INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

CRITICALITY OF SOLUBILIZER SELECTION DURING FORMULATION DEVELOPMENT OF POORLY WATER SOLUBLE CEFIXIME

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ARTICLE INFO

Article history
Received 24/04/2017
Available online
08/05/2017

Keywords
Cefixime,
Poor Solubility,
Kollidon 64,
Solid Dispersion,
Dissolution,
Solubilizer.

ABSTRACT

In Recent Years, The Pharma Industry Has A Wide Variety Of Excipients Available For The Formulation Development, Where Selecting The Effective Functional Excipient Is A Critical Step In Early Stage. For Selecting Suitable Type Of Solubilizer Through Its Solubilizing And Absorption Enhancer Property Towards Cefixime, Various Solubilizers Like Urea, PEG, HPMC, Kollidon 64 And Gaur Gum Were Investigated. Solid Binary Systems Prepared At Various Drug–Polymer Ratios By Mixing, Kneading, Solvent Evaporation, Lyophilization, Microwave Irradiation & Spray Drying Were Characterized By DSC, XRD, SEM, Attenuated Total Reflectance, Saturated Solubility Study And Tested For Dissolution Behavior. The Solubilizing Effect Of Polymers On Poorly Soluble Cefixime Was Found To Be Of Following Order: Kollidon 64>Urea>Gaur>PEG>HPMC. The Dissolution Studies Displayed A Noticeable Augment In The Dissolution Rate Than Neat Cefixime. The Dispersion Of Drug Processed By Spray Drying Demonstrated Higher Drug Dissolution Rates In Comparison To Physical Mixture And Pure Cefixime. In Vivo Experiments In Mice Demonstrated That Administration Of 4 Mg/Kg Of Drug Spray Dried Systems With Kollidon 64 Resulted In Statistically Significant ($P = 0.006$) Increase (227%) In C_{max} With T_{max} ($P = 0.03$) Of 4 Hr. The 1/1 (W/W) Drug–Carrier Spray Dried Systems With Kollidon 64 Was The Best Product Enabling An Improvement Of 4.8 Times Of Drug Dissolution Efficiency And Better Antibacterial Activity With Zone Of Inhibition 2.4 Times Higher Than The Pure Cefixime. Thus, The Demonstrated Solubilizing Ability And Antibacterial Enhancer Effect Towards Cefixime Make Kollidon 64 Peculiarly Suitable For Development Of Poorly Soluble Cefixime.

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*Please cite this article in press as **Poonam Mogal** et al. Criticality of Solubilizer Selection During Formulation Development of Poorly Water Soluble Cefixime. Indo American Journal of Pharmaceutical Research.2017:7(04).*

INTRODUCTION

Current biopharmaceutical field often suggest looking at the factors affecting the pharmaceutical dosage forms and thereby therapeutic systems, ultimately controlling them to make the competent bioavailable medicine. As stated by BCS classification work by Amidon & coworker, solubility and permeability are two important parameters responsible for the final bioavailability of drug in body. In the formulation development, due to presence of majority compounds with poor solubility characteristics, lot of consideration has been given to the water solubility because water is the unique solvent of biological systems [1]. BCS class II/IV drugs' oral absorption is mainly dependent on the water solubility of drugs. Thus, solubility enhancement is considered as vital step in formulation development of BCS class II/IV drugs given by oral route [2]. Due to off-putting physicochemical properties which are difficult to change many drug molecules show poor solubility and hence an excipient may be added externally to enhance its apparent solubility. Solubility enhancers are compounds that may raise the evident solubility of the poorly soluble drug by diverse mechanisms. In recent years, the pharma industry has a wide variety of excipients available for the formulation development. For the solid oral dosage form, excipient plays important role as it serves many functions like binders, coatings, fillers or as solubilizers and also giving finished products its stability, drug release, bioavailability, taste, and texture.

Thus, appropriate excipient selection plays a vital role for the final drug product performance in body. So, selecting the effective functional excipient is a critical step in early stage of formulation development. For the formulation development, excipients should be selected on the basis of functionality requirements and compatibility with the API. In assorting the excipient all for the API, attention also needs to be given to the desired strong interaction between excipient and API. Hence, considerations of the individual molecular structures and potential interactions between API and excipient will be useful for the formulator in smart and effective excipient selection for drug development [3-7]. The appropriate choice of solubilizer along with its good solubilizing power is of critical importance to the development of BCS class 2/4 drugs and ultimately for their use in treating various diseases.

The course of administering the drug, the API, the type of formulation, and other factors also affects the selection of appropriate excipient for the formulation. International use of appropriate quality, safety, and functionality standards for pharmaceutical excipient, as well as excipient delivery systems are developed, implemented and promoted by a pharmaceutical regulatory non-profit organization i.e. the Federation of IPEC.

Excipients like polymeric carriers are the most successful for solid dispersions, because they are able to form amorphous solid dispersions. Depending on the source of origin/ manufacture, solubility enhancers can be further divided into the subsequent groups: (1) compounds that are totally synthetic polymers i.e. Fully synthetic polymers embody povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates.; (2) compounds that have source in nature i.e. these polymeric carrier are derived from cellulose derivatives like hydroxypropylmethylcellulose (HPMC), HPC or starch derivates, such as cyclodextrins.

Thus, selection of particular solubilizer from pools of excipients available both natural and synthetic is daunting task. The present study is an attempt in selecting the appropriate solubilizer for Cefixime from natural as well as synthetic resources.

Natural compounds have been noted for a period, but recently, more importance is given for the utilization of theses natural polymers because of its lack of toxicity, its good biological properties like biocompatibility, and biodegradability besides its wide availability, low price and high versatility of use.

Chemically, Urea is Carbonyldiamide, a non toxic and effective carrier, with solubility in water greater than 1 in 1 and shows good solubility in many organic solvents [8]. While gaur gum, non toxic- non ionic, is a galactomannan i.e.polysaccharide consisting of the sugars galactose and mannose. It has the backbone that is a linear chain of β 1, 4-linked mannose residues which are having attached galactose residues at 1, 6-linked every second mannose, leading to formation of short side-branches. Higher Degree of substitution(D.S.) and Molar Substitution of guar gum offers by carboxyalkyl and hydroxyalkyl groups respectively yield improved solubility, dispersion and emulsification, thatswhy its derivatives are more popular in numerous industries [9,10].

Guar gum is a hydrocolloid, which is retrieved as of the Cyanmopsis tetragonolobus's (family Leguminosae) endosperm. It is an economical thickener and stabilizer that simply hydrates in cold water to give highly viscous solution [11, 12]. The key determinant factor of hydration kinetics is particle size that reflects the change in surface area exposed to water. The rate as well as degree of hydration of guar gum is crucial variable in influencing its biological activity [13-15].

