ISSN 2349-7203

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

HUMAN

Human Journals
Research Article
July 2016 Vol.:6, Issue:4

Enhancing the Bioavailability of Poorly Water Soluble Drug Etoroxib Using Solid Dispersion Technique" Solid Dispersion a Method to Improve Bioavailability of Poorly Water Soluble Drug

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Mathew George*[1], Lincy Joseph[2], Pooran Mal Saini[3], JyothilakshmiV Nair[4]

Head of Department and Professor,Department of Pharmacology,[1]Pushpagiri College of Pharmacy, Pushpagiri Medicity,Perumthuruthy, MC Road, Thiruvalla, India.
Head of Department and Professor ,Department of Pharmaceutical Chemistry, [2]Pushpagiri College of Pharmacy, Pushpagiri Medicity,Perumthuruthy, MC Road, Thiruvalla, India.
Department of Pharmaceutics, [3]School of Pharmaceutical Sciences, Jaipur National University, Jaipur, India.
Assistant Professor, Department of Pharmaceutics, [4]Pushpagiri College of Pharmacy, Pushpagiri Medicity,Perumthuruthy, MC Road, Thiruvalla, India.

Submission: 26 June 2016
Accepted: 1 July 2016
Published: 25 July 2016

Keywords: Dissolution, Solid Dispersion, Solubility, Cellulose Derivatives, Polyethylene glycol.

ABSTRACT

Improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. The solubility behavior of drugs remains one of the most exigent aspects in formulation development. Due to combinatorial chemistry and HTS numbers of drug molecules are rapidly developed but due to their poor water solubility about 40 to 45 % of drug molecules fails in reaching the market. With the advent of combinatorial chemistry and high throughput screening, the number of poorly water soluble compounds has dramatically increased. Among all the newly discovered chemical entities, about 40-45% of drugs fail to reach market due to their poor water solubility. Solubility of the drug molecule is major issue of concern for formulation scientist because of its effects on the bioavailability. Because of solubility problem, bioavailability of drugs gets affected and hence solubility enhancement becomes necessary. Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of drugs. This article reviews the various preparation techniques, carriers used, advantages and limitations of solid dispersions and compiles some of the recent advances. There are various methods available to improve the solubility of the new drug in which solid dispersion emerged promising. A Solid dispersion generally composed of two components- the drug and the polymer matrix. Numerous methods are existing to prepare the solid dispersions such as melting method, solvent evaporation method, fusion method, kneading method, melting method, spray drying method, co-grinding method, lyophilization technique, hot melt extrusion, melt agglomeration, supercritical fluid (SCF) technology etc. Solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. The experience with solid dispersions over the last 10-15 years indicates that this is a very fruitful approach in improving the release rate and oral bioavailability of poorly water soluble drugs. Hence, this approach is expected to form a basis for the commercialization of many poorly water-soluble and water-insoluble drugs in their solid-dispersion formulations in the near future.

INTRODUCTION

Solubility is a significant physicochemical factor affecting absorption of drug and its therapeutic effectiveness[1]. Formulation development would lead to be failure if drug is having poor aqueous solubility. The low dissolution rate and low solubility of drug substances in water in aqueous GIT fluid frequently leads to inadequate bioavailability. The venture to improve the solubility and dissolution of hydrophobic drugs remain one of the difficult tasks in drug development. Several methods have been introduced to triumph over this problem. Various methods to increase the solubility of drugs are available such as liquisolid; in which drug in solution state or dissolved drug is adsorbed over insoluble carriers. To improve wettability and solubility of various lipophilic substances surfactants can also be used in formulations. Micronization of drug is not ideal because micronized product has the propensity of agglomeration, which leads to reduced effective surface area for dissolution, but solid dispersion is the mainly promising method to formulators because of its simplicity of preparation, ease of optimization, and reproducibility. A poorly water soluble drug, more recently, has been defined in general terms to require more time to dissolve in the gastrointestinal fluid than it takes to be absorbed in the gastrointestinal tract. Drugs with low aqueous solubility have low dissolution rates and hence suffer from oral bioavailability problems. Model list of Essential Medicines of the World Health Organization (WHO) has assigned BCS (Biopharmaceutics Classification System) classification on the basis of data available in the public domain. Out of 130 orally administered drugs on the WHO list, 61 could be classified with certainty. 84% of these drugs belong to class I (highly soluble, highly permeable) 17% to class II (poorly soluble, highly permeable) 39% to class III (highly soluble, poorly permeable) and 10% to class IV (poorly soluble, poorly permeable) .The term solid dispersion refers to a group of solid products consisting of at least two different components, a hydrophilic matrix and a hydrophobic drug. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles**.** Pharmaceutical polymers are used to create this matrix and their selection is based on many factors, including physicochemical (e.g. drug–polymer miscibility and stability) and pharmacokinetic (e.g. rate of absorption) constraints. Fig. 1 categorizes various possible categories of solid dispersions. The solid-dispersion components consist mainly of active pharmaceutical ingredients (API), the polymer, plasticizers, stabilizers, and other agents. Chiou and Riegelman defined the term solid

dispersion as "A dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures" [2]

Solid dispersion systems can increase dissolution rate and bioavailability of water insoluble drugs as when these are exposed to aqueous media, the carrier dissolves, and the drug is released as very fine colloidal particles. This greatly reduces particle size and increases surface area, which results in improved dissolution rates and per oral absorption. Furthermore, no energy is required to break up the crystal lattice of a drug during the dissolution process. Drug solubility and wettability may be increased by surrounding hydrophilic carriers. This approach has been used for a variety of poorly soluble drugs such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine, ursodeoxycholic acid, carbamazepine, celecoxib and albendazole. Various hydrophilic carriers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), gums, sugar mannitol, urea, hydroxypropylmethyl cellulose phthalate, gelucires, eudragits and chitosan have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs.

In solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization, cosolvency, and particle size reduction. Based on their molecular arrangement, six different types of solid dispersions can be distinguished as described in Table 1. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions.

