD to be taken (mg)
1.	PURE DRUG	0	125	0	125
2.	SD1	1:1	125	125	250
3.	SD2	1:2	125	250	375
4.	SD3	1:3	125	375	500
5.	**SD4**	**1:4**	**125**	**500**	**625**

- **Table 9: Formulation details during development of direct compressed Naproxen solid dispersion tablets:**

Sl no.	Solid dispersion	Amount ofSD (mg)	Ingredients	Amount (mg)	Total amount (mg)
1.	PURE DRUG	0 (Drug: 125 mg)	MCC (ph102)	309.5	800
			Lactose	309.5	
			HPMC 5LV	32	
			Talc	8	
			Mg Stearate	16	
2.	SD4	625	MCC (ph 102)	59.5	800
			Lactose	59.5	
			HPMC 5LV	32	
			TALC	8	
			Mg Stearate	16	

- **Table 10: Micromeritic Properties of pre-compression powder blend:**

Formulation	Bulk Density (gm/ml) ±S.D (n=3)	Tapped Density(gm/ml) ±S.D(n=3)	Carr's Index(%) ± S.D(n=3)	Hausner's Ratio ±S.D (n=3)	Angle of Repose(θ) ±S.D (n=3)
Pure Drug	0.356±0.03	0.430±0.02	17.4±1.8	1.21±0.4	33.13±2.8
SD4	**0.410±0.04**	**0.502±0.04**	**14.11±1.32**	**1.14±0.2**	**24.57±2.17**

- **Table 11: Post compression parameters of various formulations:**

Formulation	Diameter (mm) ±S.D(n=3)	Thickness (mm) ±S.D(n=3)	Hardness (kg/cm^2) ±SD n=3)	Friability (%)±S.D (n=3)	Weight Variation (800 mg) ±S.D (n=3)	Disintegration time (min) ±S.D (n=3)	Drug Content (%w/w) ±S.D (n=3)
Pure Drug	13.03±0.02	7.04± 0.06	6.53±0.03	0.22± 0.018	790± 0.57	7±0.5	100.1± 0.3
SD1	13.01±0.02	7.02± 0.01	6.22±0.06	0.21± 0.021	789± 0.65	6±0.5	90.59 ± 0.4

- **Table 12: Cumulative percentage drug release at pH 1.2**

Time (t) min	CPR of Pure drug (%) ±S.D(n=3)	CPR of SD4 (%) ±S.D (n=3)	CPR of Marketed Product (%) ±S.D (n=3)
5	3.69±1.02	11.52±1.1	7.03±1.1
10	11.19±1.22	26.86±1.18	19.35±1.45
15	23.85±2.51	45.83±2.27	19.35±1.50
30	40.99±3.18	68.57±2.77	56.13±3.14
45	61.43±3.55	94.04±4.14	79.67±4.21
60	82.77±3.87	99.45± 4.23	95.23± 4.32

- **Table 13: Stability and compatibility study of naproxen & carrier maltodextrin hitherto Solid Dispersion preparation:**

Formulation	Physical Appearance	Time Period						
		0 week	After2 weeks	After4 weeks	After6 weeks	After8 weeks	After 10 weeks	After 12 weeks
Drug + Maltodextrin	Physical state	Solid state, Powder	No change	No change	No change	No change	No change	**No change**
	Colour	White	No change	No change	No change	No change	No change	**No change**

- **Table 14: Stability and compatibility study of prepared solid dispersion and the excipients**

Formulation	Physical Appearance	Time Period						
		0 week	After 2 weeks	After 4 weeks	After 6 weeks	After 8 weeks	After10 week	After12 week
SD4 (Optimized) + MCC	Nature	Solid state, Powder	No change	No change	No change	No change	No change	**No change**
	Colour	White	No change	No change	No change	No change	No change	**No change**
SD4 + HPMC	Nature	Solid state, powder	No change	No change	No change	No change	No change	**No change**
	Colour	White	No change	No change	No change	No change	No change	**No change**
SD4+ Lactose	Nature	Solid state, Powder	No change	No change	No change	No change	No change	**No change**
	Colour	White	No change	No change	No change	No change	No change	**No change**
SD4 + Talc	Nature	Solid state, powder	No change	No change	No change	No change	No change	**No change**
	Colour	White	No change	No change	No change	No change		**No change**
SD4 + Magnesium stearate	Nature	Solid state, powder	No change	No change	No change	No change	No change	**No change**
	Colour	White	No change	No change	No change	No change		**No change**

- **Table 15: Correlation Coefficient(R^2) of different drug release kinetics for different formulations**

Formulationcode	Correlation Coefficient (R^2)			
	Zeroorder	Firstorder	Higuchi	Korsmeyer-peppas
Pure Drug	**0.9957**	0.0136	0.9107	0.9823
SD4	**0.9469**	0.1916	0.9792	0.875
Marketed Product	**0.9898**	0.1331	0.9113	0.9850