Polyethylene glycol (PEG), a non toxic polymer, is a polyether i.e.polyethylene oxide (PEO) or polyoxyethylene (POE), depending on its molecular weight. PEG is generally considered biologically inert and safe. However, a minority of people are allergic to it [16-19]. Hydroxypropylmethyl cellulose (HPMC), is a non-ionic and water soluble polymer [20]. Hydroxy propyl methylcellulose is generally, a synthetic modification of the natural polymer compound i.e. cellulose. It's generally, a modification of alkali cellulose that is produced when purified wood pulp is treated with 18% sodium hydroxide solution. Methyl and Hydroxypropyl ether groups are inserted into the prepared molecule by reaction of the alkali cellulose with propylene oxide and methyl chloride respectively.The commercial Hydroxypropylmethyl cellulose i.e. HPMC's degree of substitution with methoxy and hydroxyl propyl groups can vary depending upon the commercial use and properties desirable for it. These added groups give the molecule its distinctive properties of being cold-water soluble, whereas it's exhibiting reversible gelation when heated and recooled [21]. The literature denote that HPMC can command the drug release rate owing to its swelling and dissolution properties in aqueous solution, that are most likely related to the formation of soluble complexes between the aqueous HPMC and inadequately soluble API [22].

In the present study these natural polymers were investigated for their solubility enhancing properties for Cefixime, a very poorly water-soluble third generation cephalosporin antibiotic. The favorable impact of Urea and Guar gum on Cefixime's solubility improvement has also been previously demonstrated [23, 24].

Kollidon® VA 64 is a vinylpyrrolidone-vinyl acetate copolymers which is used as dry binders for direct compression tableting, as granulating agents, as retarding and as a film-forming agents and likewise as in taste-masking applications. Kollidon® VA 64 is often used as a dry binder for direct compression tableting as well as a soluble binder for granulation. Hence, these properties make it good as well as cost-effective option to natural binders. It's also a perfect excipient to be used for hot-melt extrusion processes. Kollidon®VA 64 is very appropiate for markets with higher humidity exposure. Kollidon®VA 64 is superb binder for tablets and granules. Due to presence of plasticity, Kollidon®VA 64 is more prefferable than Kollidon®30 for solid state formulations. Kollidon®VA 64 have been found to be superior dry binder for direct compression and it's often additional to the materials like sorbitol, mannitol, starch, or direct compression aids, e.g. micro crystalline cellulose, whose binding strength is insufficient, to allow tablets with superb properties [25].

The various techniques are utilized for solubility enhancement of poorly soluble drug but out of several approaches dispersion of solid is mostly favored where focus is given for improving rate controlling step in dissolution [26].

Depending upon the molecular interaction of drug and carriers, amorphous solid dispersions can be classified as solid solutions, solid suspensions or a mixture of both. In amorphous solid solutions systems, API and carrier are completely miscible and soluble, arise an unvaried molecular interaction between them. Moreover, in these systems, the drug and carrier interaction energy is leading to extremely high, resulting in a true solution. Therefore, it seemed worthy of interest to extend these investigations and compare in detail the performance of such polymers in improving Cefixime dissolution behavior.

Therefore, the work performed here was intended at employment of Kollidon 64, Urea, Gaur, PEG 6000, and HPMC as hydrophilic carriers to enhance dissolution of Cefixime as well as selecting the suitable solubilizer. This study additionally investigates the impact of various methods for solid dispersion preparation with best carrier on dissolution of Cefixime. The best Solid dispersion obtained was characterized for DSC, XRD, SEM, and ATR to illuminate the mechanism involved in dissolution improvement. The most effective product was then selected to carry out in vivo experiment in mice, in order to evaluate and compare the enhancer activity of the examined polymer on the pharmacokinetic of Cefixime after its oral administration.

Differences in the chemical structures, solubilizing power and other factors may result in the differences in performance of solubilizers. Thus, SDs characterization based on solubility enhancement would make it easier to select best solubilizer and provide a more meaningful information regarding type of solubilizer to be used for particular class of drug.

MATERIALS AND METHODS

Materials

Cefixime (CFX) (Glenmark pharmaceuticals, Sinnar, Nashik), Gaur Gum (GR) (Labfine, India), Urea (UR) (Qualigen, India), PEG (Labfine, India), HPMC (HPM) (Labfine, India), Kollidon 64 (KO) (BASF, India) were utilized for the experimental work. All other reagents & chemicals used were of analytical grade.

Methods

Preparation of formulations

Physical mixtures (PM)

Physical mixtures of Cefixime were prepared in different ratios (1:1, 3, 5) by mixing Cefixime with solubilizer for three min in a mortar until a homogeneous mixture was obtained. The resulting mixtures were sieved through a 100 µm mesh and then stored in a dessicator at room temperature until use.

Kneading method (KD)

In this most common and simple method, solid dispersions of different ratios (1:1, 3, 5) were prepared. CFX and solubilizer in different ratios were taken. First polymer was added to the mortar, small quantity of methanol was added while triturating to get slurry like consistency. Then slowly drug was incorporated into the slurry and trituration or kneading was further continued for one hour. Slurry was then air dried at 25^0C for 24 hours, pulverized and passed through sieve no. 100 and stored in desiccators over fused calcium chloride [27].

Solvent evaporation method (SE)

CFX was dissolved in nonaqueous solvent and solubilizer was dissolved in water. To an aqueous system, nonaqueous system was added with continuous stirring and addition rate was maintained 5-7ml/min. Nonaqueous phase was evaporated in oven at 45 -50 ^{o}C. The product obtained was passed through sieve No. 100 and then stored in desiccator at room temperature till further analysis by UV [28].

Table 1: Composition of the CFX formulations (CFX Cefixime, POL Polymer).

Component	Quantity (mg)		
	1:01	1:02	1:03
CFX	50	50	50
POL	50	100	150

Lyophilization/Freeze-DryingTechnique (LY)

This technique involves mixing of drug and polymer in same solvent only the process of solvent evaporation is different than usual method [29]. The drug and solubilizer (1:1, 1:2, and 1:3) were accurately weighed. Solid dispersions of different ratios were prepared. Drug was dissolved in methanol and polymer was dissolved in water. To an aqueous system, nonaqueous system was added with continuous stirring and addition rate was maintained 5-7ml/min. The Nonaqueous phase (methanol) was evaporated at room temperature. This was then lyophilised in Labconco lyophilizer (USA) after initial freezing with vacuum 0.040mbar. The lyophilized product thus obtained was stored in dessicator.

Microwave Irradiation (MW)

This technique involves the microwave irradiation reaction between drug and complexing agent using a microwave oven. The drug and solubilizer (1:1, 1:2, and 1:3) were accurately weighed. A homogeneous paste was prepared by mixing the drug and polymer with minimum amounts of solvents (ethanol: water, 1:1 v/v) in mortar. The paste formed was subjected to microwave irradiation for 7-8 min at power of 510 watt in a microwave synthesizer (CATA-R, catalyst systems, Pune, India). Only one beaker was kept at a time within the microwave oven. The prepared samples were exposed to microwave radiation for the time of 7-8 min. then, the beakers containing samples were maintained at room temperatures to cool down. The solid dispersions were collected and placed in desiccator for 24 hours and then the product was pulverized using mortar and pestle. The pulverized powder was passed through sieve no. 100 and stored in desiccators. This is a new technique for manufacturing scale up because of smaller reaction period & high yield of the product [30].