MATERIALS USED AS CARRIER FOR SOLID DISPERSIONS

The selection of the carrier has the influence on the dissolution characteristics of the dispersed drug, 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, [3]. Various carriers used for preparation of solid dispersions are tabulated in Table 1

Table 1: Materials used as carriers in solid dispersions

Sr. No	Category	Carriers	Example
1	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose	Rofecoxib from sorbitol and mannitol
2	Acids	Citric acid, succinic acid	Felodipine, rofecoxib from citric acid
3	Polymeric materials	Polyvinyl pyrrolidone(PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose (HPMC), methyl cellulose (MC), hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, pectin, galactomannan	Temazepam , felodipine, etoricoxibrofecoxib from PEG 4000 & 6000 and troglitazone and rofecoxib from PVP K30
4	Insoluble or enteric polymer	Hydroxy propyl methyl cellulose phthalate,(HPMCP), Eudragit L100, Eudragit E100, Eudragit RL, Eudragit RS	Indomethacin from eudragit E100
5	Surfactants	Polyoxyethylene stearate, poloxamer 188, deoxycholic acid, tweens, spans	Felodipine and rofecoxib from poloxamer 188
6	Miscellaneous	Pentaerythritol, pentaerythrityltetraacetate, urea, urethane, hydroxy alkyl xanthins	Rofecoxib from urea

ADVANTAGES OF SOLID DISPERSION[4]

The major advantage of solid dispersions is that it improves the dissolvability of a poorly water soluble drug in a pharmaceutical composition and results in rapid dissolution rates thereby improving the bioavailability of drug. Along with this, the approach may also offer others advantages which include:

Rapid disintegration of oral tablets

Drug is formulated with hydrophilic carrier (e.g. PEG) as a solid dispersion to increase its aqueous solubility and dissolution. Then superdisintegrant (e.g. croscarmellose sodium) is used in tablet formulation to achieve rapid disintegration of tablets prepared by wet granulation method. These rapidly disintegrating tablets can be used as an alternative to parenteral therapy enabling patient for self-medication even without the aid of water.

As a formulation vehicle:

Solid dispersions can be used as formulation vehicle to facilitate the preclinical safety and early clinical studies on new chemical entities with very low aqueous solubility. It provides a means to rapidly assess the safety and efficacy profile of the drug substance that may be otherwise difficult to obtain.

Particles with reduced particle size:

Solid dispersions represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers, thus a high surface area is formed, resulting in an increased dissolution rate and consequently improved bioavailability.

Particles with improved wettability:

Enhancement of drug solubility is related to the drug wettability. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts when used, significantly increase the

wettability of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

Particles with higher porosity:

Particles in solid dispersions have been found to have a higher degree of porosity. Solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, results in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release rate.

Drugs in amorphous state:

The enhancement of drug release can usually be achieved if the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that if drugs precipitate it is as a metastable polymorphic form with higher solubility than the most stable crystal form.

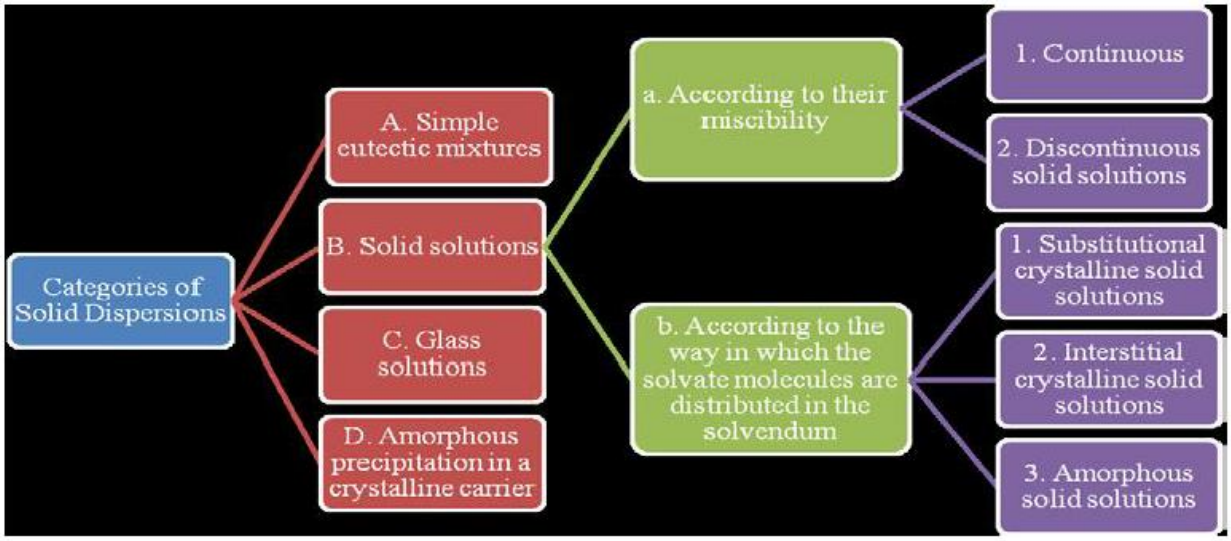


Fig. 1: Categories of solid dispersion

Disadvantages of Solid Dispersion[5]

1. Moreover, most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline

state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate.

2. Drawback of solid dispersions is their poor scale-up for the purposes of manufacturing.

METHODS OF PREPARATION OF SOLID DISPERSIONS [6]

Various methods have been developed for preparation of solid dispersions, these methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, demixing (partially or complete), and formation of different phases is observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted. Various preparative methods are shown in Fig. 2.

The brief description of the methods is as follows:

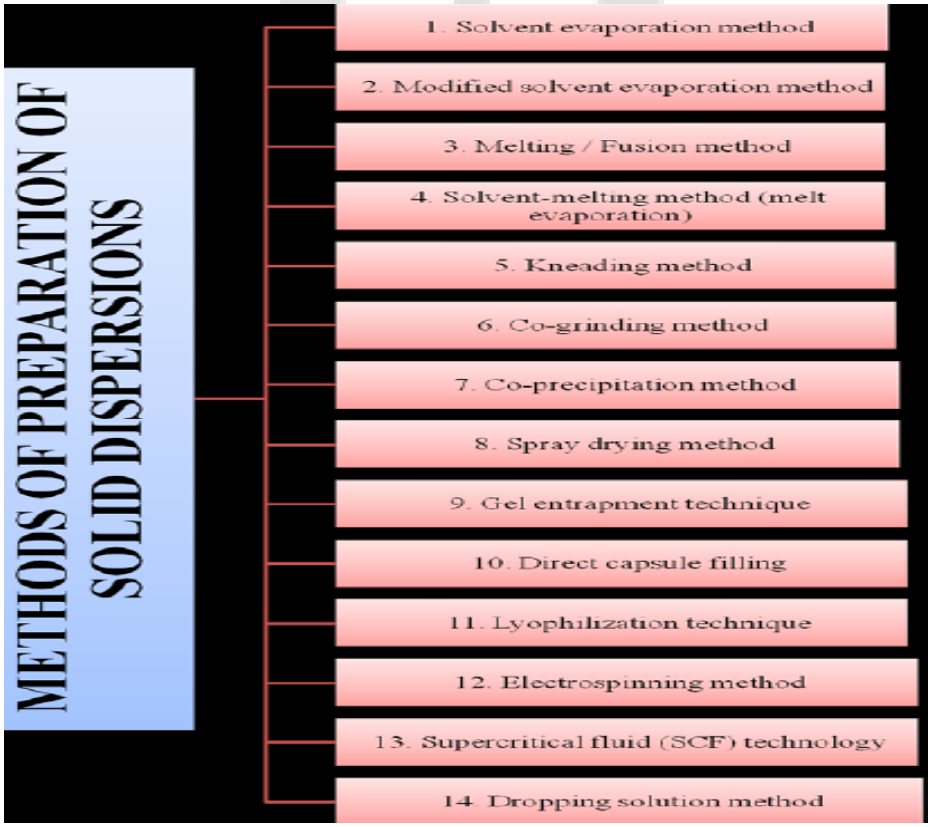


Figure 2: Various preparative methods of solid dispersions

Solvent evaporation method:

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents. However, some disadvantages are associated with this method such as

1) The higher cost of preparation.
2) The difficulty in completely removing liquid solvent.
3) The possible adverse effect of traces of the solvent on the chemical stability.
4) The selection of a common volatile solvent.
5) The difficulty of reproducing crystal form.
6) In addition, a super saturation of the solute in the solid system cannot be attained except in a System showing highly viscous properties.

