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Research

Solubility Enhancement Of Cefixime Through Solid Dispersion Technique

G.Sushmitha*[1], L.Harikiran[1]

Department Of Pharmaceutics, Princeton College Of Pharmacy, Narapally, Ghatkesar, Telangana

*Author for Correspondence: G.Sushmitha
Email: pcopaac2007@gmail.com

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Abstract

Solid dispersion is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. The solid dispersions based on the concept that the drug is dispersed in an inert water-soluble carrier at solid state. Several water soluble carriers such as Mannitol, PEG 20000 and Urea were used as carriers and Ac Di-Sol used as super disintegrate. Different ratios between drug and carriers were prepared. All formulations were evaluated for pre and post compression studies and those results were found to be within limits. Dissolution studies revealed that formulations SD3 formulation was optimised formulation which contains Drug and Mannitol in the ratio of 1:3. FTIR studies revealed that no interactions between drug and excipients. The present study demonstrated that formulation of Cefixime solid dispersion is a highly effective strategy for enhancing the bioavailability of poorly water soluble drug Cefixime.

Keywords: Cefixime, Solid dispersion.

INTRODUCTION

1.1. General introduction

From the several previous years, the pharmaceutical scientists were working to enlarge patient compliance and secure dosage forms due to improved requirement in the market for them. As a result, developing the novel technologies has been growing annually because the growth of novel drug molecule requires high cost rather than novel technology. So the current trend in the greater part of pharmaceutical industries is development of dosage form with new formulation technology using old drug molecules to improve safety, efficacy and patient compliance[1,2]. Development of solid dispersion compacts is one such technology to enhance dissolution rate of poorly soluble drugs, thereby improving efficacy of drug molecules[2].

The most convenient and commonly employed route of drug delivery has been by oral intake. The oral route is the preferred route of drug administration due to its convenience, better patient compliance and low medicinal production costs. In order for a drug to be absorbed into the systemic circulation after oral administration, the drug must be dissolved in the gastric fluids[2].It is well conventional that the active ingredient in a solid dosage form must undergo dissolution after it is available for absorption from the gastrointestinal tract. The absorption rate of poor water soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid present at the absorption site, i.e. the dissolution rate is the rate limiting step in drug absorption[3]. The poor dissolution rate of water insoluble drugs and poorly soluble drugs is still a significant problem confronting the pharmaceutical industry. Newly developed chemical entities do not reach the market because of their poor oral bioavailability due to

inadequate dissolution in G.I fluids. The active ingredient must undergo dissolution before it is available for absorption from the gastrointestinal tract. The poor dissolution characteristics of water insoluble drugs are a major challenge for pharmaceutical industries. Accordingly, many hydrophobic drugs show erratic and partial absorption from the gastrointestinal tract.

One of the major challenges in drug development nowadays is poor solubility, as estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity.[4,5] Bioavailability of poorly water-soluble drugs is inadequate by their solubility and dissolution rate. Especially for class II substances according to the Biopharmaceutics Classification System (BCS), the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. The term "water-insoluble drugs" includes those drugs that are "sparingly water-soluble" (1 part solute into 30 to 100 parts of water), "slightly water-soluble" (1 part solute into 100 to 1000 parts of water), "very slightly water-soluble" (1 part solute into 1000 to 10,000 parts of water), and "practically water-insoluble" or "insoluble" (1 part solute into 10,000 or more parts of water).

1.2. BCS classification system

Based on the solubility and permeability, drugs are classified into four categories. Biopharmaceutics Classification System (BCS) was introduced by *Amidonetal*., as a basis sfor predicting the possibility of *in vitro-in vivo* correlations for immediate release dosage forms, based on the detection that drug solubility/dissolution properties and gastrointestinal permeability are the fundamental parameters controlling the rate and extent of drug absorption.

The BCS was developed mainly in the situation of immediate release solid oral dosage forms. It is the scientific support for classifying drug substances based on their aqueous solubility and intestinal permeability. It is the drug development tool that allows estimation of the contributions of three major factors dissolution, solubility and intestinal permeability that affect oral drug absorption from immediate release solid oral dosage forms. It was first introduced into regulatory decision making process into guidance document of immediate release solid oral dosage forms:

Classification: Solid dispersion can be classified in three classes according to its generation.