Spray drying (SY)

Each solution for spray drying was prepared by adding different ratio of Cefixime and solubilizer (1:1, 1:2, 1:3) to 200ml of methanol. It was then ultrasonicated in a bath sonicator for 10 min and spray-dried in a lab spray dryer model LU-222 Advanced (Labultima, Mumbai, India) with the drying capacity of 1 L/h. The spray drying parameters were inlet temperature, 80°C; outlet temperature, 60–70°C; aspirator value, 60 m^3/h; and flow rate, 4 ml/min.

Attenuated Total Reflectance Spectroscopy (ATR) analysis

Supporting evidence for formation of solid dispersion can be obtained by IR spectroscopy. Attenuated Total Reflectance spectra of the drug samples were obtained on a Bruker Eco-ATR machine. The samples were scanned over the wave number ranging from 3600 to 400 cm–1

Differential Scanning Calorimetry (DSC)

The possibility of any interaction between Cefixime and the Kollidon in dispersion of solid was done through analysing thermal events of SD & comparing it with that of pure cefixime using DSC. Differential scanning calorimeter (Lab Mettler Star SW 10) was used for test samples by heating them in an open aluminium pan, scanning at 10°C/min over a temperature ranging from 25 to 300°C in a nitrogen run of 50 ml/min.

X-ray Diffractometry (XRD)

The X-ray diffraction spectra of pure drug and binary systems were recorded at room temperature using on Bruker's AXS D8 advance X-ray diffractometer system. The samples were irradiated with mono-chromatized Cu KA2 radiation at wavelength 1.5406 A^0 and samples were mounted on zero-background sample holder and subjected to a continuous scan over an angular range of 3° to 80° 2θ at a step size of 0.02°. The diffraction patterns were collected with voltage of 40kV and current of 35mA respectively. The scanning rate of 2^0 min^{-1} was utilized.

Scanning electron microscopy (SEM)

The topography of Cefixime and Kollidon solid dispersion was seen under a scanning electron microscope (SEM; JEOL model JSM -6390LV) operating with an excitation voltage of 15 kV.

Solubility measurements of CFX

Solubility measurements were carried out in keeping with the strategy of Higuchi and Connors (1965). An excess quantity of prepared solid dispersion was added in 10ml distilled water taken in test tubes. The samples were sonicated for 1 hr at room temperature. After that the capped test tubes were shaken at 25 or 45±0.1°C for 24 hrs. Subsequently, the suspensions were filtered through Whatmann filter paper no. 41, and the filtered solutions were analyzed at 288 nm UV-spectrophotometrically.

Dissolution studies

The dissolution was studied by means of USP eight station dissolution test apparatus (Lab India) employing USP type II apparatus. Dissolution study was carried out in a 900 ml of pH 7.2 buffer at 37 ± 0.5°C at 100 rpm. Five ml samples were taken out at time interims of 5, 10, 15, 20, 30, 45 min. The sink condition was maintained to 900 ml through replacement of each 5 ml medium drawn with 5ml of new pH 7.2 phosphate buffer. The concentrations of drug in samples were ascertained by measurement of absorbance at 288 nm. Cumulative percent drug released was determined at each time interval. Pure Cefixime was used as control for comparison.

Antimicrobial studies

In vitro antimicrobial studies of prepared solid dispersions were carried out by disk diffusion technique against Gram-positive species *S. aureus* and Gram-negative species *E. coli and P. aerugenosa*. The activities were compared with pure Cefixime. For these studies Muller Hinton Agar (MHA) medium was used as nutrient medium. The petriplates were inoculated. The plates were incubated at 37°C for 24 h and the zone of inhibition was measured in mm by zeta sizer.

Statistical treatment of data

One way analysis of variance was performed to determine the statistical significance of the data using Graph pad prism-7 software.

RESULTS AND DISCUSSION

Solubility studies

Saturation solubility study was conducted to evaluate the effect of polymer on aqueous solubility of Cefixime. All the test samples showed an increase in drug solubility over crystalline CFX. It might be due to either the reduction of the crystallinity of drug or the improved wetting of the drug particles. This phenomenon was correlated to previous reports with similar results with other drugs. Improving the wettability of the hydrophobic drug crystals might also occur.

The solubility profile of neat Cefixime & SDs with various polymers are shown in figure 1&2. Plain Cefixime was slightly soluble in water. The solubility of plain Cefixime in water was less as compared to SDs formed by means of other technique.

The equilibrium solubility of formed dispersions through solvent evaporation, microwave irradiation, lyophilization and spray drying with Kollidon, in distilled water was found to show, an almost 3.9, 4.3, 5.5 and 7.8 fold respectively increase in solubility than pure drug (Figure 2). The difference in method of preparation is causing difference in solubility augmentation of Cefixime.

While for solid dispersion by solvent evaporation method with other hydrophilic polymers like Urea, Gaur, PEG 6000, HPMC as a solubilizer displayed an approximately 2.76, 2.6, 3.58, 2.11, fold augment in solubility correspondingly comparing to pure Cefixime (Figure 1).

It was evident that Kollidon 64 had a pronounced effect in the solubility of Cefixime. The increase in solubility might be attributed to formation of soluble complex of Cefixime and Kollidon 64. But though the polymer concentration is increased to 1:3 (Drug: Kollidon 64) ratio, there is decrease in apparent solubility. Solid dispersion prepared with 1:1 drug to hydrophilic polymer showed three 7.8 folds increase in solubility but further increase in polymer level did not contribute significant improvement. This might be attributable to formation of a solid solution, whereby the drug is exhibited as a molecular dispersion within the carrier. Such system is probably going to indicate solely partial miscibility, therefore the drug could only be in 'solution' at low concentrations, and it is apprehended that partial miscibility could in theory involve quite large drug incorporation at a molecular level. The release inhibiting property of solubilizer might be at higher concentration causing decrease in solubility or attainment of saturation solubility by Cefixime may be responsible [31]. The increase in apparent solubility of a drug due to polymer might be due to the improved local solubility and wettability of the poorly soluble drug in the solid dispersion matrix [32].

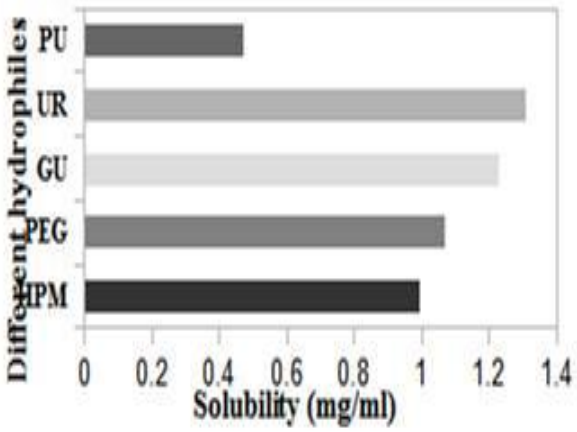


Figure 1: Solubility (mg/ml) of different hydrophiles solid dispersion in distilled water.