Modified solvent evaporation method:

Drug is dissolved in organic solvent at it's saturation solubility with continuous stirring for some time. Polymer is suspended in sufficient amount of water (up to wet mass of polymer). The drug solution is poured at once into polymer suspension. The entire solvent is evaporated. The mass obtained is dried.

Melting /Fusion method:[7]

This method involves the preparation of physical mixture of a drug and a water soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. The modification in the method can be done by pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures.

Advantage of melting method is that it is economic and solvent less process, however this method is not suitable for the drug or carrier which is unstable at fusion temperature or evaporates at higher temperature. Some of the means to overcome these problems could be by heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.

Kneading Technique:

In this method, carrier is permeated 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:

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:

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 and mannitol solid dispersion was prepared by this method.

Gel entrapment technique:

Hydroxyl propyl methyl cellulose is 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.

Spray-Drying Method:

Drug is dissolved in suitable solvent and the 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 then spray dried using spray dryer.

Electro spinning:

Electro spinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a 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 (commonly known as Taylor s cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The Coulombic 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 If the viscosity increases, the charged jet is dried. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future.

Freeze-drying:

This process consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen. Then, the frozen solution is further lyophilized. Although it is concluded in literature that this is a promising and suitable technique to incorporate drug substances in stabilizing matrices, the technique is poorly exploited for the preparation of solid dispersions. An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified.

Supercritical fluid method:

Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used as either a solvent for drug and matrix or as an anti-solvent. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with CO2. When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. The use of processes using SCF reduces particle size, residual solvent content, without any degradation and often results in high yield.

Melt Agglomeration Process:

The utility of the surfactant systems in solubilization is very important. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions.

Lyophilization Technique:

Lyophilization involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

Dropping method solution:

The dropping method, developed by 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 solvents and, therefore, has none of the problems associated with solvent evaporation.

Melt Extrusion Method:

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. The concentration of drug in the dispersions is always 40% (w/w). Melt extrusion technique is used in the preparation of diverse dosage forms in the pharmaceutical industry e.g. sustained-release pellets.

Direct capsule filling:

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug. Solvent

Melting method:

Accurately weighed drug is dissolved in organic solvent. The solution is incorporated into the melt of mannitol and cooled suddenly and mass is kept in desiccator for complete drying. The solidified mass is crushed, pulverized and passed through sieve. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose (less than 50 mg).

CHARACTERIZATION OF SOLID DISPERSIONS[8]

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Several techniques have been available to investigate the molecular arrangement in

solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. Many techniques are available which detect the amount of crystalline material in the dispersion.

Drug -carrier miscibility:

- Hot stage microscopy
- Differential scanning calorimetry
- Powder X-ray diffraction
- NMR 1H Spin lattice relaxation time

Drug carrier interactions:

- FT-IR spectroscopy
- Raman spectroscopy
- Solid state NMR

Physical Structure:

- Scanning electron microscopy
- Surface area analysis
- Surface properties
- Dynamic vapor sorption
- Inverse gas chromatography
- Atomic force microscopy
- Raman microscopy

Amorphous content:

- Polarised light optical microscopy
- Hot stage microscopy
- Humidity stage microscopy
- DSC (MTDSC)

- ITC
- Powder X-ray diffraction

Stability:

- Humidity studies
- Isothermal Calorimetry
- DSC (Tg, Temperature recrystallization)
- Dynamic vapor sorption
- Saturated solubility studies

Dissolution enhancement:

- Dissolution
- Intrinsic dissolution
- Dynamic solubility
- Dissolution in bio-relevant media

Powder X-ray diffraction:

Powder X-ray diffraction can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material.

Infrared spectroscopy (IR) :

Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinity ranging from 1 to 99% in pure material.

Water vapours sorption:

Water vapours sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different. This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples.

Isothermal Microcalorimetry:

Isothermal Microcalorimetry measures the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg). This technique has some limitations. Firstly, this technique can only be applied if the physical stability is such that only during the measurement crystallization takes place. Secondly, it has to be assumed that all amorphous material crystallizes. Thirdly, in a binary mixture of two amorphous compounds a distinction between crystallization energies of drug and matrix is difficult.

Dissolution calorimetry:

Dissolution calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample. Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.

Macroscopic techniques :

Macroscopic techniques that measure mechanical properties that are different amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity for and viscosity and thus affected by the degree of crystallinity. However, also these techniques require knowledge about the additivity of these properties in intimately mixed binary solids.

Differential Scanning Calorimetry (DSC):

Frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC). In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material.

Confocal Raman Spectroscopy:

Confocal Raman Spectroscopy is used to measure the homogeneity of the solid mixture. It is described that a standard deviation in drug content smaller than 10% was indicative of homogeneous distribution. Because of the pixel size of 2 to 3 μm uncertainty remains about the presence of nano-sized amorphous drug particles.

Temperature Modulated Differential Scanning Calorimetry (TMDSC):

Temperature Modulated Differential Scanning Calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. For example, glass transitions (reversible) are separated from crystallization or relaxation (irreversible) in amorphous materials. Furthermore, the value of the Tg is a function of the composition of the homogeneously mixed solid dispersion. It has been shown that the sensitivity of TMDSC is higher than conventional DSC. Therefore this technique can be used to assess the amount of molecularly dispersed drug. And from that the fraction of drug that is dispersed as separate molecules is calculated**.**

***In Vitro* Dissolution Studies:**[9]

In vitro dissolution studies are done for the find out dissolution behavior. The *in-vitro* dissolution study can be used to demonstrate the bioavailability or bioequivalence of the drug product through *in vitro – in vivo* correlation (IVIVC). On the other hand if absorption of the drug is dissolution rate limited that means the drug in the gastrointestinal fluid passes freely through the bio-membranes at a rate higher than it dissolves or is released from the dosage form. The specifically designed *in-vivo* dissolution study will be required in solid dispersion system to access the absorption rate, and hence its bioavailability and to demonstrate the bioequivalence ultimately. There are some apparatus used in United States pharmacopoeia for dissolution testing these are following.