- **Different release kinetics of tablets with Pure Drug Formulations. (n=3)**

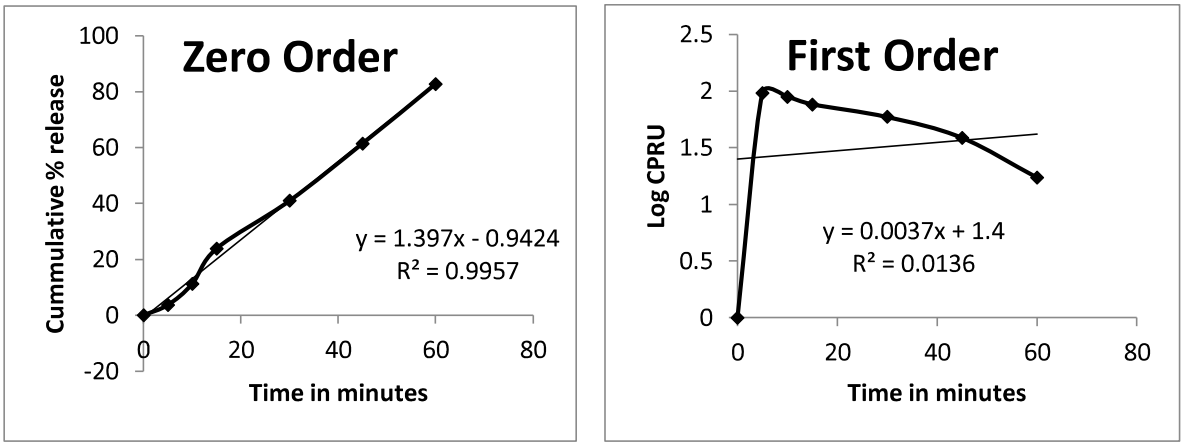


Figure 9: Zero and first order release kinetics of pure drug formulation.

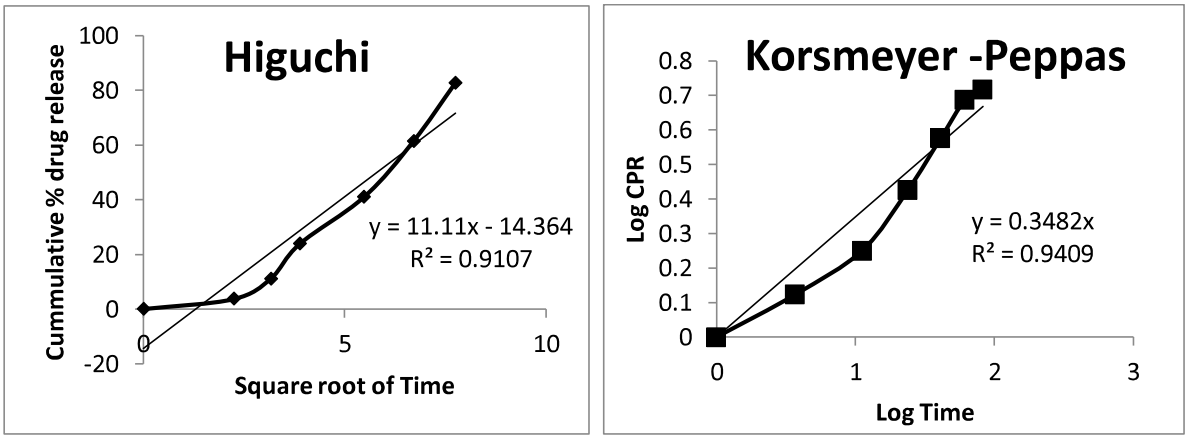


Figure 10: Higuchi and Korsmeyer- Peppas release kinetics of pure drug formulation.