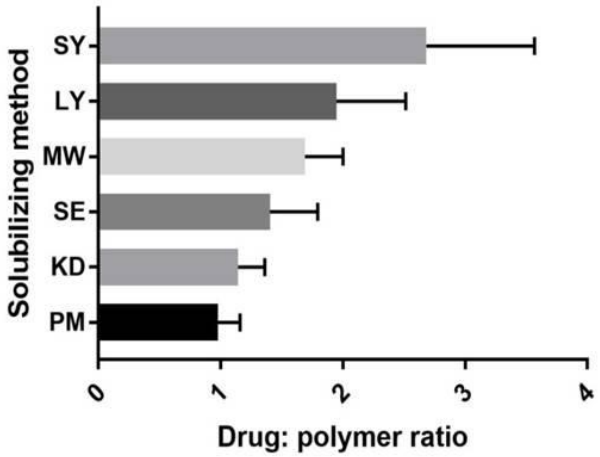


Figure 2: Solubility (mg/ml) of Kollidon 64 solid dispersions prepared by different solubilizing method in distilled water

SEM

The morphology of the CFX and SD was examined using SEM and the photographs are shown in Figure 3. SEM of pure CFX appeared as flat-broken needle-shaped crystals of varying sizes with well-developed edges. Whereas its surface was modified after solid dispersion preparation with Kollidon 64 and it was appeared as spherical shaped particles of varying sizes with smooth surface. In contrast, there was no crystal structure of CFX in SDs, indicating the transformation of CFX into an amorphous form, which agrees with the results of the DSC experiment.

a **b.**

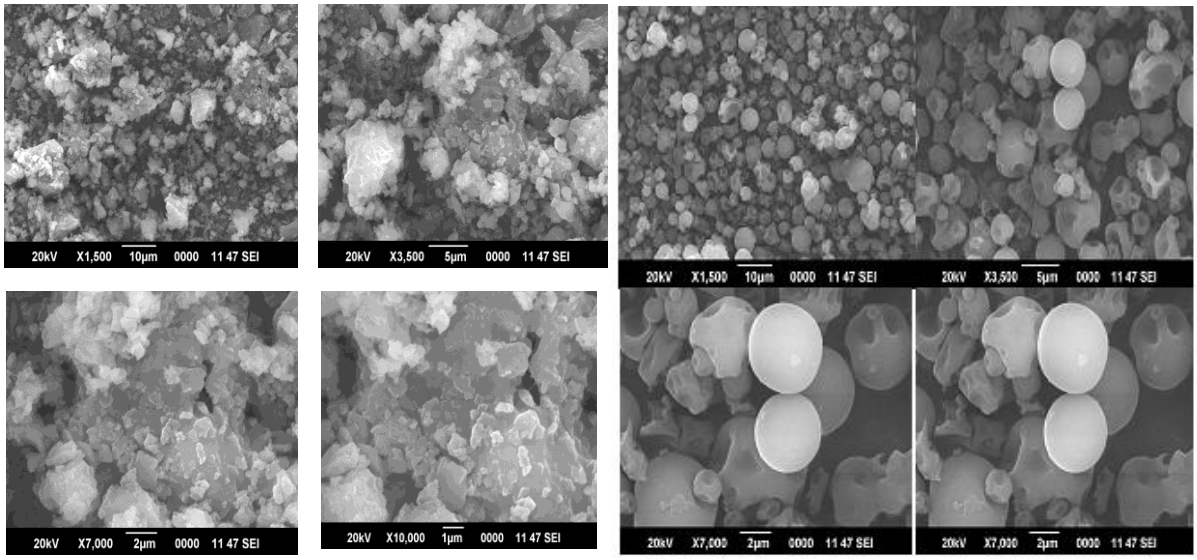


Figure 3: SEM micrograph of a: Cefixime, b: SD with Kollidon 64.

DSC

The thermal behavior of pure CFX and solid dispersions are shown in Figure 4. The thermogram of neat CFX illustrated a endotherm (melting) at 215.64°C; however, this endotherm was shifted to 211.83°C, 208.42°C in the thermogram of SD with Urea and Gaur gum (Figure 7, 8) respectively indicating the dispersion of Cefixime in solubilizer; drug and polymer were found to be compatible. While in case of Kollidon 64, this endotherm was shifted to 153.47°C. For SD with Kollidon 64 it showed oxidative decomposition peak at 288.93°C.

The DSC curves clearly demonstrated that the height of the endotherm is lowered the most in case of Kollidon followed by Gaur and Urea solid dispersion indicating the complete dispersion of drug in Kollidon matrix. Hence, this broadening of the endotherm along with shifting to lower temperature pointing towards the reasons behind the solubility enhancement by these solubilizers & Kollidon was being better in it.

The DSC curve showed broadening of endothermic peak with significant lowering in melting temperature. The decrease in melting temperature may be a result of solubilizing effect of Kollidon 64 during heating process due to its low melting temperature [33, 34]. All SDs showed no endothermic peak of Cefixime. Dispersion of drug within the polymer phase was indicated by the complete absence of thermal endotherms. The change of crystalline Cefixime to amorphous solid solution state may be responsible for an increase in dissolution of solid dispersion.