Solubility Studies:

Solubility studies are done for the finding out the solubility behavior shown by the solid dispersion system in different types of solvent system and body fluids.

MECHANISMS BEHIND IMPROVED DISSOLUTION:

The formulations of solid dispersions results into reduction in particle size, improved wettability and enhancement of the dispersibility of the drug, thereby markedly improving the dissolution rate. The suggested mechanism behind this tremendous increase in dissolution rate may include:[10]

- Partial transformation of crystalline drug to the amorphous state or altering the crystalline morphology
- Formation of solid solution
- Formation of complexes
- Intimate mixing of the drug with hydrophilic excipients
- Reduction of aggregation and agglomeration
- Improved wetting of the drug and solubilization of drug by the carrier at the diffusion layer.

Commercial Solid Dispersion Products: [11]

In spite of almost several years of research on solid dispersions, their commercial application is limited. Only a few products have been marketed so far. Amongst these few are mentioned in Table 2

Table 2: Commercially marketed solid dispersions

S. No	Commercial products	Polymer used	Manufacturer Company
1	Gris-PEG® (Griseofulvin)	Polyvinylpyrrolidone (PVP)	VIP Pharma
2	Intelence® (Etravirine)	Hypromellose, and microcrystalline cellulose	Tibotec, Yardley, PA
3	Cesamet® (Nabilone)	Polyvinylpyrrolidone (PVP)	Valeant Pharmaceuticals, Costa Mesa, CA
4	Sporanox® (Itraconazole)	Hydroxypropylmethyl cellulose (HPMC)	Janssen Pharmaceutica, Titusville, NJ
5	lopinavir and ritonavir	Polyvinylpyrrolidone–vinyl acetate copolymer	Abbott Laboratories, Abbott Park, IL

APPLICATIONS OF SOLID DISPERSION[12]

Solid dispersion systems can provide numerous additional benefits; some of them are as follows:

1. In improving immunosuppressive therapy in lung transplant patients, dry powder formulation consisting of a solid dispersion (e.g. Cyclosporine A) for inhalation is prepared. It can avoid many problems like use of local anaesthesia and irritating solvents.

2. Solid dispersion formulations were demonstrated to accelerate the onset of action for drugs such as nonsteroidal anti-inflammatory drugs (NSAIDS) where immediacy of action is crucial in relieving acute pain and inflammation.

3. Solid dispersion systems were shown to provide bio available oral dosage forms for anti-cancer drugs, which could be substituted for standard injections to improve patient comfort and compliance.

4. Solid dispersion systems were also found to reduce food effect on drug absorption, thus increasing the convenience of drug therapy as the need for some drugs to be taken with food was eliminated.

5. Solid dispersion- based dosage form allowed for greater drug loading per dose and improved stability over a soft gelatin capsule formulation which thereby improved the convenience of drug therapy by reducing the dosing regime and eliminating the need for refrigerated storage.

6. Improved absorption efficiency demonstrated for solid dispersion systems allows for a reduction in the content of active agent per dose, thus decreasing the cost associated with these drug therapies.

7. It also act as a functional carriers that offer the added benefit of targeting the release of highly soluble forms of poorly water soluble drugs to an optimum site for absorption.

These benefits demonstrate the current contributions and future potential of solid dispersion systems toward improving drug therapies for a variety of important medical conditions whose treatment involves poorly water soluble drugs.

SUMMARY

"ENHANCING THE BIOAVAILABILITY OF A POORLY WATER SOLUBLE DRUG ETORICOXIB USING SOLID DISPERSION TECHNIQUE"

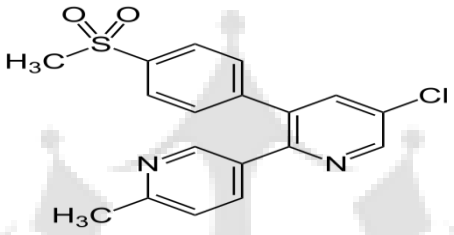
ETOROXIB

Chemical name :5-Chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine

Formula : $C_{18}H_{15}ClN_2O_2S$

Molecular weight : 358.84

Chemical structure:



Description:

Etoricoxib is a synthetic, nonsteroidal anti-inflammatory drug (NSAID) with antipyretic, analgesic, and potential antineoplastic properties. Etoricoxib specifically binds to and inhibits the enzyme cyclooxygenase-2 (COX-2), resulting in inhibition of the conversion of arachidonic acid into prostaglandins. Inhibition of COX-2 may induce apoptosis and inhibit tumor cell proliferation and angiogenesis. Etoricoxib is a new COX-2 selective inhibitor. Current therapeutic indications are: treatment of rheumatoid arthritis, osteoarthritis, ankylosingspondylitis, chronic low back pain, acute pain and gout. Like any other COX-2 selective inhibitor, Etoricoxib selectively inhibits isoform 2 of cyclo-oxigenase enzyme (COX-2). This reduces the generation of prostaglandins (PGs) from arachidonic acid.

Mechanism of action[13]

Etoricoxib is selective COX 2 inhibitor.

Like any other selective COX-2 inhibitor ("coxib"), etoricoxib selectively inhibits isoform 2 of the enzyme cyclooxygenase (COX-2). It has approximately 106-fold selectivity for COX-2

inhibition over COX-1. This reduces the generation of prostaglandins (PGs) from arachidonic acid. Among the different functions exerted by PGs, their role in the inflammation cascade should be highlighted.

Selective COX-2 inhibitors show less activity on COX-1 compared to traditional non-steroidal anti-inflammatory drugs (NSAID). This reduced activity is the cause of reduced gastrointestinal side effects, as demonstrated in several large clinical trials performed with different coxibs.[2][3]

Pharmacokinetics[14]

Absorption

Orally administered etoricoxib is well absorbed. The mean oral bioavailability is approximately 100%. Following 120mg once daily dosing to steady state, the peak plasma concentration (geometric mean Cmax= 3.6mcg/mL) was observed at approximately 1hour (Tmax) after administration to fasted adults.

The geometric mean AUC0-24hr was 37.8mcg•hr/mL. The pharmacokinetics of etoricoxib are linear across the clinical dose range.

A standard meal had no clinically meaningful effect on the extent or rate of absorption of a dose of etoricoxib 120mg.In clinical trials, etoricoxib was administered without regard to food.The pharmacokinetics of etoricoxib in 12 healthy subjects were similar (comparable AUC, Cmax within approximately 20%) when administered alone, with a magnesium/aluminium hydroxide antacid, or a calcium carbonate antacid (approximately 50mEq acid-neutralising capacity).

Distribution

Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5mcg/mLThe volume of distribution at steady state (Vdss) is approximately 120L in humans.

Etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism

Etoricoxib is extensively metabolized with <1% of a dose recovered in urine as the parent drug. Five metabolites have been identified in humans.