- **Different release kinetics of tablets of marketed formulations. (n=3)**

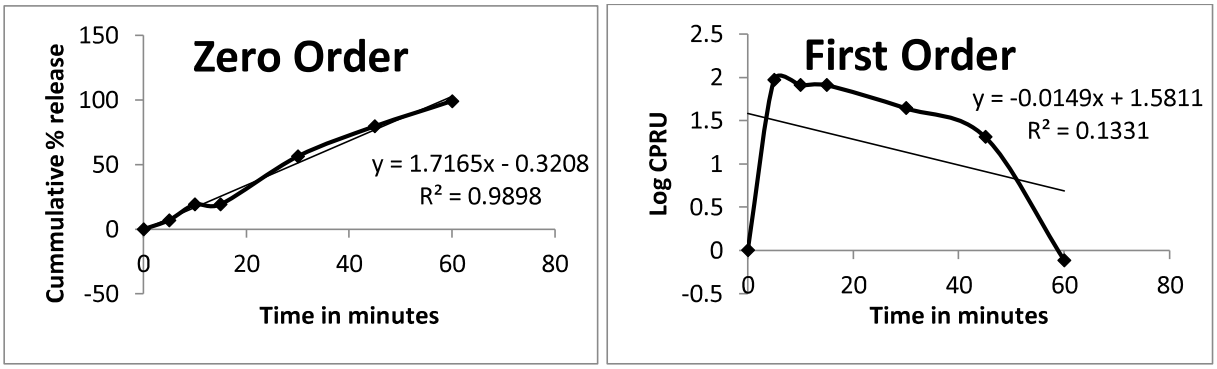


Figure 11: Zero and first order release kinetics of marketed formulation.

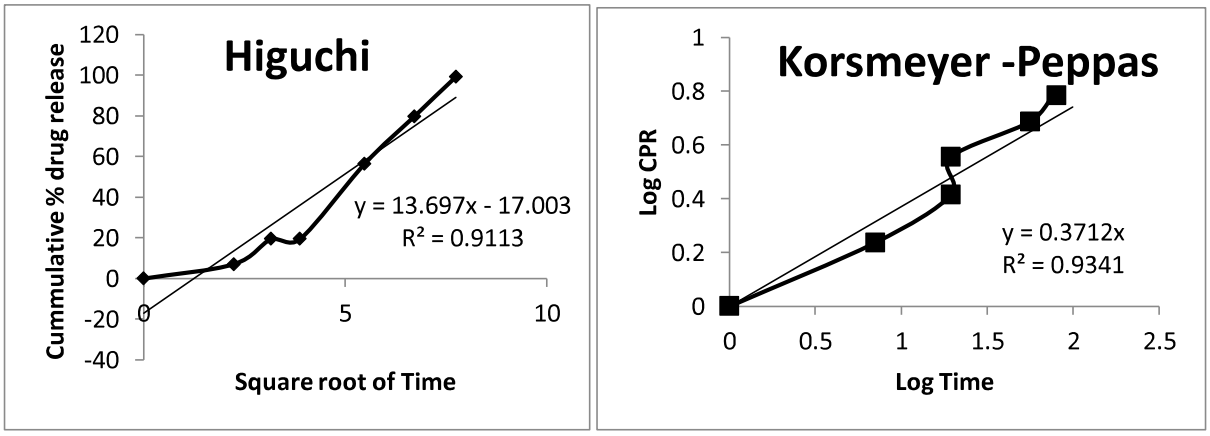


Figure 12: Higuchi and Korsmeyer- Peppas release kinetics of marketed formulation.

- **Different release kinetics of tablets containing SD4 Formulations. (n=3)**

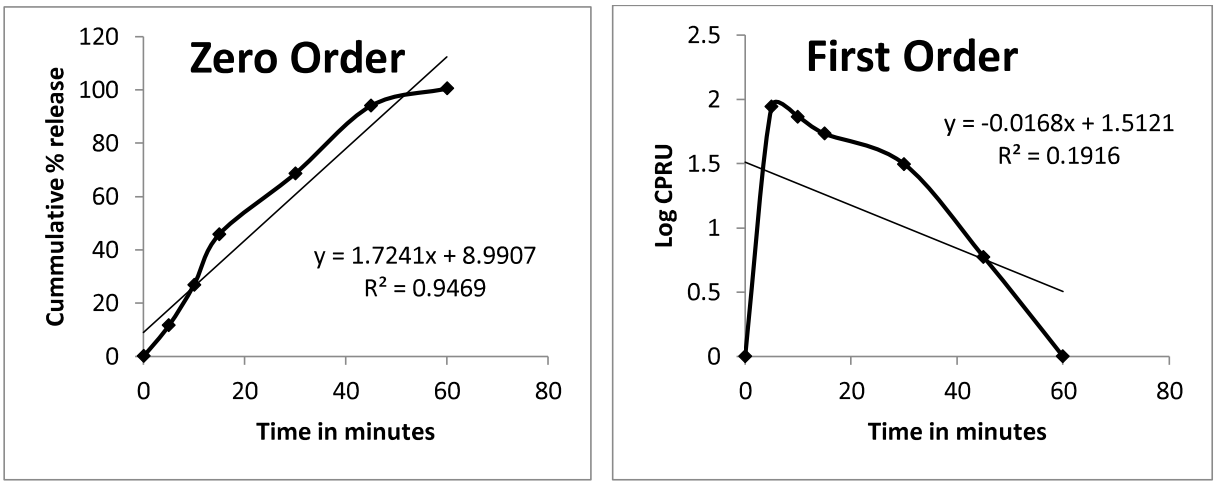


Figure 13: Zero and first order release kinetics of solid dispersion (1:4) formulation.

