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International Journal of Research in Pharma & Pharmaceutical Sciences
Volume 1 Issue 2

Solubility Enhancement of Cefadroxil Using Polymer PVP K-30 by Solid Dispersion Method

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ABSTRACT

The drug administration through oral route is mostly preferred because ease of ingestion and convenient route of drug delivery. But the disadvantage of this route is low bioavailability which associated with the poor solubility of drug in water. The solid dispersion is mostly used for the solubility enhancement of poorly soluble drug. Cefadroxil, is an anti-bacterial drug, poorly soluble in water. Therefore, cefadroxil solid dispersion is prepared with different amount of polymer (PVP K30) and solvent (methanol). Three solid dispersion formulations were prepared and evaluated for production yield, Entrapment efficiency and dissolution studies. The result indicates that solid dispersion formulations 1:2 and 1:3 significantly improved the cefadroxil solubility.

Keywords : *Solid dispersion, solubility enhancement, PVP K30, solvent evaporation,drug release.*

INTRODUCTION

Therapeutic effectiveness and absorption are mainly dependent on the solubility of the drug. Drug with a good solubility can get absorbed speedily as a result drug action can be achieved at a greater pace. Poor solubility of drug can hinder the therapeutic action because of decreased bioavailability [1]. A large number of new drugs are lipophilic in nature and hence are not well absorbed after administration of oral route so the oral delivery of the drugs can be related with low bioavailability. Therefore, to obtain the desired action of drug solubility of the formulation should be monitored and improved in every possible way. Various approaches like drug micronization, nanosizing, salt formation, complexation and liquisolids are developed. There is ongoing research on many hydrophilic carriers which can improve the dissolution and solubility of the drug drastically. There are different methods to increase the solubility of the drug by modification of various physical and chemical characteristics. One such potent method to enhance the physicochemical property (solubility) is “Solid Dispersion”, is a technique in which one or more pharmaceutically active substances are dispersed in the solid medium (carrier) using different ways in order to get a better solubility [2]. The term “Solid dispersion” refers to two different components ‘Hydrophobic Drug ’ and ‘Hydrophilic carrier’. As the solid dispersion comes in contact with the aqueous media, the carrier dissolves and the drug gets released as fine particles hence enhancing the solubility and dissolution of the drug.

It has always been challenging to make the formulation with good aqueous solubility by using conventional methods but modern techniques have opened the rooms for improvement and helped to increase the therapeutic effectiveness irrespective of

the dose. Solid dispersion systems provide bio available oral dosage forms and can also act as functional carriers which can benefit by targeting the release of soluble drugs for good rate of absorption. Solid dispersions were found to reduce the food effects on drug absorption therefore the improved absorption efficiency was demonstrated to accelerate the onset of action for drugs such as NSAIDS. From this, we can say, solid dispersion using hydrophilic polymer is very easy, convenient and cost-effective method for solubility enhancement [3].

Cefadroxil is first generation cephalosporin acting as broad-spectrum antibacterial drug. The antibacterial activity is due to beta-lactam ring which gets hydrolyzed in aqueous medium. It can bind with penicillin binding protein present inside the bacterial cell and inhibit the growth of microorganism.

It can be characterized by poor solubility and dissolution leading to low bioavailability of drug. It is widely used for the treatment of urinary tract infections, skin structure infections caused by staphylococci and throat infections like pharyngitis and tonsillitis.

Cefadroxil is BCS class II drug which has low solubility and good permeability. Cefadroxil is consumed orally with dose of 1 gram, once or twice a day as per requirement. The water solubility of drug is 0.399mg/ml therefore there is a need of enhancement of dissolution and solubility and dissolution which can be achieved by the method of solid dispersion [4].

PVP K is hydrophilic polymer and has amorphous physical state. Solubility in water as well as organic solvents like ethanol, isopropyl alcohol and chloroform makes it suitable for solid dispersion via solvent evaporation or precipitation method.

The Aim of the study was to enhance the oral solubility and dissolution of Cefadroxil using solid dispersion method using PVPK30 a hydrophilic carrier with solvent methanol for further improvement of drug dissolution.

MATERIALS AND METHODS

Materials

Cefadroxil drug and PVPK-30 polymer was purchased from Chemdyes Vadodara, Gujarat, India, Methanol from the Samir tech-chem Pvt. Ltd. All other ingredients used are of analytical grade.