Metabolism

in vitro involves conversion primarily to the 6'-hydroxymethyl derivative, mainly (ca.60%) by CYP3A4, with less contribution by CYPs 1A2, 2C9, 2C19 and 2D6 (ca.40% collectively).The 6'-hydroxymethyl derivative is ARCOXIA Tablet further metabolised by oxidation to the principal metabolite, the 6'-carboxylic acid derivative of etoricoxib. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibit COX-1

Excretion

Following administration of a single 25mgradiolabelled intravenous dose of etoricoxib to healthy subjects, 70% of radioactivity was recovered in urine and 20% in faeces, mostly as metabolites. Less than 2% was recovered as unchanged drug.Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations of etoricoxib are reached within seven days of once-daily administration of 120mg, with an accumulation ratio of approximately 2, corresponding to an accumulation half-life of approximately 22hours. The plasma clearance is estimated to be approximately 50mL/min.

Warnings and Precautions [15]

Caution should be exercised in patients with history of heart, liver, kidney disease, high blood pressure, blood clotting disorder, any allergy, children, elderly, during pregnancy and breast feeding. Drink adequate fluid to avoid dehydration. Stop the medication immediately if gastrointestinal lesions occur. Monitor blood pressure regularly while taking this medication.

Side Effects

Central Nervous System - Headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo and ringing in the ear.

Heart - Chest pain, high blood pressure and fluid retention.

Metabolic - Taste disturbances, mouth ulcer, loss of appetite and weight loss.

Miscellaneous - Kidney damage, fever, GI disorders, muscle pain and influenza-like syndrome.

Other Precautions:

Avoid excess dosage.

USES

- Etoricoxib is used to treat a number of problems affecting the joints.
- It is a selective COX-2 inhibitor, which belong to a family of pain killers called non-steroidal anti-inflammatory drugs (NSAIDs).
- It is used to relieve pain, reduce swelling and joint stiffness.
- In general this drug is used to treat patients suffering from joint pain and swelling caused by osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and gout.
- Benefits of being on this drug can include relieving pain and reducing the swelling and stiffness in joints allowing you to do more of your normal daily activities.

INTERACTIONS[16]

This drug should not be used with the following medications because very serious, possibly fatal interactions may occur:

- Medicines that thin your blood (anticoagulants), such as warfarin
- Rifampicin (an antibiotic)
- Methotrexate (a drug used for suppressing the immune system, and often used in rheumatoid arthritis)
- Medicines used to help control high blood pressure and heart failure called ACE inhibitors and angiotensin receptor blockers, examples include enalapril, ramipril, losartan and valsartan
- Lithium (a medicine used to treat some types of depression)
- Diuretics (water tablets)

- Ciclosporin or tacrolimus (drugs used for suppressing the immune system)
- Digoxin (a medicine for heart failure and irregular heart rhythm)
- Minoxidil (a drug used to treat high blood pressure)
- Salbutamol tablets or oral solution (a medicine for asthma)
- Birth control pills
- Hormone replacement therapy
- Aspirin, the risk of stomach ulcers is greater if you take etoricoxib with aspirin.

INDICATION AND DOSAGE:

❖ For osteoarthritis, the recommended dose is 30 mg once a day, increased to a maximum of 60 mg once a day if needed.

❖ For the relief of gout attacks, the recommended dose is 120 mg taken once a day, which should only be used during the painful period, to a maximum of 8 days treatment.

❖ For the relief of cramp-like pain or discomfort before or during a menstrual period, the recommended dose is 120 mg taken once a day, which should only be used during the painful period, to a maximum of 8 days treatment.

❖ For the relief of short term pain after dental procedures, the recommended dose is 90 mg taken once a day, which should only be used during the painful period, to a maximum of 8 days treatment.

❖ If you have mild liver disease, do not take more than 60 mg once a day.

❖ If you have moderate liver disease, do not take more than 60 mg every second day or 30mg once a day.

POLYETYLENE GLYCOL 6000 (PEG – 6000)[17]

Polyethylene glycol 6000(PEG) is a polyether compound with many applications from industrial manufacturing to medicine.

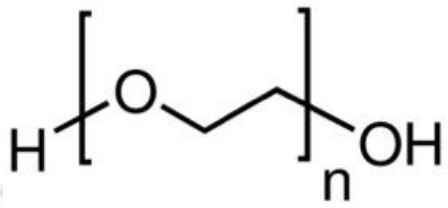
The structure of PEG is:HO-CH2-(CH2-O-CH2-)n-CH2-OH.

PEG is also known aspolyethyleneoxide(PEO) or polyoxyethylene (POE), depending on its molecular weight.

Polyethylene glycol, referred to as PEG, is used as an inactive ingredient in the pharmaceutical industry as a solvent, plasticizer, surfactant, ointments and suppository base, and tablet and capsule lubricant. PEG has low toxicity with systemic absorption less than 0.5%.PEGylation occurs when PEGs are attached to various protein medications, allowing for greater solubility for certain drugs. Examples of PEG medications include PEG-interferon alpha (Pegintron) and PEG-filgrastim (Neulasta). PEG is also available as a bowel prep for colonoscopy procedures and as a laxative.PEG 400 indicates the average molecular weight of the specific PEG at 400.

PEG 3350 is a laxative available over-the-counter by the name of Miralax. In this case, PEG is considered an "active" ingredient, even though systemic absorption is less than 0.5%.

Structure



Nonproprietary Names

1. Carbowax, GoLYTELY
2. GlycoLax, Fortrans
3. TriLyte, Colyte
4. Halflytely,
5. Macrogol,
6. MiraLAX

Boiling Pt: Min. 250°C (1013 hPa)

Melting Pt: 55 to 62 °C

Density: 1.13 g/cm³ (20°C)

Appearance: White or almost white, waxy or paraffin-like

Solubility: Soluble in water

Synonyms:

PEG; Macrogol; Polyoxyethlene; Aquaffin; Nycoline alpha-hydro-omegahydroxypoly (oxy1,2ethanediyl); polyethylene glycols; Poly Ethylene Oxide; Polyoxyethylene; Polyglycol; 1,2-ethanediol Ehoxylated; Polyoxyethylene ether; Polyoxyethylene; Poly(ethylene glycol);

Chemical Name

poly(oxyethylene)

Empirical Formula and Mol. Weight

H(OCH2CH2)nOH[average 6000 g/mol]

Functional Category:

Lubricating agent,
Solubilizing agent,
Coating agent

Applications in Pharmaceutical Formulation or Technology and Chemical uses

Polyethylene glycol has a low toxicity and is used in a variety of products.

❖ The polymer is used as a lubricating coating for various surfaces in aqueous and non-aqueous environments. Since PEG is a flexible, water-soluble polymer, it can be used to create very high osmotic pressures (on the order of tens of atmospheres). It also is unlikely to have specific PEG-6000interactions with biological chemicals. These properties make PEG one of the most useful molecules for applying osmotic pressure in biochemistry, and biomembranes experiments, in particular when using the osmotic stress technique.