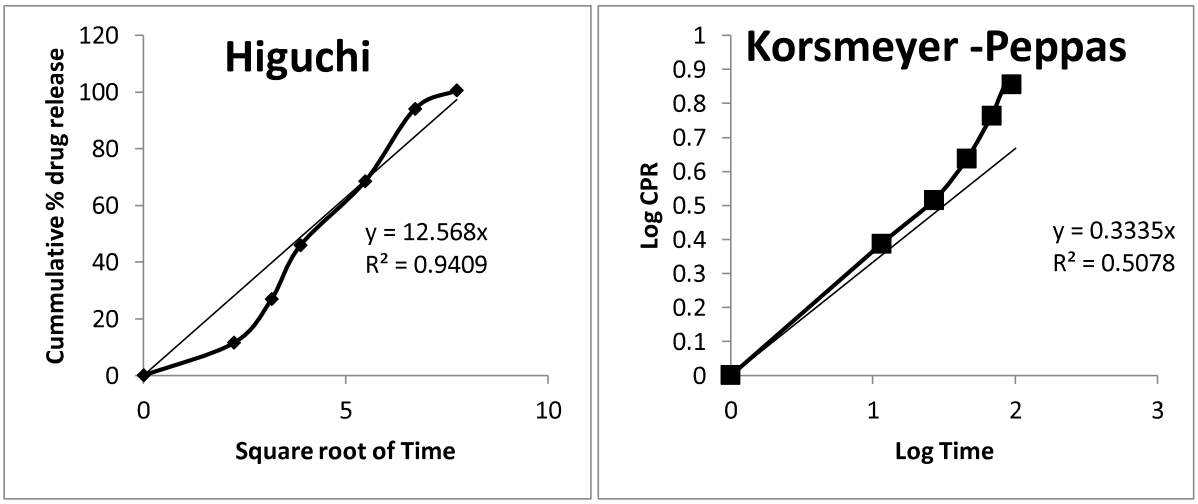


Figure 14: Higuchi and Korsmeyer- Peppas release kinetics of solid dispersion (1:4) formulation.

- **Comparative Release study with the marketed product (n=3)**

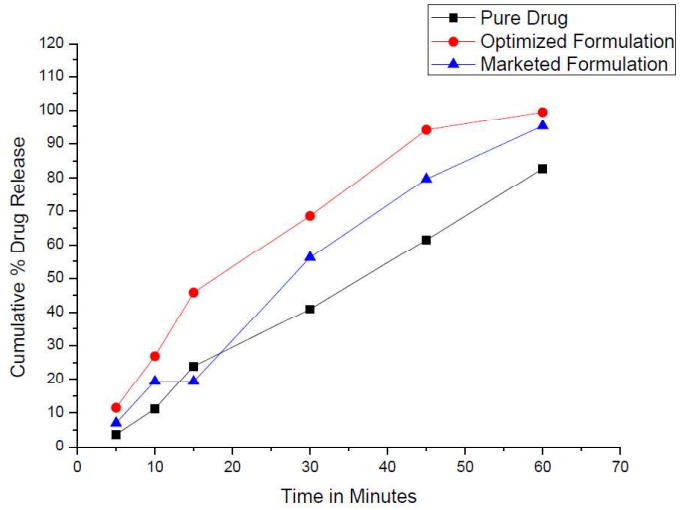


Figure 15: Comparative release study of pure drug, solid dispersion and marketed formulation.

- **Comparative Analysis of FT-IR curve of different formulations:**

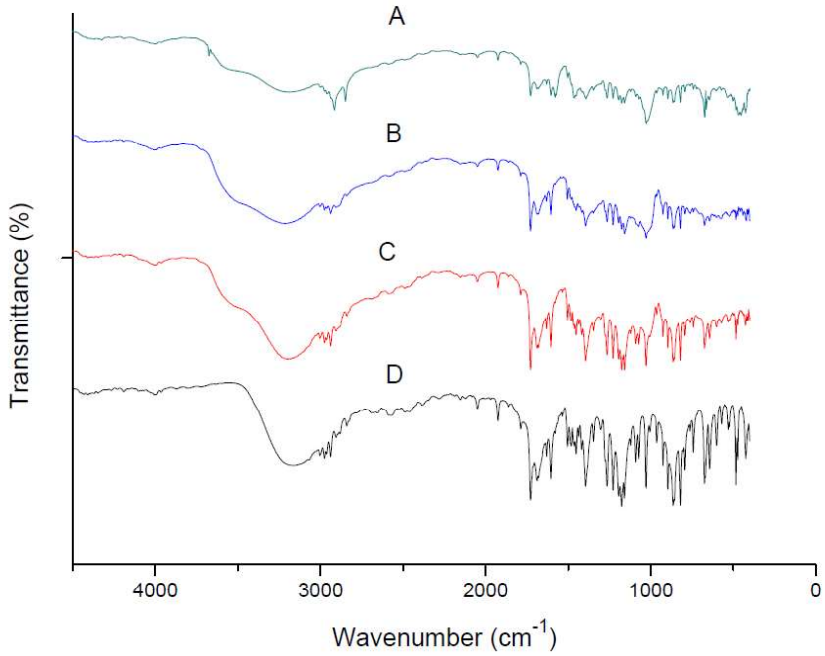


Figure 16: FT-IR analysis of all formulations.