Classification of solid dispersion with examples

First generation solid dispersion

Sekiguchi and Obi is the first who describe solid dispersions in 1961. They noted that the drug release rate and bioavailability of poor water soluble drugs was improving by formulation of eutectic mixtures. Solid dispersion of Sulfathiazole and chloramphenicol was prepared using urea as a carrier which is high water soluble. These solid dispersions produced faster drug release and higher bioavailability than conventional formulations. The reasons for improvement s in bioavailability were small particle size and the better wettability of the drug. In the first generation solid dispersion crystalline carriers was used earlier, for example urea, sugars, etc.

Second generation solid dispersions

In the second generation solid dispersions contains amorphous carriers instead of crystalline. In the latter, the drugs are molecularly dispersed in an irregular form within an amorphous carrier, which are usually polymers. The most successful for solid dispersions can be obtained by using polymeric carriers. Carriers used in second generation solid dispersion are polyvinylpovidone (PVP), polyethyleneglycols (PEG) and polymethacrylates.

Third generation solid dispersions

Recently, it has been studied that the dissolution profile can be improved by using surface active carrier which is consider as third generation solid dispersions. These third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion. Surfactants use in third generation solid dispersion are inulin, inutec SP1, gelucire 44/14 and poloxamer 407.

Methods for preparing solid dispersion

Simple physical mixture

This method is simple and it was earlier used. Solid dispersion can be prepared by simple mixing of the drug and carrier in mortar-pestle.

Fusion method

In fusion method first mix the drug and carrier in require proportion. Then melt the resultant mixture in china dish by giving of heat up to melting point. Cool the melted mixture in ice bath and convert in solid. Afterward pass the prepared solid dispersion through small size screen. Sekiguchi and Obi used a fusion method to prepare simple eutectic mixtures. They use Sulphathiazole and urea (carrier) melted together at a temperature above the eutectic point and then cooled in an ice bath. Molecular dispersion can be depends on the degree of supersaturation and rate of cooling in the process.

The important limitation of this method is the thermostability of the drug and the carrier. If temperature required to high, the drug may decompose or evaporate.

Complexation with Cyclodextrins

Complexation is the association between two or more molecules to form a non bonded entity with a well-defined stoichiometry. The beta and gamma cyclodextrins and several of their derivatives are unique in having the ability to form molecular

inclusion with hydrophobic drugs having poor aqueous solubility. The two types of complexation that are most useful for increasing the solubility of drugs in aqueous media are stacking and inclusion. Stacking complexes are formed by the overlap of the planar regions of aromatic molecules, while inclusion complexes are formed by the insertion of the nonpolar region of one molecule into the cavity of another molecule (or group of molecules).

The α-, β- and γ-cyclodextrins are cyclic oligosaccharides consisting of six, seven, and eight glucose units respectively. One of the important properties of these naturally occurring cyclodextrins is their ability to form inclusion complexes with smaller molecules that fit into the hydrophobic cavity of the cyclodextrin. The formation of inclusion complexes alters a variety of the physicochemical properties of the drug molecule such assist solubility, dissolution rate, membrane permeability, chemical reactivity, and dissociation constant. In some cases, as the concentration of cyclodextrin increases, the solubility increases initially, levels off, and then decreases.

Among them, liquisolid compacts is one of the most promising and new technique which promotes dissolution rate of water insoluble drugs.[9] The term liquisolid compact refers to immediate release or sustained release tablets or capsules, combined with the inclusion of appropriate adjuvant required for tablets or encapsulating.[3,11] Sublimation is the transition of a substance directly from the solid to the gas phase without passing through an intermediate liquid phase. Sublimation is an endothermic phase transition that occurs at temperatures and pressures below a substance's triple point in its phase diagram. The reverse process of sublimation is desublimation, or deposition.

At normal pressures, most chemical compounds and elements possess three different states at different temperatures. In these cases, the transition from the solid to the gaseous state requires an intermediate liquid state. Note, however, that the pressure referred to here is the partial pressure of the substance, not the total (e.g., atmospheric) pressure of the entire system. So, all solids that possess an appreciable vapor pressure at a certain temperature usually can sublime in air (e.g., water ice just below 0 °C). For some substances, such as carbon and arsenic, sublimation is much easier than evaporation from the melt, because the pressure of their triple pointis very high, and it is difficult to obtain them as liquids.