Method

Preformulation studies Cefadroxil

Determination of Cefadroxil Melting Point

Capillary tube method was used to determine the melting point of Cefadroxil powder. The tube was dipped in the drug powder closed from one end and placed inside the melting point apparatus; the temperature was increased gradually. The temperature at which the powder converts into liquid was marked as melting point [5]. (This procedure was carried three times and the results were presented as mean ± standard deviation).

Solubility Study

For the preparation of solid dispersion, proper solvent selection was necessary. So, the solubility of cefadroxil was examined using different solvents such as, water, ethanol, methanol and chloroform [6].

Determination of Cefadroxil λ Max

The solution of Cefadroxil 10µg/ml in methanol was prepared. λ max of the drug was calculated by UV-visible spectrophotometer at 200-400nm.

Calibration Curve of Cefadroxil

Calibration curve of Cefadroxil was made by preparing series of dilutions of Cefadroxil with different concentrations (2,4,6,8,10,20 µg/ml) in methanol from a

stock solution containing 100µg/ml. Then the absorbance was measured at λ max. The graph of absorbance vs concentration was plotted [7].

Phase Solubility of Cefadroxil

A phase solubility study of Cefadroxil was performed based on the method described by Higuchi and Connors. The miscibility of Cefadroxil with PVP K30 was evaluated. In beaker stock solution of polymer PVP K30 (100 µg/ml) was prepared. From these different solutions in range of 20 to 100 µg/ml were prepared. An excess quantity of Cefadroxil was added to 10 ml each of the solutions. The solutions were shaken in an environmental shaker at 37 °C for 12 hours. Samples were filtered with Whattman filter paper and analyzed spectrophotometrically (Shimadzu U-1800, Japan) for dissolved drug at 263nm. The apparent (1:1) stability constant was calculated from the phase solubility graph using following equation.

$$Ks = \frac{slope}{S°(1 - slope)}$$

Where, S^0 is the solubility of Cefadroxil in absence of polymer.

Values of Gibb's free energy of transfer (ΔG°) of Cefadroxil from pure distilled water to polymer solution was calculated using

$$\Delta G° = -2.303RTlog(\frac{S}{S°})$$

Where S / S^0 is the ratio of the solubility of Cefadroxil in solution of polymer to that of the pure distilled water [8].

Preparation of Cefadroxil Physical Mixtures

There were three cefadroxil physical mixtures (1:1, 1:2, 1:3) were prepared by mixing the appropriate amount of pure cefadroxil powder and polymer (PVP K-30) in mortar and pestle.

Preparation of Cefadroxil Solid Dispersion Formulations

These formulations were prepared by taking drug and polymers in different ratios and using the solvent evaporation method. Three solid dispersion formulation 1:1, 1:2, 1:3 was prepared according to Table 1, the drug and polymer were dissolved in appropriate amount of methanol, poured in Petri dish and placed in oven at 40^0C overnight to ensure complete evaporation and the solid dispersion was collected [7,9].

Table 1: The Composition of Cefadroxil Solid Dispersion Formulation

Formula code	Cefadroxil (%)	PVP K-30 (%)
F1	1	1
F2	1	2
F3	1	3

Evaluation of Cefadroxil Solid Dispersion Formulations

Determination of Production Yield

Production yield of all three solid dispersion was determined using three steps

1) Amount of initial weight of solid raw materials
2) Final weight of Solid dispersion
3) Calculation according to the following equation

$$Production\ yield = \frac{Practicalweight}{Theoreticalweight} X100$$

Entrapment Efficiency of Cefadroxil Solid Dispersion

The Cefadroxil content in solid dispersion was determined by UV spectroscopy. Weight prepared solid dispersion equivalent to 10 mg of Cefadroxil was dissolved in 10 ml of methanol. The spectrophotometric absorbance was measured and the drug content was calculated from the calibration curve and represented as percent entrapment efficiency [10].

$$Entrapmentefficiency = \frac{ActualweightofCefadroxil}{TheoreticalweightofCefadroxil} X100$$

Fourier Transform Infrared (FTIR) Spectroscopy of Cefadroxil

FTIR spectra of pure Cefadroxil, PVP K-30 and the drug with its solid dispersion was obtained by a Perkin-Elmer Fourier transform infrared spectrophotometer. The scanning range used was 2000 to 400 cm^{-1}.