Where,

A = FT-IR Curve of Physical mixture of Solid Dispersion and Excipients

B = FT-IR Curve of Solid Dispersion

C = FT-IR Curve of Drug + Carrier

D= FT-IR Curve of pure Drug

- **X-Ray Diffraction Analysis of pure Naproxen**

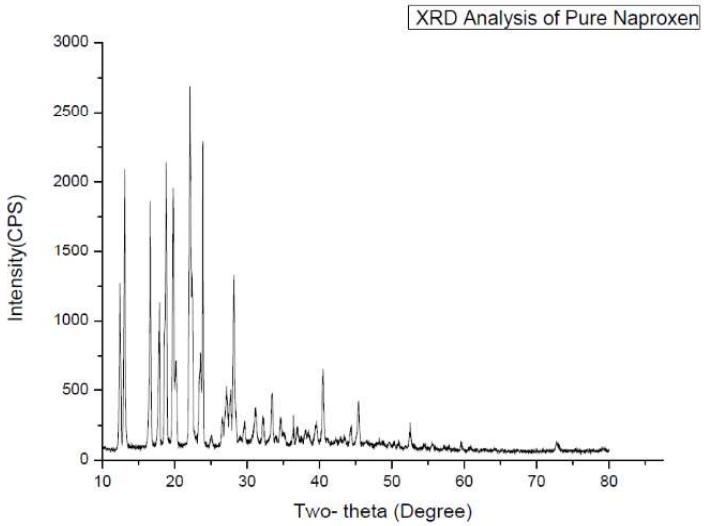


Figure 17: X-Ray Diffraction analysis of pure drug naproxen.

- **X-Ray Diffraction analysis of physical mixture of Drug and Carrier (1:4)**

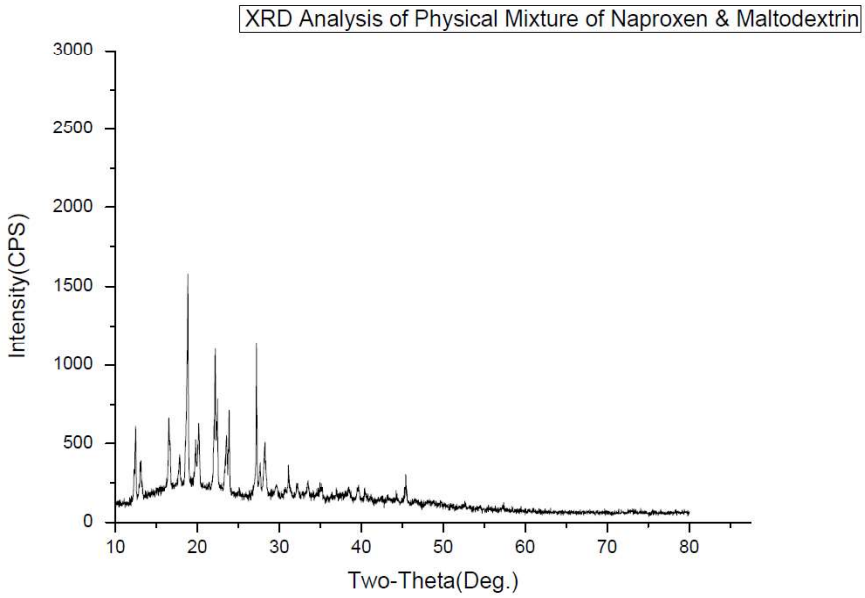


Figure 18: X-Ray Diffraction analysis of physical mixture of drug and carrier.

