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Research Article

SOLUBILITY AND DISSOLUTION ENHANCEMENT OF CEFIXIME USING NATURAL POLYMER BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Solid dispersions (SDs) are one of the most promising strategies used to improve the solubility of poorly water soluble drugs. This technology is mainly applied to improve the solubility of Class II and Class IV drugs. Cefixime is an oral third generation cephalosporin antibiotic used in the treatment of gonorrhea and tonsillitis, which has oral bioavailability of 40-50% and it belongs to the BCS class-II. Many attempts are made in the past to increase its solubility by preparing its solid dispersions. However, very few literature reports are available wherein natural polymers are used for preparation of solid dispersions. In the present work, an attempt is made to increase the solubility of Cefixime by preparing its solid dispersions using natural polymer i.e.., guar gum. Various techniques used for preparing Solid dispersions are by Physical mixture, Kneading and Solvent evaporation methods using different drug-polymer ratio. Thus prepared solid dispersions were evaluated for percentage yield, drug content, saturation solubility and in-vitro dissolution studies. The result obtained from above studies indicated that, the solubility and dissolution of Cefixime solid dispersions was improved as compared to pure drug by all the methods employed. Among various methods employed, solvent evaporation method produced good results compared to Physical mixture, Kneading method. Hence, Solid dispersion technology can be used to improve the solubility of Cefixime.

Key words: Solid Dispersions, Cefixime, solvent evaporation method, in-vitro dissolution study.

INTRODUCTION

The therapeutic efficacy of a drug product intended to be administered by the oral route mainly depends on its absorption by the gastrointestinal tract. However, for a drug substance to be absorbed, it needs to be solubilised. Solubility is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and low permeability. By improving the dissolution profile of these drugs, it is possible to enhance their bioavailability and reduce side effects. Solid dispersions are one of the most successful strategies to improve dissolution rate of poorly soluble drugs. SDs can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties[1-2]. Solid dispersion is a unique approach which was introduced by Sekiguchi and Obi. In this method, the drug is dispersed in extremely fine state in an inert water soluble carrier in solid state.

Number of insoluble drugs has shown to improve their dissolution character when converted to solid dispersion. Solid dispersion technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers[3]. A number of freely water soluble materials such as citric acid, succinic acid, bile acids, sterols and related compounds and polymers like polyvinyl pyrrolidone and poly ethylene glycols are used as carrier for solid dispersions. By this approach the dissolution rate and bioavaibility of poorly soluble drugs can be increased[4]. The use of hydrophilic polymers as carriers for the dissolution enhancement of poorly water-soluble drug is increasing.Various hydrophilic carriers such as natural polymers viz. guar gum has been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs[5].

Cefixime is an oral third generation cephalosporin antibiotic which is used in the treatment of gonorrhea, tonsillitis and pharyngitis[6-7]. Cefixime is employed in the treatment of a variety of respiratory tract infections and otitis media[8]. However, the low aqueous solubility and poor dissolution of this drug in gastric fluid affects its rate of absorption, resulting in a low and variable oral bioavailability. Hence, the present study was aimed to increase the solubility and bioavailability of Cefixime using natural polymer i.e. gaur gum. Cefixime solid dispersions were prepared by different techniques viz. physical mixture, solvent evaporation method and kneading method.

EXPERIMENTAL

Materials

Cefixime was received as gift sample form the Karnataka antibiotics pharmaceutical Limited, Bangalore and all chemicals used are purchased from the S.D Fine chemicals, Mumbai of analytical grade.

Methods

Preparation of Physical Mixtures (PM) and Solid dispersions

PM were prepared by taking Cefixime and guar gum in the glass mortar and mixed by light trituration for 3 min. PMs of different proportions of Cefixime and Guar Gum were prepared i.e.. 1:1, 1:2, 1:3. The mixture was sieved and the powder fraction corresponding to mesh size less than 30 was collected for further investigation.[9-10]

Kneading method

Drug and polymer was mixed with the small amount of the solvent i.e. water to form a thick paste by kneading and hence it was dried at 45°C in an oven. The mass was passed through the sieve no. 30 and stored in the dessicator.[11]

Solvent evaporation method

The drug and the polymer were dissolved in sufficient volume of dichloromethane with continuous stirring. The solvent was then completely evaporated at room temperature with continuous stirring to obtain dry granules. The resulting solid dispersion was stored in airtight container till further use.[12]

Evaluation of prepared solid dispersions

Percentage yield

Percentage practical yield were calculated to know about percent yield or efficiency of any method, thus it helps in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation:[13]

$$\text{Percentage yield} = \frac{\text{Practical mass (solid dispersion)}}{\text{Theoretical mass (drug + carrier)}} \times 100$$