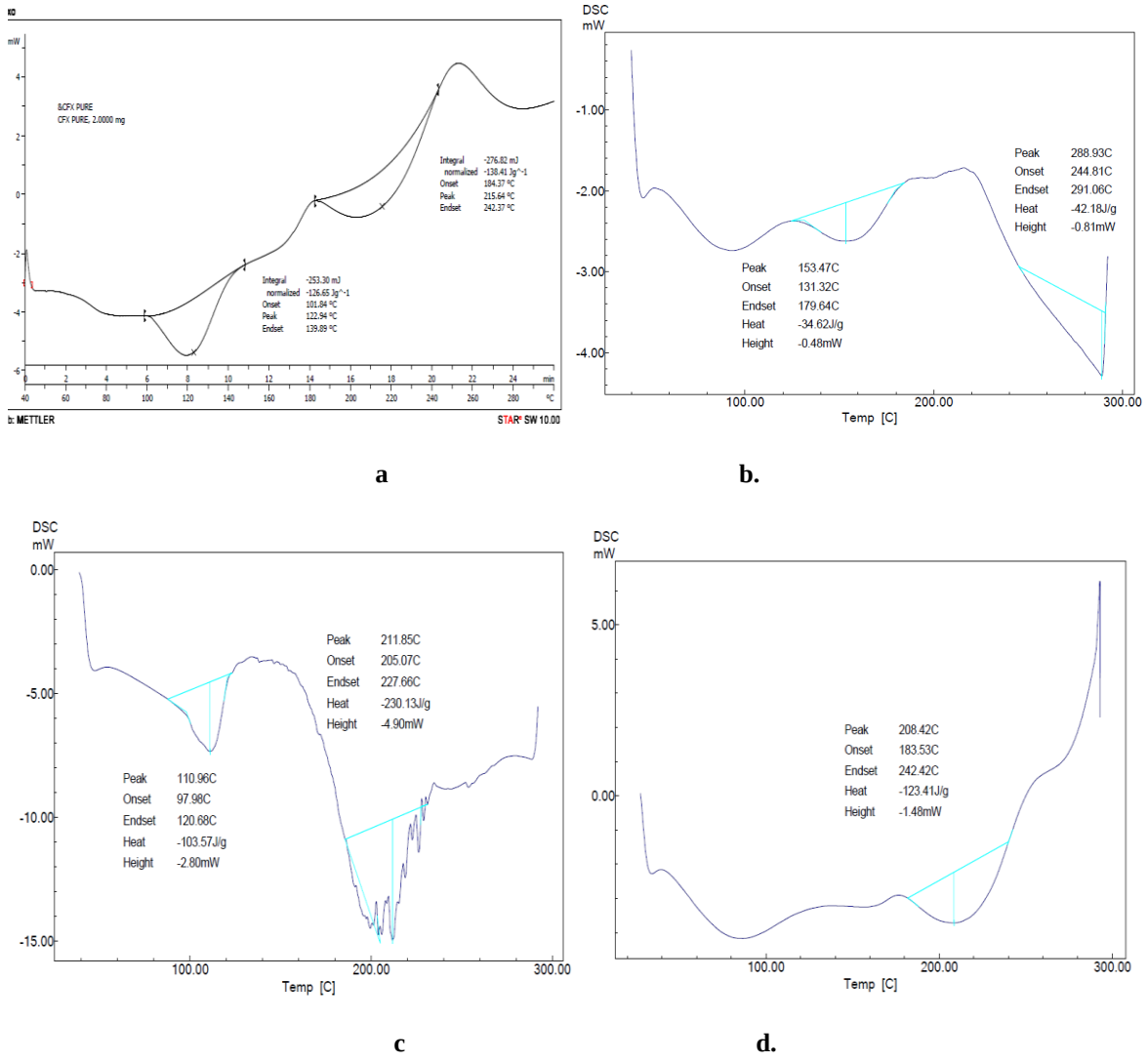


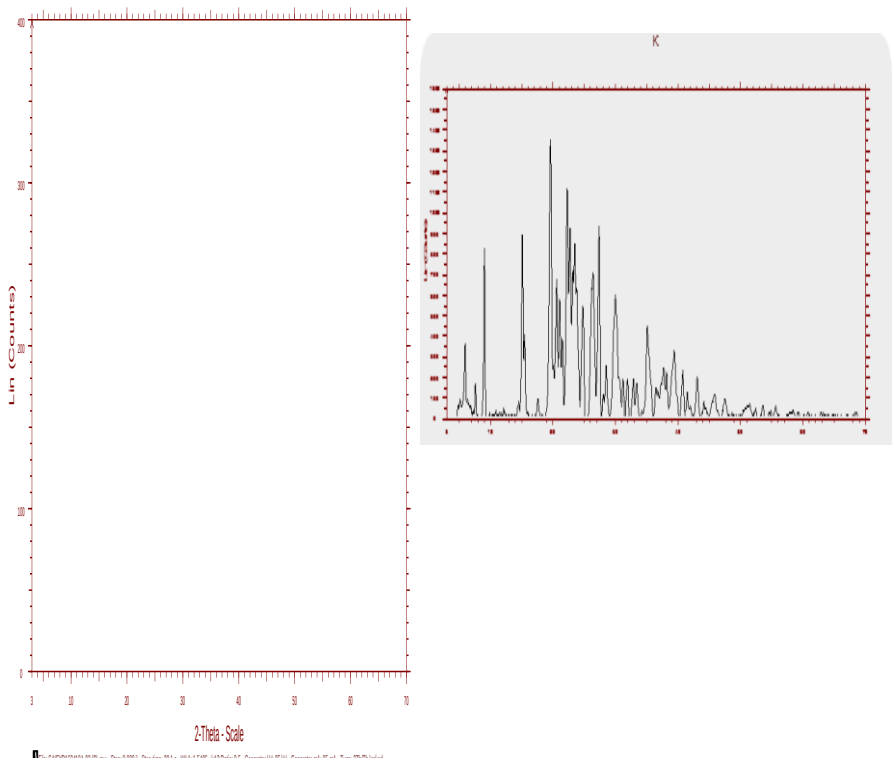
Figure 4: DSC thermogram a. Cefixime b. SD with Kollidon. SD with Urea, d.SD with Gaur Gum.

X-ray Diffraction (XRD)

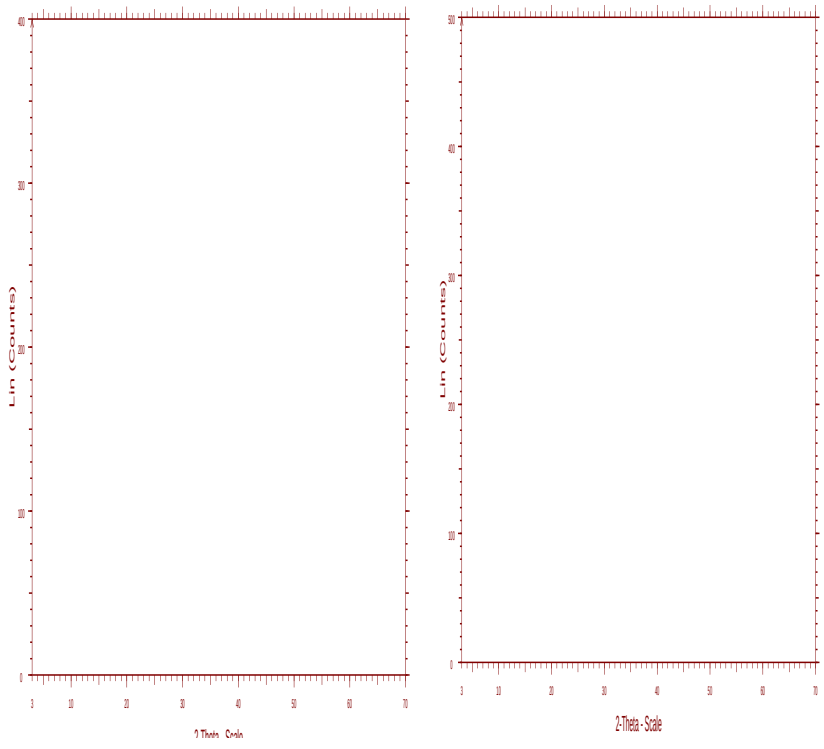
The X-ray powder diffraction images of CFX and SD are shown in Figure 5. Pure CFX showed characteristic diffraction peaks at 2θ positions of 5.89, 8.97, 19.55, 24.745, 26.36, 27.34, 31.88 and 35.112. Pure CFX exhibited sharp and intense peaks in the range of 5°–60° at 2θ angles, which suggested that CFX was present in crystalline form.

The XRD spectrum of solid dispersions with Urea & Gaur both showed the absence of diffraction peaks with lowering of peak heights. This haloness of amorphous system observed in this solid dispersion may be the reason for solubility & dissolution rate enhancement.