- **X-Ray Diffraction Analysis of SD4 (Drug and Carrier ratio 1:4)**

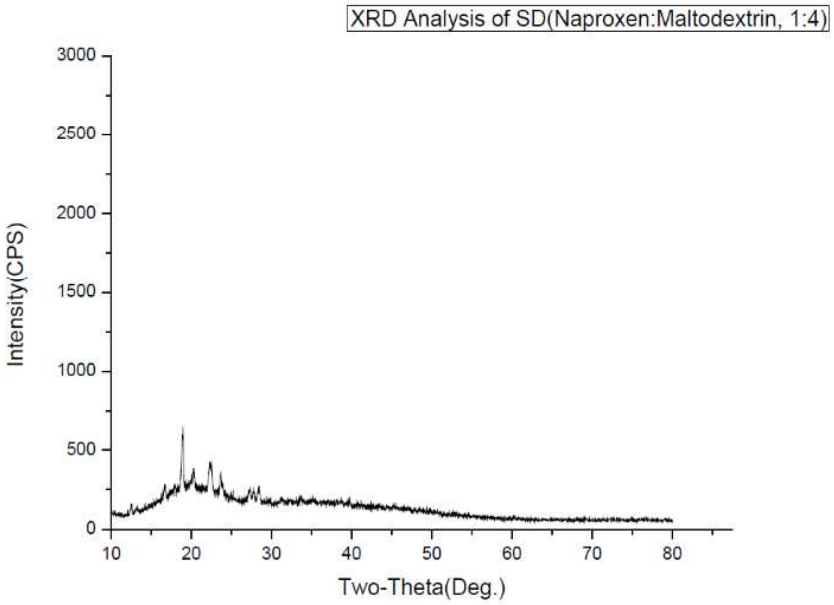


Figure 19: X-Ray Diffraction analysis of solid dispersion of drug and carrier (1:4).

6. RESULT AND DISCUSSION

1. Determination of maximum absorbance of Naproxen

Figure 6 exhibits the maximum absorbance of the naproxen scanned according to the procedure given in chapter 4. The absorbance spectra was characterised by maxima at 232nm in the distilled water.

2. Preparation of the calibration curve for naproxen in pH 1.2 using distilled water

Figure 7 shows the calibration curves of naproxen in pH 1.2, which was obtain when concentration in µg/ml (**Table 6**) was plotted against absorbance. It gave straight line that passes through the origin in pH 1.2. The correlation coefficient has been determined and found to be 0.9996.

3. Stability & compatibility study of drug and carrier(Maltodextrin)

As shown in **Table 13**, after removal of predetermined time interval, all the samples were subjected to visual inspection in terms of its physical state and colour. No significant variations were found in results. It is indicated that the drug and the carrier are compatible to each other and are stable under an accelerated storage conditions, hence they were used together in the same formulation.

4. Preparation of the solid dispersion

Solid dispersions of various ratios were prepared using the premediated doses of naproxen and the carrier. The solid dispersion was prepared by employing the solvent evaporation technique, using ethanol as solvent for naproxen and distilled water in case of naproxen.

5. Solubility study

As shown in figure 8 and table 7, the solubility of the pure drug which is in crystalline form, was much less than the solid dispersions, that are in amorphous form. As the amount of the hydrophilic carrier maltodextrin was increasind gradually, the solubility of the drug also increased. But here we can see that the solubility of the formulation SD (1:4) i.e. 0.77 mg/ml was more than double the solubility of formulation SD1 (1:1) i.e. 0.31 mg/ml. Hence maltodextrin as hydrophilic carrier improved the solubility of the naproxen to a great extent.

6. Characterisation of Solid Dispersion

- **Fourier Transform Infrared Spectroscopy(FT-IR)**

If the drugs have different crystal form, there may be difference in chemical bond length and angle, which could affect vibrational-rotational transitions and some characteristics such as IR absorption band frequency, peak shape, peak position and intensity. Remarkably, IR spectrum could provide this information about chemical bonds, characteristic functional groups and generally detect possible molecular interactions between drugs and carriers in the solid dispersion system.[122] The Fourier transform infrared study was done for the pure drug, physical mixture of the pure drug and the carrier maltodextrin, and the solid dispersion and the result is shown in **Figure 16**.The pure naproxen showed a characteristic peak at 1256 cm-1 for C=O(carboxyl) group stretching, 1594 cm-1 for C-O (hydroxyl) group stretching, 1628 cm-1 for C-C (aromatic) group stretching and 2838 cm-1 for C-C (aliphatic) group stretching. While, in the prepared solid dispersion, stretching the drug showed similar peaks at 1250 cm-1 for C=O(carboxyl) group stretching, 1593 cm-1 for C-O (hydroxyl) group stretching, 1630 cm-1 for C-C (aromatic) group stretching and 2840 cm-1 for C-C (aliphatic) group stretching, revealing that there was not much interaction between drug and the carrier, maltodextrin. No additional new peaks in physical mixture confirm the absence of chemical interaction occurred during the preparation process.