Drug content

The Physical mixture and solid dispersion equivalent to 50 mg of drug were taken and dissolved separately in100 ml of phosphate buffer 7.4. The solutions were filtered and were further diluted such that the absorbance falls within the range of standard curve. The absorbances of solutions were determined at 266 nm by UV-visible spectrophotometer. The actual drug content was calculated using the following equation as follows:[14]

$$\%\ \text{drug content} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

Fourier Transform Infra red spectroscopy (FTIR)

IR spectra of Cefixime and its solid dispersions are identical. The principle IR absorption peaks of Cefixime solid dispersions were observed and found to be identical with the spectra of Cefixime pure drug. Thus, from the spectra it was understood that there was no interaction between Cefixime and the carriers used in the preparation of solid dispersions which can be observed in fig-1, 2, and 3.[15]

Determination of saturation solubility

Saturation solubility was determined by using shake flask method. Excess quantities of drug and prepared SDs were added in 25 ml distilled water in 250 ml flasks which were then incubated in orbital shaker at 37°C and at 100 rpm for 72 hrs. Absorbance of resulting solution was measured on UV spectrophotometer at 266 nm. [16]

***In- vitro* dissolution studies**

In- vitro dissolution studies were done in USP Dissolution apparatus containing dissolution medium (phosphate buffer pH 7.4). Pure drug and SDs powder was put in 900 ml of the dissolution media, temperature maintained at 37 ± 2□C and speed was set at 50 rpm (USP XXVI). The samples (5.0 ml) were withdrawn at various time intervals, filtered through Whatman filter paper and analyzed by UV spectrophotometer at 266nm. The dissolution was evaluated as dissolution efficiency at 90 min.[17-18]

RESULTS AND DISCUSSION

Solid dispersions of the Cefixime with guar gum were prepared by physical mixture, kneading and solvent evaporation methods in various ratios. The prepared solid dispersions of Cefixime were evaluated for percentage yield, drug content, phase solubility studies and in-vitro dissolution studies**.** Data of evaluation study was represented in Table-2. The percentage yield of the solid dispersions was found to be high in SA_3 (94.5%) and the drug content was found to be high in SA_1 (94%) as compared to other formulations. The results of IR spectra confirmed that, there was no interaction between Cefixime and Guar Gum (fig: 4, 5, 6). Solid dispersions for 1:3 ratio have shown maximum increase in Saturation solubility as compared to other ratios (table-2). The observed increase in the solubility of Cefixime in solid dispersions is thought to be attributable to the solubilization effect of the guar gum. Fig:-1, 2, 3 gives the in-vitro dissolution profiles of pure drug of Cefixime and its solid dispersions by different methods. The result indicated that, maximum percentage of drug release was found in SA_3 (44.73) and the dissolution rate of other solid dispersions are also high in contrast to the pure drug (table-2). As the proportion of Guar Gum increased, dissolution rates have also been increased. The improvement of dissolution may be due to its hydrophilic nature of the carrier. Thus it can be concluded that the solubility of the poorly soluble drug, Cefixime can be improved markedly by using solid dispersion technique and the carrier, guar gum has increased the dissolution of the drug without any interaction.

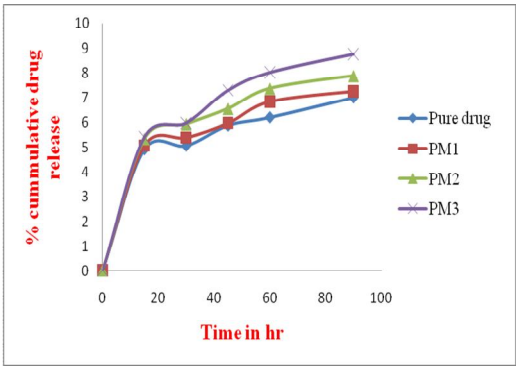

Fig. 1: Dissolution of cefixime from guargum solid dispersion (physical mixture method) of different drug:carrier ratios

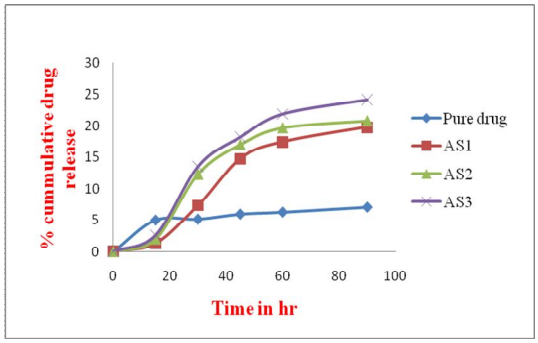

Fig 2: Dissolution of cefixime from guargum solid dispersion (kneading method) of different drug:carrier ratios