When change of a solid substance directly to a vapor without first passing through the liquid state. The term is also used to describe the reverse process of the gas changing directly to the solid again upon cooling. An example of sublimation is seen when iodine, on being heated, changes from a dark solid to a purplish vapor that condenses directly to a crystalline solid upon striking a cool surface. In this way pure crystals of iodine are prepared. Some other substances, e.g., mercuric chloride, can be prepared by sublimation. Solid carbon dioxide, commonly known as dry ice, sublimes at -78.5°C (-109.3°F). Sublimation also occurs when air saturated with water vapor is suddenly cooled below the freezing point of water. Frost and snowflakes are thus formed by water changing directly from the gaseous to the solid state. Sublimation requires additional energy and is an endothermic change. The enthalpy of sublimation (also called heat of sublimation) can be calculated as the enthalpy of fusion plus the enthalpy of vaporization.

Crystals of ferrocene after purification by vacuum sublimation

Sublimation is a technique used by chemists to purify compounds. A solid is typically placed in a sublimation apparatus and heated under vacuum. Under this reduced pressure, the solid volatilizes and condenses as a purified compound on a cooled surface (cold finger), leaving a non-volatile residue of impurities behind. Once heating ceases and the vacuum is removed, the purified compound may be collected from the cooling surface. For even higher purification efficiencies a temperature gradient is applied, which also allows for the separation of different fractions. Typical setups use an evacuated glass tube that is gradually heated in a controlled manner. The material flow is from the hot end, where the initial material is placed, to the cold end that is connected to a pump stand. By controlling temperatures along the length of the tube the operator can control the zones of recondensation, with very volatile compounds being pumped out of the system completely (or caught by a separate cold trap), moderately volatile compounds recondensating along the tube according to their different volatilities, and non-volatile compounds remaining in the hot end. Vacuum sublimation of this type is also the method of choice for purification of organic compounds for the use in the organic electronics industry, where very high purities (often > 99.99%) are needed to satisfy the standards for consumer electronics and other applications

Class I: High permeability and solubility.

Formulation independent: The bioavailability of class I compounds is determined only by delivery of the drug solution to the intestine.

Examples: Benzapril, Loxoprofen, Sumatriptan etc.

Class II: High permeability but low solubility

Formulation dependent: The bioavailability of class II compounds is limited by drug solubility/dissolution.

Examples: Valsartan, Nimesulide, Loratadine, Aceclofenac etc.

Class III: Low permeability but high solubility

Dependent on barrier properties: The bioavailability of class III compounds is limited by intestinal permeability.

Examples: Gabapentine, Topiramate, Atropine etc.

Class IV: Low permeability and low solubility

Formulation and barrier properties dependent: The bioavailability of class IV compounds is limited both by solubility/dissolution and intestinal permeability.

Examples: Hydrochlorthiazide, Furosemide, Meloxicam etc.

1.3 Techniques for Dissolution Enhancement

There are various techniques available to improve the solubility subsequently improves dissolution rate of poorly soluble drugs. Some of the approaches to improve the solubility and dissolution rate are

1.3.1Micronization: Particle size reduction leads to increase in the effective surface area resulting in enhancement of solubility and dissolution velocity of the drug. Micronizationis used to improve dissolution rates of drugs into the biological environment, in order to improve the oral bioavailability. Micronization of drugs is widely done by milling techniques using a jet mill, rotor stator, colloidal mill, and air attrition. But, the effect of micronization is often unsatisfactory, particularly when the drugs are encapsulated or tablet. Micronized drugs also have the affinity to agglomerate as a result of their hydrophobicity, thus reducing their available surface area. A hydrophobic powder with small particle size leads to aggregation, making it difficult to disperse. The particles float on the dissolution medium because of entrapped air. It is difficult to remove or wet these particles. All these effects, in fact, reduce the rate ofdissolution.[5]

1.3.2. Nanonization: Recently, various nanonization strategies have emerged to increase the dissolution rates and bioavailability of several drugs that are poorly soluble in water. Nanonization broadly refers to the study and use of materials and structures at the nano scale level of approximately 100 nm or less. Nanonization can result in improved drug solubility and pharmacokinetics, and it may also decrease systemic side-effects.[6]There are different techniques used for nanonization of drug including Wet milling, Homogenization, Emulsification-solvent evaporation technique, Pear milling, Spray drying etc.

1.3.3. Salt form: Salts have improved solubility and dissolution characteristics in comparison to the original drug. Example: Salt of basic drug like Atropine is more soluble than parent drug. Salt formation may increase hygroscopicity leading to stability problems. Solubilization technique lead to liquid formulations that is typically unattractive from patient acceptability and commercialization.