- **Powder X-Ray Diffraction(PXRD)**

Powder X-ray diffraction could provide further verification of drug crystal conversion. The PXRD pattern of pure drug naproxen, the solid dispersion and the physical mixture of drug and carrier were depicted in **Figure 17, 18, 19**. The diffraction pattern of pure drug showed characteristic high intensity peaks at 12.36, 13.06, 16.67, 17.72 22.08, 23.81, 28.14, 33.40 40.26, 45.45 which indicates that the drug is present in the crystalline form, but in case of solid dispersion, most of the peaks were absent indicating the transformation from crystalline to amorphous state. Whereas, in case of physical mixture, some intensity peaks can

be seen in the region similar to the pure drug indicating the presence of crystalline structure of naproxen in the mixture.

7. Solid dispersion and excipients compatibility study

As shown in **Table 14,** after removal of predetermined time interval, the samples [Solid dispersion with different excipients being used in the tablet formulation] were subjected to visual inspection in terms of its physical state and colour. No significant variations were found in results. It is indicated that the drug and the excipients are compatible to each other and are stable under an accelerated storage condition, hence they were selected together in the same formulation exclusively due to its compatibility.

8. Physical parameter testing of prepared solid dispersions

- **Bulk Density and Tapped Density**

Bulk Density & Tapped Density of the selected naproxen and maltodextrin of the optimized batches were determined as per the procedure describes in Chapter 4.

It was found from the results (**Table 10**) that bulk densities of all batches examined varied in the ranges from 0.356 gm/ml to 0.468 gm/ml, whereas tapped densities are ranged from 0.430 gm/ml to 0.542 gm/ml. From these two densities, further analysis, such as compressibility index and Hausner's ratio were determined.

- **Compressibility Index and Hausner's Ratio**

The flow ability of the powders was also indicated by Compressibility Index and Hausner's Ratio. Values of Compressibility Index & Hausner's Ratio and the nature of the flow property have shown in **Table 2 & 1** respectively in the Chapter 4. The Compressibility Index of the optimized batches (**Table 10**) were found to be withinrange from 11.20% - 17.4% indicating accepted flow properties.

The Hausner's Ratio of the optimized batches (**Table 10**) were found to be within range from 1.16-1.24, indicating accepted flow properties.

- **Angle of Repose**

The method angle described previously in Chapter 4 is called a dynamic angle and it is generally the preferred means of measurement because it more closely mimics the manufacturing situation, in which the powder is in motion. In this formulation, presence of MCC ph 102 (which is in granular form) increases the flowability of the formulation. The value of θ of a matter and the nature of flow property it tends to exhibit have shown in TABLE 3. The θ values of the optimized batches are shown in **Table 10**. The value ranges in between 26.8- 33.13, indicating that the powders have good to moderate flow properties.

9. Assessment of the prepared tablets

Tablets are prepared by weighing the calculated amount of ingredients shown in **Table 9**. The method of preparation of the tablets has already been mentioned in Chapter 4. Microcrystalline cellulose(MCC) and lactose has been used as filler, HPMC 5LV as binding agent, magnesium stearate and talc as lubricant and glidant respectively. Different batches of tablets were prepared by considering varying active ingredients like, pure naproxen drug, Solid dispersion of naproxen and the carrier in the ratio 1:4[SD4]. These tablets as well as the powder blends were subjected to various *in-process* quality control tests for evaluation of their different physical parameters. These *in-process* quality control was very much important not only because these parameters determine the uniformity of flow properties of powders & uniformity of tablets in respect to weight, size, shape & content but also, they determine the suitability of tablets for further processing like *in-vitro* release studies.

- **Weight Variation Test**

The maximum percentage weight variation that can be allowed for tablets according to USP, IP, BP is specified in **Table 4** of Chapter 4. In **Table 11**, the

weight of the optimized batches falls between 785.65-808.52 mg. Hence the percentage deviation falls under 0.98 % & 1.01%. No tablet was found to be outside this range. Hence, the tablets were statistically significant with respect to weight.

- **Content Uniformity**

This is an important test to ascertain the uniformity of tablets with respect to drug content. The percentage variation of drug content should be within ±15%. In all the prepared batches, on which the content uniformity tests were carried out as specified in chapter 4, the content variation was very less (within the compendia limits) as shown in **Table 11**. Thus, the tablets were very much uniform in respect to drug content.

- **Thickness and diameter**

Crown thickness uniformity is necessary not only for consumer requirement but also for packaging. Usually, ± 5% variation is permissible. The thickness of all tablets was tested by the method described in Chapter 4. It was observed that thickness of all tablets ranged well between the permissible range of ± 5% as shown in **Table 11.**

- **Hardness**

The hardness of all naproxen solid dispersion tablets was tested by the method described in Chapter 4. It was found that hardness of the prepared tablets varied between 6.22-6.53 kg/cm^2 as shown in **Table 11.** This result ensured that the formulation was free from transportation damage, and also adequate shelf life during its transportation.