However, for the SD, the discriminatory peaks of CFX were clearly absent and halo pattern was observed for spray dried formulation indicating the absence of crystallinity. However, the XRD pattern of the spray drying complex with Kollidon 64 was found to be diffused and different form that of pure cefixime confirming formation of new solid phase. The XRD pattern of spray drying complex is totally diffused, indicating the formed complex has an amorphous nature**.** This amorphous nature of formed SDs may be the reason behind dissolution & solubility elevation of Cefixime [35-37].



a. **b.**



c. **d.**

Figure 5: XRD spectrum of solid dispersion of a. SD with Kollidon 64, b. Cefixime c. Urea d. Gaur.

ATR

ATR spectroscopy was carried out for characterizing the interaction between Cefixime & Kollidon in solid state. Hydrogen bonding is anticipated between Hydroxyl groups of Kollidon 64 & the carbonyl function of Cefixime from the chemical structures. For assessing any possible solid-solid interactions between the drug and carriers, ATR spectra of Cefixime and SDs were noted and the results are shown in Figure 6A and 6B.

ATR spectra of SDs showed presence of all the major peaks of drug indicates absence of chemical interaction.

Broadenings & disappearance of some peaks were observed in IR spectra of solid dispersions. It showed peaks of reduced intensity. Some peaks of Cefixime were disappeared indicating formation of complex in solid state. The stretching vibration of functional group were found to be within range in all solid dispersions as well as in physical mixture indicating absence of any significant chemical interaction in solid state.

The spectrum of SDs showed that a weak-OH stretching vibration peak was observed at 3410.01 cm^{-1}, while Carbonyl stretching at 1761.16 cm^{-1} of drug was absent and only the C=O peak at 1634.23 cm^{-1} was present.

This finding suggested that CFX interacted with Kollidon 64, presumably by hydrogen bonding. Noteworthy here is that the interaction between components increased API's solid solubility by the hydrophilic carrier that is additionally acting as inhibitor of the drug's crystallization [39, 40].

The ATR spectra of neat drug with its solid dispersions are shown in figure 6. Pure Cefixime showed vibrational peaks of -NH2 primary amine at wave number 3287.89 cm^{-1}, N-H stretch at 1661.43 cm^{-1}, C-H at 1545.69 cm^{-1}, C-N stretching at 1591.41 cm^{-1}, N-O stretching at 1382 cm^{-1}, Carbonyl stretching at 1761.16 cm^{-1}. Polymer Kollidon 64 showed presence of a stretching band of ester (-COO) at 1657.33 cm-1.

For Urea, it showed N-H stretching at 3353.59 and 3259.01cm-1, C=O stretching at 1602 cm-1, C-N stretching at 1443.36, C-O stretch at 1018.19 cm -1 while characteristic peak at 865.45 and 835.32 cm-1. The spectrum of Urea- SDs showed that a weak-OH stretching vibration peak was observed at 3452.35 cm^{-1}, while Carbonyl stretching at 1761.16 cm^{-1} of drug was absent and only the C=O peak at 1600.29 cm^{-1} was present.

Gaur gum showed vibrational peaks of N-H stretching at 3244.94 cm-1, C-H stretching at 2907.59, 2841.21, C=O stretching at 1638.02 cm-1, C-N stretching at 1543.59, C-O stretch at 1016.11 cm-1, and characteristic peak at 787.09 cm-1. The spectrum of gaur gum-SD showed that OH- stretches at 3400 cm-1, N-H stretching vibration peak was observed at 3054.48 cm^{-1}, while Carbonyl stretching at 1761.16 cm^{-1} of drug was absent. The spectrum of PEG-SD showed weak O-H stretching at 3415 cm-1, N-H stretching at 3012 cm-1, C-O stretching at 1787.43 and 1613.61 cm-1, and C-N stretching at 1477.33, C-O stretch at 1094.76 cm-1. The spectrum of HPMC-SD showed O-H stretching at 3475.77 cm-1, N-H stretching at 3136.98 cm-1, C-O stretching at 1603.48 cm-1 and C-N stretching at 1467.30 while C-O stretch at 1069.31 cm-1.

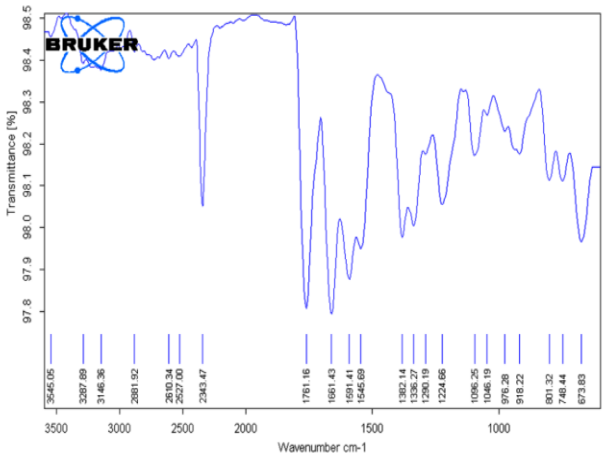


Figure 6A: ATR spectrum of Cefixime.

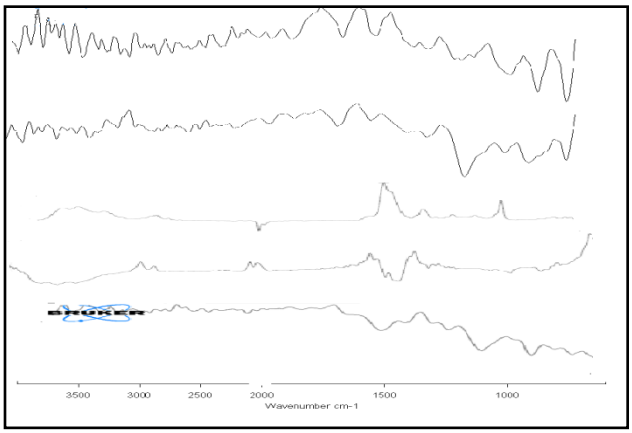


Figure 6B: ATR spectrums of SDs with a: HPMC, b: PEG, c: Guar, d: Urea, e: Kollidon 64.

The IR spectrum of solid dispersion showed peaks of reduced intensity and also some peaks of Cefixime were disappeared indicating formation of complex in solid state. The stretching vibration of above all mentioned functional group were found to be within range in all solid dispersions as well as in physical mixture indicating absence of any significant chemical interaction in solid form.

***In vitro* drug release**

The dissolution outlines of the different SDs of CFX in PBS pH 7.2 are illustrated in Figure 7 & 8. The SDs were capable of increasing the dissolution rate of Cefixime which is in conformity amid the enhancement of Cefixime's solubility in these formulations. Drug dissolution rates were comparably high for SDs than their physical mixture and drug alone, suggesting that compaction processes with hydrophilic polymers improve the drug dissolution rate. It may be due to stagnant layer formed by polymer by increasing contact between drug particle and dissolution medium [41].