1.3.4. Use of surfactants: Solubilization enhanced by using surfactants, to solubilize a poorly soluble substance is to reduce the interfacial tension between the surface of solute and solvent for better wetting and salvation interaction. Various surfactants like Polyglycolized glyceride (Labrasol), Tweens, Spans, Polyoxyethylene stearate and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide) – poly (propylene oxide), Poly (beta-benzyl-Laspartate), b-poly (ethylene oxide) etc., used as carrier for solubility and dissolution enhancement .Improvement of drug solubility by using the amphiphilic surfactants is due to lowering of surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilization of the drugs. To get some significant solubility enhancement, the surfactant concentration must be at least above the critical micelle concentration (CMC). The CMC will depend upon the surfactant itself and the ionic strength of the media. The amount of surfactant required depends on the CMC and the degree to which the compound partitions into the surfactant micelles but the solubilization of drugs in aqueous media by the use of surfactants leads to liquid formulations that are generally less patient acceptability and commercialization.

1.3.5. Use of Co-solvents: Co-solvent is a highly effective technique for enhancement of solubility of poorly soluble drugs. It is well-known that the addition of an organic co-solvent to water can significantly change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be enhanced by changing polarity of the solvent. This can be achieved by addition of another solvent. This process is known as co-solvency. Solvent used to increase solubility is known as co-solvent. Co-solvent system mechanism is reducing the interfacial tension between the aqueous solution and hydrophobic solute. The use of mixed solvent system is frequently necessary in pharmaceuticals when a drug is poorly soluble. Co-solvents such as ethanol, propylene glycol, glycerin, sorbitol and polyoxyethylene glycols, dimethylsulfoxide, ethanol and N, N dimethyl formamide can be used[6]but the solubilization of drugs in inorganic solvents or in aqueous media by the use of co solvents leads to liquid formulations that are generally less patient acceptability and commercialization.

1.3.6. Use of Metastable Polymorphs: The presence of metastable, polymorphic crystalline forms can exert a great influence on the solubility, dissolution rate, and biological activity of medicaments. The separation and selective use of a definite polymorphic form to have the highest solubility, is a technique that can be useful in certain cases for the increase of dissolution rates. Melting followed by rapid cooling or recrystallization from different solvents can produce metastable forms of a drug. For example, a metastable form of chloramphenicol palmitate is more water-soluble than the A and C forms.[7]

1.3.7. Drug Dispersion in Carriers

a) Solid Solutions: A solid solution is a binary system comprising a solid solute molecularly dispersed in a solid solvent. Since the two components crystallize together in a homogeneous one-phase system, solid solutions are also called molecular dispersions or mixed crystals. They are generally prepared by a fusion method, whereby a physical mixture of solute and solvent are melted together followed by rapid solidification. Ex; solid solution of griseofulvin–succinic acid dissolves 6–7 times faster than pure griseofulvin.[8]

b) Eutectic Mixtures: These systems are prepared by a fusion method. Eutectic melts differ from solid solutions in that the fused melt of solute and solvent show complete miscibility but negligible solid–solid solubility. When the binary mixture is exposed to water, the soluble carrier dissolves rapidly leaving the insoluble drug in a state of microcrystalline dispersion of very fine particles. Examples of eutectic mixtures include paracetamol–urea, griseofulvin–urea, and griseofulvin–succinic acid.[8]

The advantage with solid solutions and eutectics is that they are melts, are easy to prepare, and are economical because no solvent is used. Some limitations are that it cannot be applied to drugs that fail to crystallize from the mixed melt, thermolabile drugs, and carriers such as succinic acid that decompose at their melting points.

c) Solute–Solvent Complexation Reactions: Molecular complexation between molecules of dissolving solutes and certain solvents have been known to affect dissolution rates. The major complexation mechanism in these systems is hydrogen bonding.

d) Solid dispersion: The dispersion method allows the preparation of physically modified forms of the drug that are much more rapidly soluble in water than the pure compound. The most regularly used hydrophilic carriers for solid dispersions include polyvinyl pyrrolidone, polyethylene glycols, and plasdone-S630. Surfactants may also be used in the formation of solid dispersions. Surfactants like Tween-80, Myrj-52, Pluronic-F68 and sodium lauryl sulfate are used as water-soluble polymer, as an excellent universal carrier for improving the dissolution rate and oral absorption of water-insoluble drugs. Various methods are used in preparation of solid dispersion like fusion (melting), solvent evaporation, lyophilization (freeze drying), melt agglomeration, extrusion, spray drying, surfactant use, electrostatic spinning, and super critical fluid technology. In the preparation, the use of vast amount of organic solvent may cause environment and safety concern. The surface solid dispersions were introduced to overcome this limitation. But still there are limitations for this technique which be positioned with the use of solvents for preparation of surface solid dispersions. Finding an appropriate solvent to dissolve the drug and carrier is difficult. Complete removal of solvent is complicated and residual solvent cause toxicity.