- **Friability**

During the compression of the powders, sufficient force was applied to get the final hardness of the tablet of around 6.22-6.53 kg/cm^2 hardness as measured in Digital Tablet Hardness Tester. But tablet hardness is not an absolute indicator of tablet strength. Friability test is done to ascertain whether the tablets are resistant

to chipping and cracking during handling and/or subsequent processing. Weight loss should be less than 1% for good tablets. This test was performed on all optimized batches of tablets as per the procedure given in Chapter 5. The percentage loss for all the batches was found to fall within the range of 0.21 to 0.22 %. This ensures that the tablets were free from transportation damage/loss.

10. *In-vitro* Drug Release Study

The release of the pure drug naproxen, solid dispersion of naproxen and carrier maltodextrin from the directly compressed tablets and marketed formulation of naproxen (Naprosyn) were analyzed by plotting the cumulative percentage release of drug vs time. As given in **Table 12** , the cumulative percentage release of the pure drug in 1 hour was found to be 82.77% (n=3). For marketed formulation (Naprosyn) of the drug was found to be 95.23% (n=3). The cumulative percentage release of optimized solid dispersion was found to be 99.23% (n=3). But within 45 minutes optimized formulation released 94.04%(n=3) which is much higher than the marketed product's release 79.67%(n=3).Thus, it can be concluded that as the amount of maltodextrin is increased in the solid dispersion, the solubility has increased gradually. The prepared solid dispersion of naproxen and maltodextrin in the ratio of 1:4 increased the solubility of naproxen to a significant level than the pure drug and slightly more than the commercial product. The solid dispersion having drug-carrier ratio of 1:5 was discarded because it showed little additional solubility even after using more amount of carrier than the amount required in solid dispersion of 1:4 ratio. It was evident that the prepared solid dispersion has improved the solubility and cumulative percentage drug release than the pure drug and the marketed product (Naprosyn) in the specified time due to the reduction in particle size and change from crystalline nature to the amorphous form.

In the **Figures 9-14** of drug release patterns, the drug release from all the formulations followed zero order kinetics, as the plot observed between amount of drug released vs. time was found to be linear. To analyze the mechanism of drug

release from these formulations, the data were analyzed through Higuchi model and Korsmeyer-Peppas model. From the Higuchi model it can be said that the process of drug release is a diffusion process, as the correlation coefficient (0.9792) is more inclined toward 1. From the Korsmeyer-Peppas model, it may be attributed that the drug release pattern followed anomalous or non-fickian diffusion.

11. Comparison with the commercially available product

The cumulative percentage drug release of the prepared solid dispersion(1:4) was compared with the cumulative percentage drug release of Naprosyn, a commercially available formulation **(FIGURE 15)**. It was found that the cumulative percentage drug release of the prepared solid dispersion at 45 minutes was 94.04% which was much higher than the commercially available formulation (79.67%). Through this result, the solid dispersion showed promising future for further research work on it.

7. CONCLUSION

The main aim of solid dispersion technique was to increase the dissolution rate and solubility of naproxen, a BCS Class II drug by decreasing the particle size of the drug & transforming the crystalline state to amorphous one by solid dispersion technique. In amorphous form, inter molecular hydrogen bonding between the drug and water molecule is less rigid than the intra molecular hydrogen bonding present in crystalline state. Hence less energy is required to break the bond of an amorphous structure than to dissolve a crystal lattice. Since naproxen dispersed in solid dispersion has a large surface area, it increased the interfacial area of contact between the drug particles and dissolution medium, leading to improved dissolution and bioavailability.

As the study progresses, we can see that increasing the amount of maltodextrin in the solid dispersion increases the solubility and dissolution rate of the drug. But at the same time, the solubility and dissolution rate were highest in the solid dispersions containing drug and carrier ratio 1:4 and the 1:5 variant, which showed a little additional effect. Hence it can be concluded that to the enhance the solubility and dissolution rate of the naproxen, solid dispersion of the drug with hydrophilic carrier maltodextrin with ratio 1:4 is the most efficient, economic and cost-effective option to choose from.

Thus, solid dispersion of demonstrates better bioavailability, dissolution rate through *in-vitro* analysis, confirming that the solid dispersion will improve the efficacy of the poorly water-soluble drug to a great extent in the days ahead.

8. FUTURE SCOPE

This research work concluded in improving the solubility rate of the drug, naproxen through solid dispersion technique using maltodextrin as the carrier. However further detailed research work is necessary for establishing this technique for improving the solubility and bioavailability of naproxen. *In-vivo* analysis of these solid dispersion is required for further development of this formulation. For NSAIDS, animal model like carrageenan- rat hind paw model etc. can be used to check the therapeutical benefits of using solid dispersion techniques. Further insights are required for precision and accuracy of the solid dispersion production which are required for scaling up of the process of This technique can also be used to improve the solubility and bioavailability of the other BCS Class II drugs, who have the same issue of solubility.

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