Pure Cefixime exhibit a small dissolution rate, by way of a 43.52% release, within 30 min where it reached just 51.37% after 45 min. For Kollidon 64 SD physical mixture released 61.02% of drug at 45 min. Physical mixture did not show any significant improvement in dissolution rate. This result attributed to hydrophobic nature of drug due to which drug particle float on the plane of the dissolution medium and prevents its intimate contact with the dissolving medium. The dissolution of SD formed by spray drying by means of Kollidon, inside 7.2 po4 buffer showed 88.68%, Cefixime release in 20 min, The dissolution of SD formed by solvent evaporation method with other hydrophilic polymers like Urea, Gaur, PEG 6000, HPMC in 7.2 po4 buffer showed 84.7%, 52.71% 50.25%, 49.48% drug being released within 20 min.

These differences in the % drug release from these solid dispersion might be due to formation of different types of solid dispersions like glass matrix in case of Kollidon or PEG (Tantoshaiyakul 1996) while for Urea, Gaur, HPMC it may be present as amorphous phase.

The formulation of Kollidon 64 KD released 69.95% of Cefixime within 20 min, showing a 3-fold raise in its dissolution through this period. The formulations by SE, LY displayed a release of 85.57% and 87.45% correspondingly within 20 min. The formulations by means of MW (86.05%) within 20 min with SY displayed parallel release curves along with higher dissolution rates as compared to the pure CFX and other dispersions. So, the formulation SY with 97.28% release in 45 min was preferred for more study.

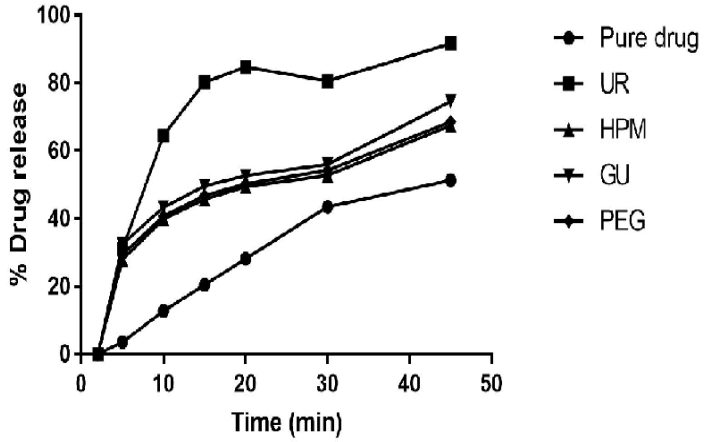


Figure 7: The dissolution profiles of solid dispersion (SD) with UR: Urea, HPM: HPMC, GU: Guar Gum, PEG: Polyethylene glycol.

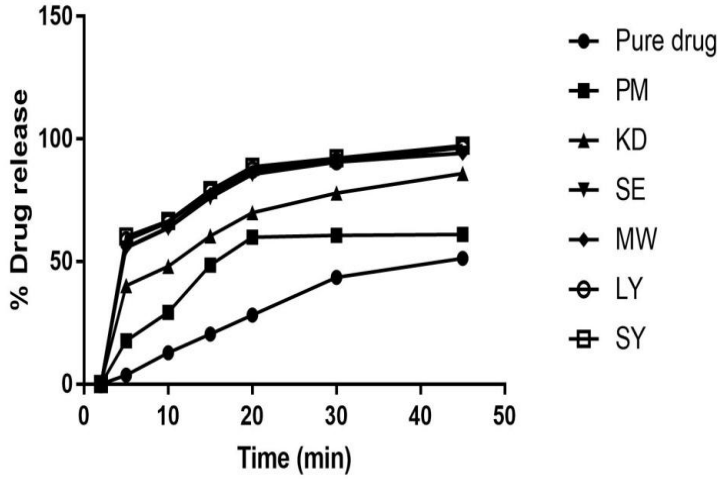


Figure 8: Dissolution of solid dispersions with Kollidon 64 prepared by different solubilizing method in phosphate buffer

In solid dispersions, faster dissolution of CFX can be explained by increased drug wetting in the dissolution medium and the transformation from crystal to the amorphous nature (as displayed by XRD & DSC outcomes) [42].

Riegelman & Chiou showed that the glass solution configuration can enlarge drug dissolution & absorption. This homogeneous system, have vitreous form of the hydrophile that solubilizing the API in its matrix. The Polyvinylpyrrolidone, dissolve in organic solvents transform to a glassy condition after solvent evaporation [43-45]. The decrease in particle size may have lead to increase dissolution of Cefixime in solid dispersion. The amorphous state tends to be more soluble given that no energy is requisite to rupture up the crystal lattice through the dissolution course [46].

The small increase of drug dissolution after physically mixed with the hydrophilic Kollidon might be accredited to the local solubilization action of the carrier operative in the micro-environment or the hydrodynamic layer surrounding drug particles in the primary stages of the dissolution process or due to the surfactant-like properties of Kollidon that improve the drug wettability by reducing the interfacial tension between the water insoluble Cefixime's particles with dissolution medium, consequently mounting the wettability & in effect dissolution of the Cefixime. The kneaded products display slightly more enhancement in Cefixime dissolution than physical mixing. The small raise in Cefixime dissolution than physical mixtures is probably owing to the augment in the Cefixime-Kollidon contact surface which occurred due to increased mechanical treatment [47].

Binary systems prepared by microwave irradiation showed more enhancements in the dissolution of Cefixime than material mixture & knead prouduct which may possibly be endorsed toward the better contact amid the Cefixime & the Kollidon by virtue of the power of microwave irradiation. The period of irradiation using microwave was selected on the basis of preliminary study where different times ranging from 4 to 8 min were applied for the preparation of the binary systems. The optimum irradiation timing was 7-8 min. The higher irradiation time gives reduction of dissolution time that might be due to increased bond interaction between the Kollidon and drug.

The spray-dried systems showed marked increase in CFX dissolution compared to the other methods. This distinct dissolution increment could be accredited mainly to the formation of soluble structure of the Cefixime by means of the Kollidon plus augmented energy owing to diminished crystallinity subsequent to dispersion [42].

In lyophilization, configuration of solid solution of the Cefixime in the lyophilized products & diminished drug's particle size to the molecular level using carrier into the dissolution medium, leading to faster dissolution [48-50].

This enhanced cumulative effect might be due presence of Kollidon, a hydrophilic polymer causing wetting of drug particles in both methods and also formation of micron size particles with increased surface area in case of spray drying where it showed complete drug release and high solubility compared to earlier method hence it was further characterized. Solid dispersion, enhanced wettability by polymer along with reduction in particle size may be the reason behind dissolution rate enhancement.

We studied the effect of Kollidon-64 on solubility Cefixime while work was focused on employing simpler and cheap techniques namely; kneading, microwave irradiation and freeze-drying method, spray drying method. Kollidon 64-SD prepared by spray drying method showed complete drug release and high solubility compared to earlier method hence it was further characterized.