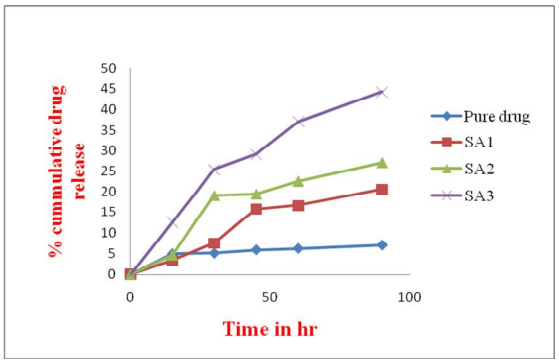

Fig 3: Dissolution of cefixime from guargum solid dispersion (solvent evaporation method) of different drug:carrier ratios

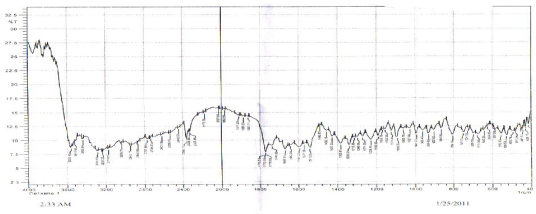

Fig. 4: IR spectra of the Cefixime

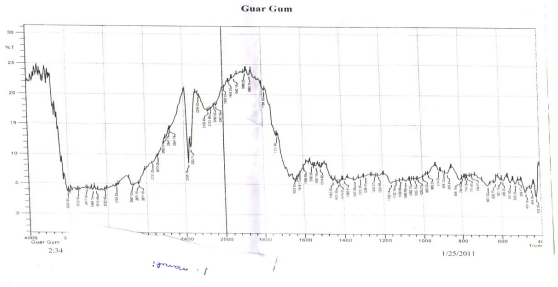

Fig. 5: IR spectra of the guar gum

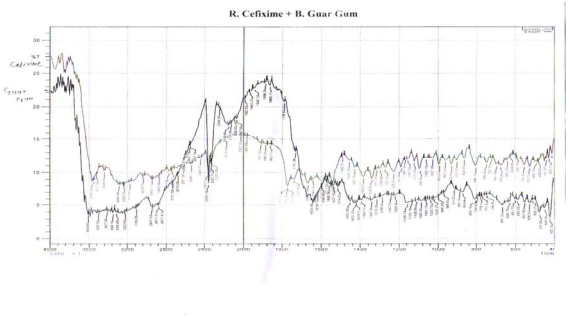

Fig. 6: IR spectra of the Cefixime and guar gum

CONCLUSION

The solid dispersions of Cefixime with the guar gum as carrier were prepared and evaluated. IR has shown that there was no interaction between the drug and carrier (fig 4, 5, 6). The solubility and dissolution studies have shown that there is a possibility of improved solubility of Cefixime through solid dispersion with natural polymer viz..,guar gum. A maximum increase in dissolution rate was obtained with Cefixime: guar gum solid dispersion with a weight ratio of 1:3 prepared by solvent evaporation method (Table-2) though solid dispersion prepared by kneading method showed faster dissolution rate when compared with that of pure drug.

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Table 1: Formulation of Solid Dispersions

Formulation code	Carrier	Drug: polymer ratio	Method used
PM_1	guar gum	1:1	Physical mixture
PM_2	"	1:2	
PM_3	"	1:3	
AS_1	"	1:1	Kneading method
AS_2	"	1:2	
AS_3	"	1:3	
SA_1	"	1:1	Solvent evaporation Method
SA_2	"	1:2	
SA_3	"	1:3	

Table 2: Evaluation parameters for the different formulations

S. No.	Formulation code	Percentage yield (%)	Drug content (%)	Saturation solubility in distilled water (mg/ml)	% Cumulative drug release at the end of the dissolution
1	PM_1	94.18	93.31	0.35	5.72
2	PM_2	91.58	89.26	0.54	7.87
3	PM_3	91.03	90.72	0.61	8.30
4	AS_1	92.5	86.82	0.75	19.79
5	AS_2	91.33	90.28	0.89	20.78
6	AS_3	95.5	87.84	1.04	24.19
7	SA_1	93	94	1.16	20.62
8	SA_2	91.66	89.71	1.27	26.98
9	SA_3	94.5	87.14	1.32	44.23

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