e) Sono crystallisation: This technique is successfully employed to reduce particle size by using ultrasound, is son crystallisation which is a novel approach by use of anti-solvents and liquid solvents. By adding these anti-solvents and liquid solvents, recrystalllization of poorly water soluble drugs occurs.

f) High Pressure Homogenization: It is basically involves the use of high pressure with very high velocity by passing the crystalline drug aqueous dispersion through a narrow gap. The proposed mechanism for this process is by shear forces and cavitations due to which particles get disintegrated. In this homogenization process drug particle which are obtained is dependent on directly pressure, nature of drug substance and number of homogenization cycles undergone. It can be performed in two ways: either in water (that is in disso cubes) or in water reduced media (nanopure).

g) Nanomorph Technology (Nt): By use of NT low water soluble drug substances are converted into amorphous nanomorph from crystalline state. In this suspension of drug substance is prepared in a solvent which is mixed with other solvent in a chamber, due to this a conversion of drug suspension into a true molecular solution occur. Precipitation of drug substance is induced by the aqueous solution of polymer. These polymers play an important role in preventing of aggregation or growth and maintain their nanoparticulate state. The example is CAP, Calcium-phosphate based nanoparticles which improve the oral bioavailability of hormones and proteins.

h) Evaporative Precipitation: In this technique there is a rapid phase separation for nucleation and growth of microparticles and nanoparticles of water insoluble drugs. In this low boiling solvent is selected and a suitable amount of drug is added to it and the resultant solution is passed and pumped through a inert tube which is heated to a temperature under pressure above the selected organic solvent boiling point and sprayed into the heated aqueous solution through a fine atomizing nozzle. Further the surfactants are added so as to optimize the particle size.

MATERIALS

Cefixime-Procured From Aurobindo Pharma Ltd, Mannitol-S.D. Fine chemicals, Mumbai, India, PEG 20000-Rubicon Research Pvt. Ltd.,Mumbai, India, Urea-Merck Specialities Pvt Ltd, Mumbai, India, Ac-Di-Sol-Merck Specialities Pvt Ltd, Mumbai, India, Mg.stearate-S J Chemicals, Talc-Nikita Chemicals, India, MCC-Rubicon Research Pvt. Ltd., Mumbai, India.

METHODOLOGY

Preformulation Studies

Pre formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Analytical method development for Cefixime

a) Determination of Absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λmaxwas found to be 283.0 nm. Hence all further investigations were carried out at the same wavelength.

b) Preparation of standard graph in pH 6.8 medium

10 mg of Cefixime was dissolved in 10 ml methanol (Primary stock). From this primary stock 1 ml was transferred to another volumetric flask made up to 10ml with Phosphate buffer of pH 6.8 (Secondary stock). From this secondary stock was taken to produce 5, 10, 15, 20 and 25 µg/ml respectively. The absorbance was measured at 283.0 nm by using a UV spectrophotometer.

Preparation of Solid Dispersions of Cefixime

Solvent Evaporation Method

Solid dispersion is one of the most commonly used techniques to improve the solubility of water insoluble drugs which in turn improves the bioavailability. Cefixime solid dispersions were prepared by using carriers (i.e. Mannitol, PEG 20000, and Urea) in proportions viz. 1:1, 1:2 and 1:3 (Drug: Carrier) by solvent evaporation method. Ethanol was added to the mixture of drug and carrier and triturated in dry mortar until the solvent evaporated and a clear film of drug and carrier was obtained. The resultant solid dispersion was scraped out with a spatula. Dispersions were pulverized in a mortar and pestle and passed through a sieve no 60. Then the prepared formulations were stored in a desiccator until further use.

Physical Mixture Method

Accurately weighed Cefixime and polymer taken in glass vial according to Table. The physical mixing was carried out by means of shaking the vials slowly and then the mixture was poured in the wax paper and mixed by the help of a spatula. Finally, the mixture was passed through 40 mesh sieve. After mixing well, the formulations were kept in desiccators until further study.

Kneading Method (KN)

A mixture of carrier and Drug were weighed accurately in specified quantity. The mixture was wetted with water: Ethanol (50% v/v) and kneaded thoroughly for 45 min in glass mortar. Further, the products was dried at 40^0C for 48 hr, passed through sieve No.85 and stored in a desiccator over fused calcium chloride.