❖ Polyethylene glycol is also commonly used as a polar stationary phase for gas chromatography, as well as a heat transfer fluid in electronic testers.

❖ PEG has also been used to preserve objects that have been salvaged from underwater, as was the case with the warship Vasain Stockholm, the Mary Rosein England and the Ma'agan Michael Shipin Israel. It replaces water in wooden objects, making the wood dimensionally stable and preventing warping or shrinking of the wood when it dries.

❖ In addition, PEG is used when working with green wood as a stabilizer, and to prevent shrinkage.

❖ PEG is often used (as an internal calibration compound) in mass spectrometry experiments, with its characteristic fragmentation pattern allowing accurate and reproducible tuning.PEG derivatives, such as narrow range ethoxylates, are used as surfactants.

❖ PEG has been used as the hydrophilic block of amphiphilic block copolymers used to create some polymersomes.

Industrial uses

❖ Nitrate ester -plasticized polyethylene glycol is used in Trident II ballistic missile solid rocket fuel.

❖ Dimethyl ethers of PEG are the key ingredient of Selexol, a solvent used by coal -burning, integrated gasification combined cycle (IGCC) power plants to remove carbon dioxide and hydrogen sulfide from the gas waste stream.

❖ PEG has been used as the gate insulator in an electric double-layer transistor to induce superconductivity in an insulator.

❖ PEG is also used as a polymer host for solid polymer electrolytes. Although not yet in commercial production, many groups around the globe are engaged in research on solid polymer electrolytes involving PEG, with the aim of improving their properties, and in permitting their use in batteries, electro-chromic display systems, and other products in the future.

MATERIALS AND METHODS

2.1 Materials: Etoricoxib has been obtained as a gift sample from Alembic Ltd, Vadodara**,** PEG 6000, absolute alcohol, Methanol, acetone S.D. Fine-Chem. Ltd, Mumbai. All other ingredients, reagents and solvents were of analytical grade.

Solubility profile:

The solubility of etoricoxib was tested in various solvents and in various buffers. The solubility studies were conducted by adding excess amounts of drug into screw capped vials containing 10ml of solvents/buffers. The tightly sealed vials were shaken in water bath at 25°C for 48 hours. The saturated solutions were then analyzed**.**

Table 3: Solubility of Etoroxib in various organic solvents

SOLVENTS	SOLUBILITY
Methanol	++
Ethanol	+
Acetonitrile	+
Chloroform	+
Dichloromethane	+++
Dimethylformamide	+++
Water	-

+++Freely soluble, ++ Soluble , + Slightly soluble, -Practically insoluble

Table 4: Solubility of Etoricoxib in various buffer solutions

BUFFER(pH)	SOLUBILITY(µg/ml)
1.2	6.79±0.18
2.2	8.52±0.10
6.8	14.31±0.28
7.0	15.32±0.26
7.4	16.38±0.16

Melting method [18]

The melting or fusion method, first proposed by Sekiguchi and Obi involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures.

Evaluation of etoricoxib solid dispersion [19]

***In-vitro* dissolution rate studies:** Dissolution studies are the most important part in the evaluation of solid dispersions. In this test the rate and extent of dissolution of both pure drug (etoricoxib capsules) and solid dispersions (etoricoxib -PEG-6000) is calculated. Dissolution rate studies of various solid dispersions were carried out in pH6.8 phosphate buffer using USP Type II dissolution rate apparatus (Dangprasirt and Limwong, 2005). Solid dispersions equivalent to 50mg of Etoricoxib was taken in a hard gelatin capsule. The paddle type stirrer was adjusted to 50 rpm and the temperature was maintained at 37º + 1º C. The capsule was then dropped into the apparatus and time noted. 5ml aliquot dissolution medium was withdrawn at different time intervals and volume withdrawn was replaced with fresh quantity of dissolution medium. The samples were analyzed for Etoricoxib after suitable dilution by measuring absorbance at 233 nm using Shimadzu UV-vis. spectrophotometer. The percentage of etoricoxib dissolved at various time intervals was calculated and plotted against time.

A comparative in - vitro drug release study was done between the pure drug etoricoxib, etoricoxib PEG 6000 solid dispersion and marketed formulation of etoricoxib capsules.

Comparison of *In-vitro* release profile[20]

Mean dissolution time (MDT) of all batches were calculated using the following equation:

$$MDT_{in\ vitro} = \frac{\sum_{i=1}^{n} T_{mid}\,\Delta M}{\sum_{i=1}^{n} \Delta M}$$

Here, i is the dissolution sample number, n is the number of dissolution sampling times, Tmid is the midpoint between times Ti and Ti−1, and ΔM is the amount of CA dissolved between times Ti and Ti−1.

The percent dissolution efficiency (% DE) was also computed to compare the relative performance of various concentrations .The % DE of a pharmaceutical dosage form is defined as the area under the dissolution curve up to a certain time, t, expressed as a percentage of the area of the rectangle described by 100 % dissolution at the same time (Khan et al., 1975). The % DE can be calculated from:

$$\% DE = \frac{\int_0^t Y dt}{Y_{100} t}$$

Where *Y* is the percent drug dissolved at time *t*.

RESULTS AND DISCUSSION

The *in-vitro* dissolution study of etoricoxib solid dispersion was found to be around 81.37% drug release within 30minutes using PEG 6000 and for marketed formulation it was around 30-35% in 120 minutes and for pure etoricoxib the drug release was found to be 26.83% at the end of 120 minutes.

In-vitro release study

Determination of rate of release of pure etoricoxib

Release rate of pure etoricoxib was studied in phosphate buffer pH 6.8.

Table 5: Pure etoricoxib release rate in phosphate buffer pH 6.8

TIME(MIN)	%DRUG RELEASE
0	0
5	8.68
10	12.45
20	17.40
30	18.42
45	22.02
60	23.75
90	26.38
120	26.83

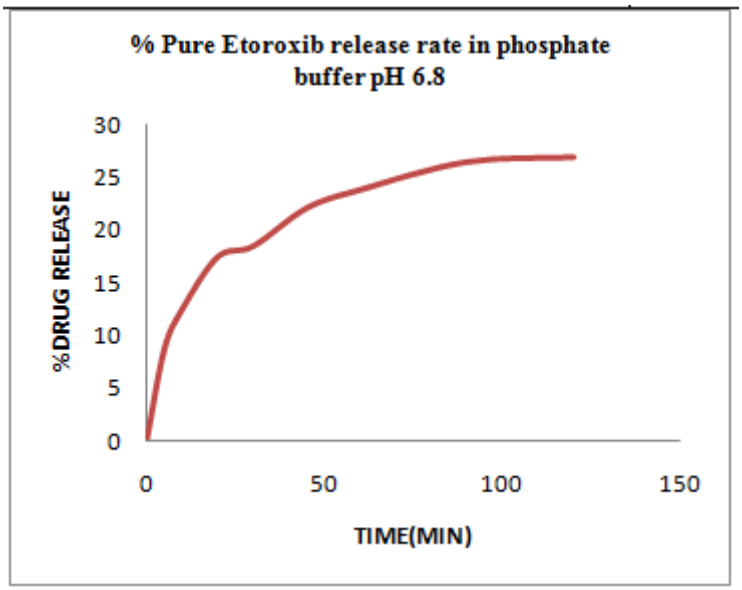


Figure 3: Pure etoricoxib release rate in phosphate buffer PH6.8

The figure clearly depicts that pure etoricoxib was released 26.83% within 120 minutes**.**