Dispersion of drug into glassy matrix of amorphous polymer (Kollidon VA64), transition of solid drug from crystalline to amorphous form, reduced particle size and improved surface wetting are the mechanisms responsible for dissolution rate enhancement of solvent evaporated Sds. These mechanisms are supported by data obtained from PXRD, DSC, and SEM. Various studies have shown that freely water soluble carriers inhibit crystallizing the drugs in dispersed system ensuing within amorphous form. This inhibiting property may be possibly because of hydrogen bond formation in polymer & drug as well as due to entrapping the drug in the polymer matrix at some point in evaporating the solvent otherwise a mixture of both [51-53].

More than a few reasons like better wet ability, speedy dispersion inside dissolution medium, the solubilizing outcome of the hydrophile, surface tension reduction between solid insoluble drug and dissolution medium were responsible for dissolution improvement.

Antimicrobial studies

The antimicrobial activity of binary systems of CFX with Kollidon against Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) species was checked by disk diffusion method and compared with the pure CFX. The zone of inhibition can be seen in figure 9. These studies revealed that binary systems of CFX have shown greater antimicrobial activity than CFX alone. However, CFX–KOL spray dried has shown significant and highest zone of inhibition against both the microorganisms as compared to pure CFX alone and other binary systems. The greater antimicrobial activity of CFX–KOL spray dried could because of the Kollidon 64's capability in releasing greater Cefixime quantity as of the binary system [43].

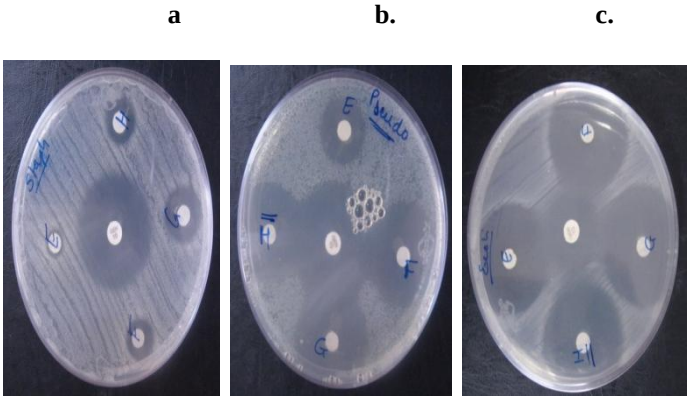


Figure 9: Antimicrobial study: zone of inhibition. *Staphylococcus aureus* a. *Pseudomonas aerogenosa* b. *E. coli.* Where E; Cefixime, F: Kollidon 64 sd, G: Gaur sd, H: Urea sd

***In-Vivo* absorption study in wistar rats:**

The mean plasma concentration time profile for CFX following oral administration of pure CFX and KOL-SD are shown in Figure 10. And the pharmacokinetic values are illustrated in Table 2. The differences in the profile of the concentration time profile between the two treatments were found, expressed by higher Cmax and almost same tmax for the KOL-SD. Dosing the aqueous suspensions of Cefixime resulted in the average Cefixime plasma concentrations. However, the AUC was 1.9 times greater when Cefixime was administered as SD, compared with the AUC obtained for the aqueous Cefixime suspension. The T_{max} (4 hr) after SDs dosing was different than the T_{max} obtained within aqueous suspensions (3 hr). For two treatments, the differences for Cmax ($p = 0.006$) and tmax ($p = 0.03$) were statistically significant. These results reveal that formulation of Cefixime as SDs results in a significantly ($p= 0.05$) increased absorption of Cefixime, compared with that from the aqueous suspensions.

Based on these results, it can be concluded that the rapid and enhanced absorption of CFX obtained from the KOL-SD, with higher C_{max} and almost same t_{max}, could be due to improved dissolution resulting from diminished unit dimension (of particle), augmented effective surface area, increased contacting in solubilizer & Cefixime, and enhanced wettability.These results are in agreement with what was reported in literature regarding the enhanced solubility of poorly soluble drugs. Observations similar to this have been documented for solid dispersions of poorly soluble drug like Naproxen in PEG 4000, 6000 and 20,000 [54]. The better oral availability of SD could be described by the effects like the smaller drug particles & diminished stagnant layer width due to which drug absorbed more rapidly through the gastrointestinal wall.

Table 2: Pharmacokinetic parameters following oral administration of solid dispersion and CFX (n = 6).

Parameter	CFX	SD
$AUC_{0-12\ h}$ µg·h/mL	11.28	20.39
C_{max} µg/mL	1.365±0.01607	3.093±0.0732
T_{max} h	3	4

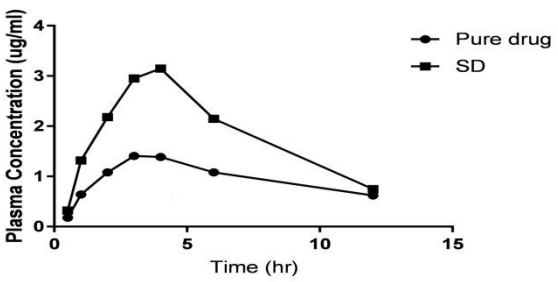


Figure 10: The mean plasma concentration-time profiles of solid dispersion And CFX.

CONCLUSION

The present study gave interesting insights into the capability of various pharmaceutical interventions in enhancing the solubility of CFX. A clear impact of particle size reduction could be observed, wherein spray drying improved solubility marginally, whereas solvent evaporation, lyophilization and microwave irradiation provided significant improvement in solubility of CFX.

From the above results, it is likely to conclude that spray drying method showed better solubility and dissolution enhancement for Cefixime compared to other methods. These conditions showed an initial burst effect of more than 50 % in the first 5 min and more than 80% dissolution within 30 min. Therefore, this system can be considered as efficient tool for enhancing the dissolution of Cefixime with the possibility of improving the bioavailability and thus reducing the dose of the drug.

Molecular dispersion of CFX in solid dispersion by spray drying with Kollidon 64 gave significant improvement in AUC (0−t), C_{max}, and thus subsequently oral bioavailability of poorly soluble drug. Formulation approach involving incorporation of hydrophilic polymer, Kollidon 64, increases its antibacterial activity by enhancing its solubility, indicating improvement in its antibacterial use for treating infections. Thus, Kollidon 64 can be utilized as hydrophilic solubilizer in solid dispersion preparation of BCS class 2/4 drugs.

This work emphasize the value of using multiple delivery hurdles like solubility, dissolution kinetics, and its antibacterial study, to achieve considerable improvement of oral absorption CFX. This study leads to conclusion that selection of solubilizer is critical for the development of formulation of BCS class 2/4 drugs. Hence, in developing orally administered formulation depending on experimental data, the type of polymer and drug-polymer ratio are the critical factors. In future, other solubilizers should be assessed using various advanced techniques going to the molecular level for particular class of drugs which would help formulators in drug development process.

ACKNOWLEDGMENTS

The authors are grateful to Sophisticated Analytical Instrumentation Facility (SAIF) at Cochin University, Kochi for the PXRD, SEM studies. I am also thankful to the Glenmark pharmaceuticals, Sinnar, Nashik for providing gift sample required for the research work. I would like to thank BASF for giving gift sample for the research.

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