Table 1: Formulation of solid dispersion showing various compositions

	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8	SD9
Drug	100	100	100	100	100	100	100	100	100
Mannitol	100	300	500	-	-	-	-	-	-
PEG 20000	-	-	-	100	300	500	-	-	-
Urea	-	-	-	-	-	-	100	300	500

Table 2: Formulation of fast dissolving tablet by using solid dispersion

Ingredients	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8	SD9
Cefixime equivalent to 100mg	200	400	600	200	400	600	200	400	600
Ac-Di-Sol	7	7	7	7	7	7	7	7	7
Mg.stearate	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3
MCC	485	285	85	485	285	85	485	285	85
Total weight	700	700	700	700	700	700	700	700	700

RESULTS AND DISCUSSION

Determination of λ max

The prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 283.0 nm.

Calibration curve of Cefixime

The standard graph of Cefixime was obtained and good correlation was obtained with R^2 value of 0.998. The medium selected was pH 6.8 phosphate buffer. The standard graph values of Cefixime are tabulated as below-

Table 3: Standard Graph values of Cefixime at 283.0 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
5	0.129
10	0.241
15	0.354
20	0.465
25	0.571

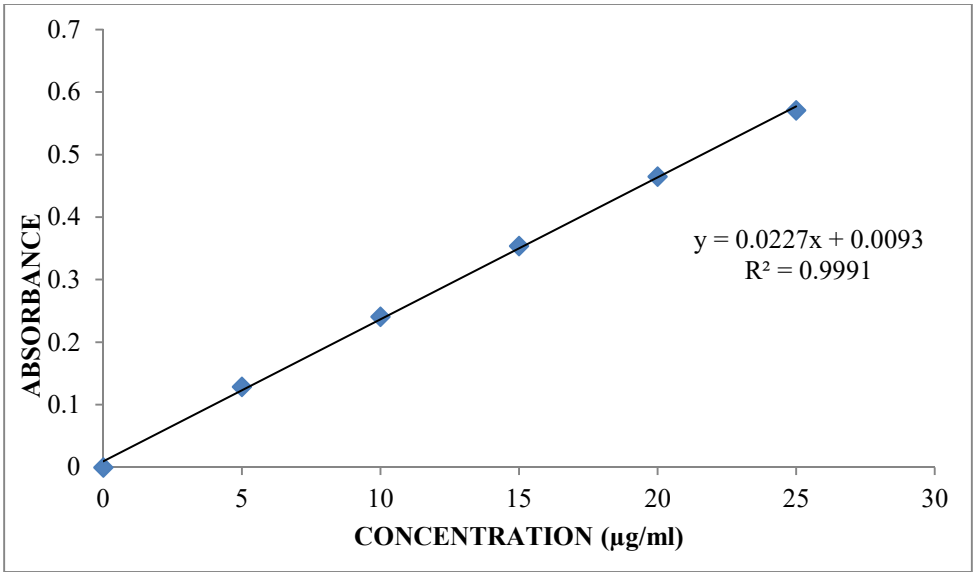

Fig 1: Standard Curve of Cefixime

Evaluation

Characterization of Precompression Blend

The precompression blend of Cefixime solid dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** Angle of repose was less than 30 ±0.08^0, Carr's index values were less than 16.92 for the precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.19 for all the batches indicating good flow properties.

Table 4: Physical properties of precompression blend

Formulation Code	Angle of repose (Ɵ)	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)	Carr's Index (%)	Hausner's ratio
F1	25 ±0.06	0.46±0.04	0.55 ±0.05	16.36±0.07	1.19±0.06
F2	26 ±0.05	0.43 ±0.05	0.52 ±0.06	17.30±0.07	1.20±0.08
F3	27±0.09	0.41 ±0.05	0.50 ±0.06	18±0.03	1.21±0.09
F4	26 ±0.11	0.54 ±0.08	0.63±0.03	14.2±8 0.05	1.16±0.07
F5	28 ±0.07	0.49 ±0.06	0.60 ±0.02	18.33±0.02	1.22±0.07
F6	27 ±0.07	0.54±0.07	0.54±0.07	16.92±0.03	1.20±0.08
F7	30 ±0.08	0.53 ±0.06	0.64 ±0.07	10.47±0.06	1.20±0.06
F8	29±0.12	0.47±0.06	0.56±0.02	16.04±0.04	1.19±0.06
F9	28±0.05	0.52±0.02	0.61±0.04	14.75±0.03	1.17±0.04