Table 6: Drug release rates of marketed formulations of etoricoxib in phosphate buffer pH 6.8

TIME(IN MIN)	% DRUG RELEASE		
	ETOXIB-60	TORCOXIA-60	NUCOXIA-60
0	0.00	0.00	0.00
5	7.85	18.1	18.1
10	12.14	19.75	25.50
20	16.55	24.81	25.80
30	18.48	26.24	31.57
45	20.78	28.09	35.36
60	22.73	33.55	36.39
90	27.96	33.90	36.77
120	28.17	34.25	37.15

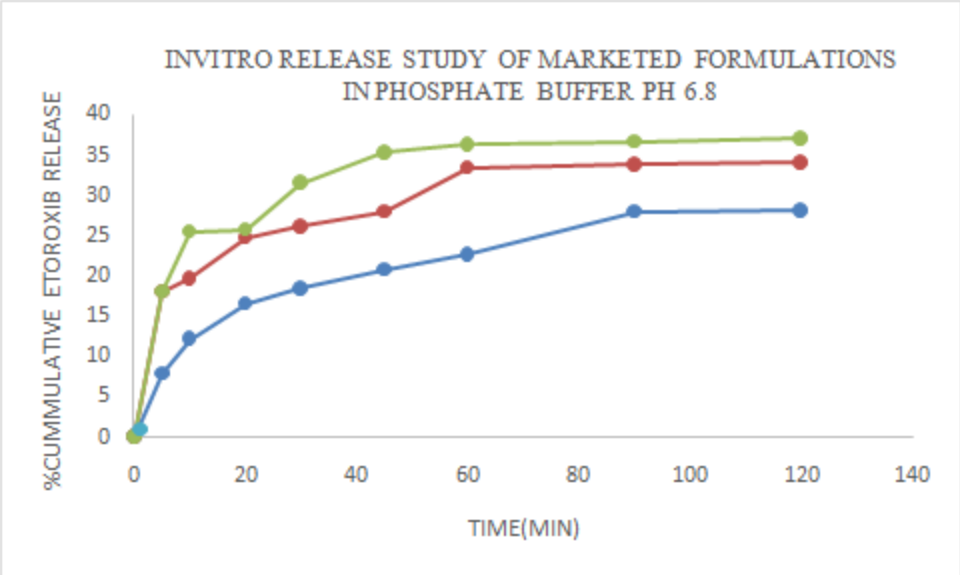


Figure 4: Drug release rates of marketed formulations of etoricoxib in phosphate buffer pH 6.8

Preparation of etoricoxib dispersion[21]

Accurately weighed amounts of PEG-6000 were placed in small Petri dish on water bath and melted; with constant stirring with a glass agitator at 60°C .Fusion was reached in 15 minutes at this temperature. An accurately weighed amount of etoricoxib:PEG 6000 (in ratio 1:1 – 1:7) was incorporated into the melted carrier with stirring was obtained. This mixture was filled into the bodies of size 00 or 0 capsules using medicine droppers. These were then allowed to cool for 2 hours before being capped. The fill weight of capsules was 120-600mg, containing 60mg etoricoxib.

Table 7: *In vitro* release study of etoricoxib -PEG 6000 in phosphate buffer pH 6.8

TIME (MIN)	PERCENTAGE DRUG RELEASE						
0	C1	C2	C3	C4	C5	C6	C7
	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	11.57	12.47	11.57	11.57	12.68	11.57	18.90
10	17.08	17.75	21.36	24.12	20.17	20.83	36.08
20	17.30	18.90	29.76	46.13	41.48	37.36	59.25
30	22.06	20.93	40.92	60.25	83.18	69.19	81.37
45	22.66	28.20	46.52	60.25	83.18	69.19	81.37
60	30.18	47.20	71.61	60.25	83.18	69.19	81.37
90	32.95	63.04	71.61	60.25	83.18	69.19	81.37
120	40.80	63.04	71.61	60.25	83.18	69.19	81.37

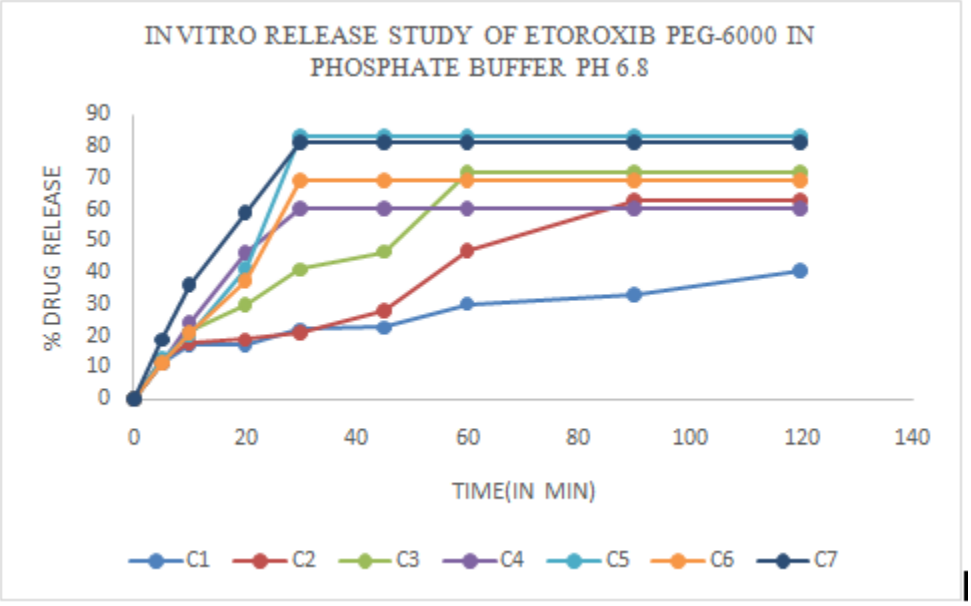


Figure 5: *In vitro* release study of Etoricoxib – PEG 6000 in phosphate buffer pH 6.8

PEG – 6000 were chosen as the hydrophilic polymers for the present studies as these are highly water soluble and non toxic polymers which are known to enhance the dissolution rate of

insoluble drugs. The results of the dissolution efficiencies at 120 minute, MDT, DP30 and $t_{50\%min}$ of various etoricoxib dispersion formulations are collected in the table below:

Table 8: Dissolution parameters of etoricoxib PEG 6000 dispersion

BATCH NO	DISSOLUTION PARAMETERS			
	DP_{30min}	%DE 120min	MDT	$T_{50\%min}$
C1	22.06	27.69	34.52	-
C2	20.93	42.28	33.12	64.02
C3	40.92	55.28	32	47.8
C4	60.25	54.67	32.05	22.09
C5	83.18	72.61	30.05	22.15
C6	69.16	60.94	29.61	24
C7	81.37	73.94	27.07	15.05

Formulation

DP_{30min} = percentage of drug dissolved after 30 minutes

$\%DE_{120min}$ = dissolution efficiency after 120 minutes

t_{50}= time taken to release 50% of drug.