Evaluation of Tablets

Physical Evaluation of Cefixime solid Dipersion tablets

The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in Table 8.3 .All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 4.1 to 5.8 kg/cm^2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 5.10 to 5.85 mm. All the formulations satisfied the content of the drug as they contained 96.25 -99.89 % of Cefixime and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

Table 5: Physical Evaluation of Cefixime tablets

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)
F1	698.25	5.85	4.1	0.18	98.34
F2	699.56	5.34	4.6	0.32	96.25

F3	698.72	5.15	5.2	0.47	99.81
F4	696.35	5.81	5.6	0.69	97.14
F5	697.89	5.12	4.7	0.25	99.89
F6	698.61	5.28	5.0	0.71	97.62
F7	697.28	5.10	4.7	0.32	98.12
F8	698.12	5.37	5.3	0.54	99.58
F9	498.97	5.19	5.8	0.28	97.42

***In vitro* release studies**

The drug release rate was studied using the USP type II dissolution test apparatus. The dissolution medium was 900 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 1 hr and analysed after appropriate dilution by using UV Spectrophotometer at 283.0 nm.

Table 6: *In vitro* drug release results for all formulations

TIME (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	28.58	32.12	14.29	27.12	20.18	16.84	15.20	29.57	23.14
10	45.24	48.78	33.16	31.75	36.01	22.63	30.79	36.69	29.56
15	59.69	53.26	39.76	56.98	58.34	27.32	49.36	45.92	35.80
20	66.12	69.39	45.51	63.52	63.96	37.18	50.12	58.36	46.79
30	71.86	78.45	58.99	77.39	67.78	55.26	68.55	63.21	58.18
45	78.49	86.71	74.52	87.59	76.24	67.72	79.28	82.76	66.51
60	87.34	90.89	98.93	97.31	85.53	79.54	86.43	97.12	78.19

The *In vitro* release profile of Cefixime Solid Dispersions in Mannitol the drug release at the end of 60 minutes for Formulation Code SD1, SD2, and SD3 were found to be 87.34 %, 90.89 % and 98.93 % for Pure Drug 1:1, 1:2 and 1:3 ratios respectively. For Formulation prepared with PEG 20000 formulation Code SD4, SD5 and SD6 were found to be 97.31 %, 85.53 %, 79.54 % 1:1, 1:2 and 1:3 ratios respectively. The % drug released from the Cefixime Solid Dispersions with Urea as carrier, the formulations containing physical mixtures in different drug to carrier ratios i.e., SD7, SD8 and SD9 showed drug release of 86.43 %, 97.12 %, 78.19 % respectively. Among all formulations SD3 formulations containing Drug and Mannitol in the ratio of 1:3 was shown maximum drug release at 60 min. Hence SD3 formulation was concluded as optimised formulation because Highest drug release in 60 minutes i.e., 98.93%. From the comparison graphs revealed that Formulation SD3 was shown maximum drug release at 60 min. Hence Among all formulations SD3 was considered as optimised formulation. The present study has shown that dissolution rate of the solid dispersion by Mannitol was highest than by other carriers. The solid dispersion have been prepared by different carriers in different ratios and found that Mannitol (SD3) shows the better enhancement of solubility in comparison to the other carriers.