Selection of best batch

The above table and figure clearly shows 80-85% drug release in the studies.

After the preparation of etoricoxib PEG 6000 dispersions, batch C7(1:7) shows highest drug release (81.37%) in 30 minutes. as the drug:polymer ratio increases, MDT was decreased. after obtaining the results of DE_{120MIN}, it was analyzed that there was 40-70% dissolution in all media, but batch C7 indicates 73.94% dissolution efficiency after 120 minutes .the results of $T_{50\%min}$showed that it took only 15.05 minutes for C7 to release 50% of the drug. also the results of DP_{30min}follows the same.

The stability study indicated that etoricoxib -PEG 6000 dispersion was stable at room and normal humidity conditions. from the above results it can be concluded that etoricoxib -PEG 6000 dispersion batch C7(1:7) is optimum for obtaining dissolution enhancement of poorly water soluble drug etoricoxib.

CONCLUSION

Despite of many disadvantages of solid dispersions, successful development of solid dispersion systems for preclinical and commercial use have been feasible in recent years due to the availability of surface active agents and self emulsifying carriers with relatively low melting points. The application of melting method to the production of solid dispersions is a particularly important breakthrough for scale up for formulation.

REFERENCES

1.AhujaN,Katare O.P, and Singh B(2007) Studies on dissolution enhancement and mathematical modelling on drug release of a poorly water-soluble drug using water-soluble carriers,Eur.J.Pharm. Biopharm., 65, 26-38.
2. Allen L.V, Levinson R.S, and MartonoD.D(1978). Dissolution rates of hydrocortisone and prednisone utilizing sugar solid dispersion systems in tablet form, J.Pharm.Sci., 67(7), 979-981.
3. Appa Rao B, Shivalingam M.R, Kishore Reddy Y.V, S. Rao, Rajesh K, and SunithaN(2010).Formulation and evaluation of aceclofenac solid dispersions for dissolution rate enhancement, Int.J.Pharm.Sci. Drug Res., 2(2), 146-150.
4.Arias M.J, Gines J.M, Moyano J.R, and Rabasco A.M(1994). The application of solid dispersion technique with D-mannitol to the improvement in oral absorption of triamterene, J.Drug Target, 2(1), 45-51.
5.Chauhan B, Shimpi S, and Paradkar A(2005). Preparation and characterization of etoricoxib solid dispersions using lipid carriers by spray drying technique, AAPS.Pharm.Sci.Tech., 6(3), 50.
6.Chiou WL, Rielman S.(1971). Pharmaceutical application of solid dispersion system,J.Pharm.Sci., 60, 1281-1302.
7.Dangprasirt P, Limwong V.(2005). Preparation of fast release indomethacin solid dispersion by spray-drying using lactose as water-soluble carrier,Thai.J.Pharm.Sci., 29, 103-111.
8.Dhirendra K, Lewis S, Udupa N, and Atin K(2009). Solid dispersions: A review,Pak.J.Pharm.Sci., 22(2), 234-246.
9.Hirasawa N, Okamoto H, Danjo K(1999).Lactose as a molecular weight carrier of solid dispersions for carbamazepine and ethenamide,Chem.Pharm.Bull., 47(3), 417-420.
10.Karekar P, Vyas V, Shah M, Sancheti P, and Pore P(2009). Physicochemical investigation of the solid dispersion systems of etoricoxib with poloxamer 188, Pharm.Dev.Technol., 14 (4), , 373-379.
11.Lin S.Y, Kao Y.H, and Yang J.C(1988). Grinding effect on some pharmaceutical properties of drugs by adding β-cyclodextrin, Drug Dev.Ind.Pharm., 14, 99-118.
12.Mura P, Faucci M.T, and Parrini P.I(2001). Effects of grinding with microcrystalline cellulose and cyclodextrins on the ketoprofen physicochemical properties, Drug Dev.Ind.Pharm., 27, 119-128.
13.MuralidharS, Rao SD, Ramesh R, Narayana T(2010). Studies to enhance dissolution properties of etoricoxib, Int.J.Pharma.Res.Dev., 2(4), 124-129.
14.Nagabhushanam M.V, Beena Devi M, and Swathi K(2009). Studies on enhancement of dissolution rate of mefenamic acid using solid dispersions, The Indian Pharmacist, 8, 67-70.

15.Patel DM, Patel MM(2008). Optimization of fast dissolving etoricoxib tablets prepared by sublimation technique, Indian J.Pharm.Sci., 70(1), 71-76.
16.Patel HM, Suhagia BN, Shah SA, Rathod IS, Parmar VK(2007). Preparation and characterization of etoricoxib-β-cyclodextrin complexes prepared by kneading method, Acta.Pharm., 57, 351-359.
17.Saharan VA, Kukkar V, Kataria M, Gera M, and Choudhury P.K(2009).Dissolution enhancement of drugs, Part II: Effect of carriers, Int.J.Health Res., 2(2), 207-223.
18.Saito M, Ugajin T, Nozawa, Sadzuka Y, Miyagishima A, and Sonobe T(2002). Preparation and dissolution characteristics of griseofulvin solid dispersions with saccharides, Int.J.Pharm, 249, , 71-79.
19.Suhagia BN, Patel HM, Shah SA, Rathod IS, Parmar VK(2006). Preparation and characterization of etoricoxib-PEG 4000 plus PVPK 30 solid dispersions, Acta.Pharm., 56, 285-298.
20.Tiwari R, Tiwari G, Srivastava B, Rai A.K(2009). Solid dispersions: An overview to modify bioavailability of poorly water soluble drugs, Int.J.Pharm.Tech.Res., 1(4), 1338-1349.
21.Yadav VB, Yadav AV(2009). Indomethacin solid dispersions by kneading method with lactose monohydrate and different polymers, J Pharm Res., 2(9), 1489-1492.
22.Zajc N,Obreza A, Bele M, and Srcic S(2005).Physical properties and dissolution behavior of nifedipine/mannitol solid dispersions prepared by hot-melt method, Int J Pharm., 291, 51-58.