Drug – Excipient Compatibility Studies By FTIR Studies

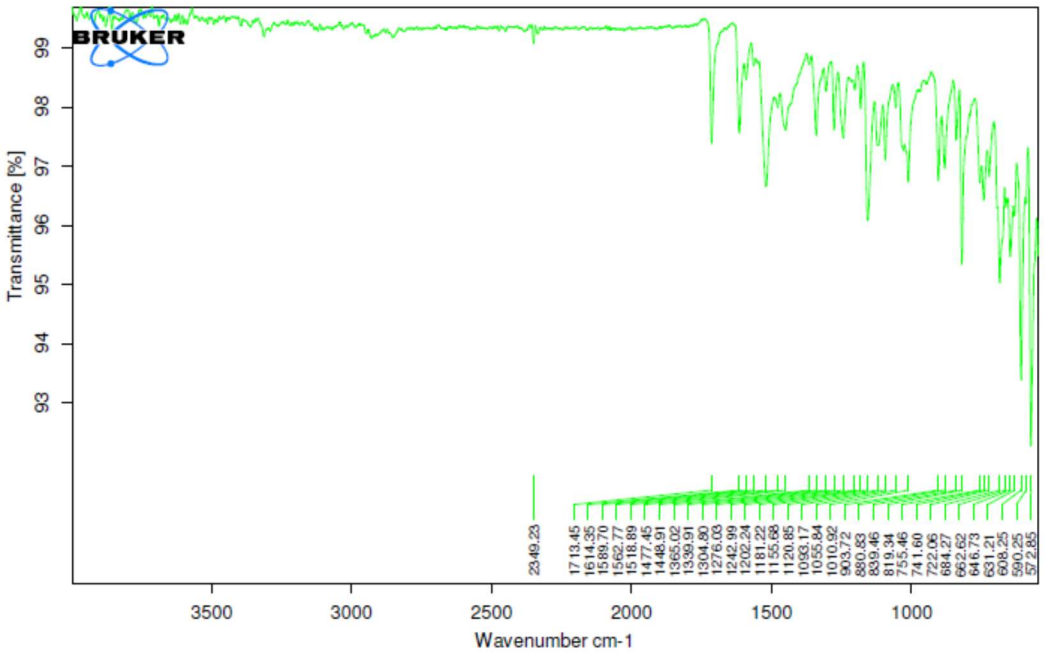

Fig 2: FTIR Spectra Of Pure Drug

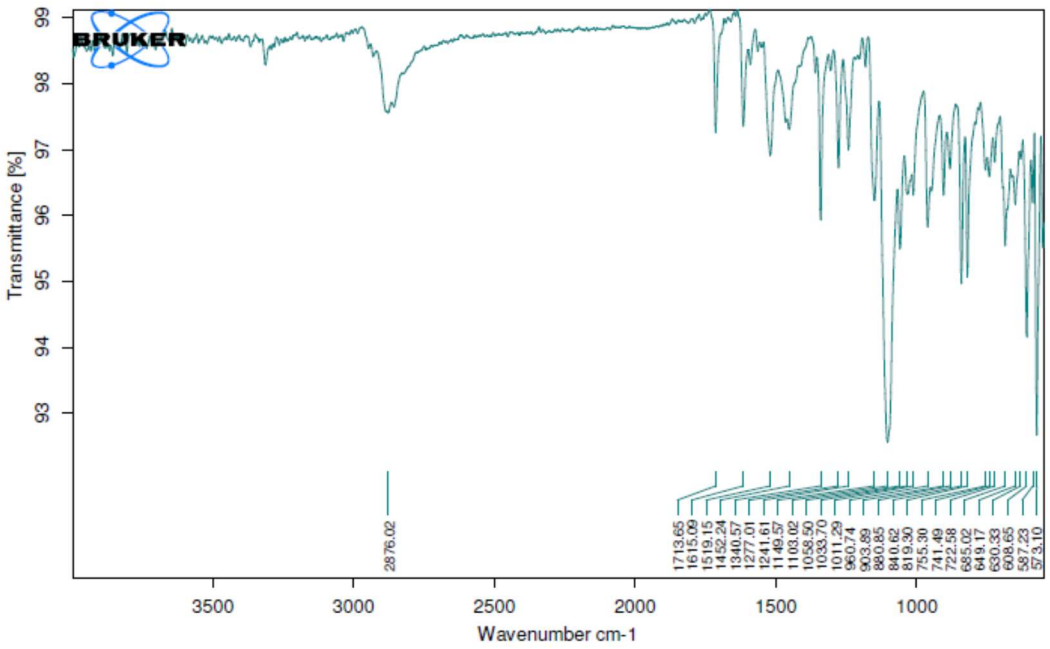

Fig 3: FTIR Spectra Of Optimised Formula

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Cefixime and excipients used in the preparation of different Cefixime solid dispersion formulations. Therefore the drug and excipients are compatible to form stable formulations under study. The FTIR spectra of Cefixime and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

CONCLUSION

Cefixime is an antibiotic useful to treat a number of bacterial infections, includes otitis media, strep throat, pneumonia, urinary tract infections, gonorrhea, and Lyme disease. The standard curve of Cefixime was obtained and good correlation was obtained with R^2 value 0f 0.999. The medium selected was pH 6.8 phosphate buffer. FTIR studies revealed that no interactions between drug and excipients. The pre compression blend of Cefixime soild dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** The precompression blend of all the batches indicating good to fair flowability and compressibility. Solid dispersions were prepared with various concentrations of carriers, the prepared solid dispersions were compressed into tablets. The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests. Among all the formulations F3 formulation containing, Drug and Mannitol in the ratio of 1:3 showed good result that is 98.93 % in 60 minutes.

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