Drug Release Rate Studies (Dissolution Studies)

Dissolution studies were performed for pure Cefadroxil and prepared solid dispersion by using USP type 2 apparatus. 40 mg pure cefadroxil and solid dispersion equivalent to 40 mg pure cefadroxil were filled into empty gelatin capsule. The dissolution test was performed by using 900 ml water as dissolution medium, maintained at 37° C. The basket was rotated at 50 RPM which mimic the peristaltic movement of gastric fluid. With different time interval (20, 40, 60, 80, 115, 145 min) a sample (5 ml) was collected and analyzed using UV spectrophotometer. The sink condition was maintained [11].

RESULT AND DISCUSSION

Characterization of Cefadroxil

Determination of Cefadroxil melting point

The melting point of Cefadroxil was found to be 197°C. The results were verified from several references. It also, indicates the purity of cefadroxil powder which has been used for the further studies [12].

Solubility Study

The solubility of cefadroxil was examined in different solvents in various descriptive terms according to the drug dissolved in the solvent and discussed in Table 2.

Table 2: Definition of Solubility

Descriptive terms	Approximate volume of solvent in milliliters per gram of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Insoluble	More than 10,000

Cefadroxil is very slightly soluble in water and ethanol. In methanol it is freely soluble and it is sparingly soluble in chloroform.

Methanol is selected for this solubility enhancement experiment because the drug and polymer both having good solubility in methanol. Therefore, the solid dispersion was prepared using the methanol, and it was found that the solubility was improved, solid dispersion was sparingly soluble in water that leads to increase the bioavailability and also helpful in reduction of dosage strength.

Determination λmax of Cefadroxil

The solution which was used for scanning includes 10 µg/ml of Cefadroxil mixed with methanol using UV spectrophotometer at the wavelength of 200-400nm. The highest peak was observed at 263nm. The result was affirmative when cross-checked with the given result [13].

Calibration curve of Cefadroxil

The calibration curve obtained by using methanol was depicted the following figure 1. Straight line was observed when the graph of absorbance vs concentration was plotted. From the obtained results, we can conclude that calibration curve follows the Beer's law among the concentrations which have been used for the testing [14].

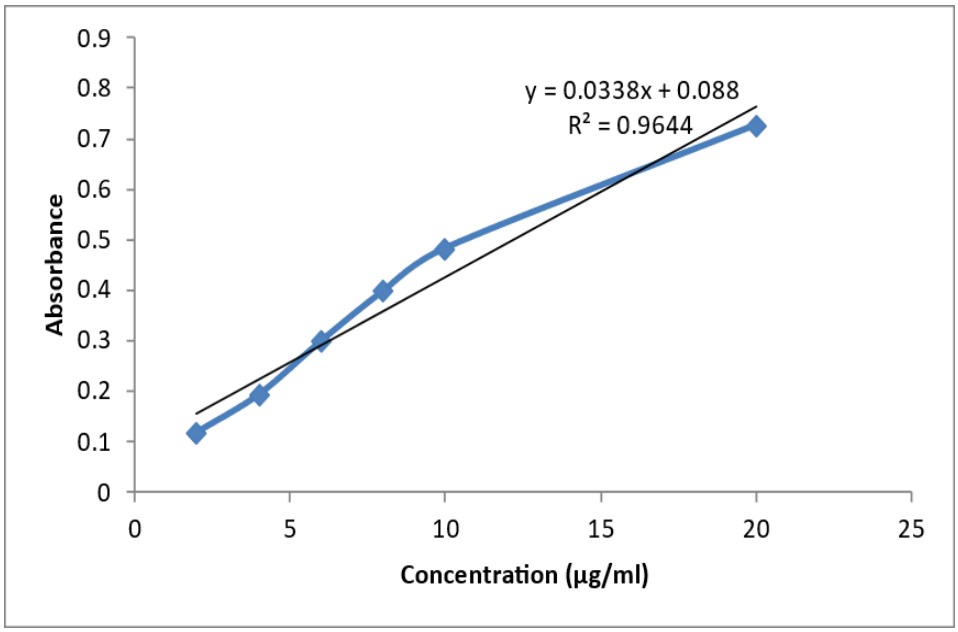

Fig.1. Calibration Curve of Cefadroxil

Phase Solubility study

Following table 3 shows the Gibb's free energy of transfer (ΔG°tr) for the solubilization process of Cefadroxil in different concentration of polymer PVP K 30 solutions.

Table 3: ΔG° for the Solubilization Process of Cefadroxil in Polymer Solution

Concentration of polymer (%)	ΔG° KJ/mol at 37 □C
2	-1972
4	-3044
6	-4341
8	-4957
10	-5627

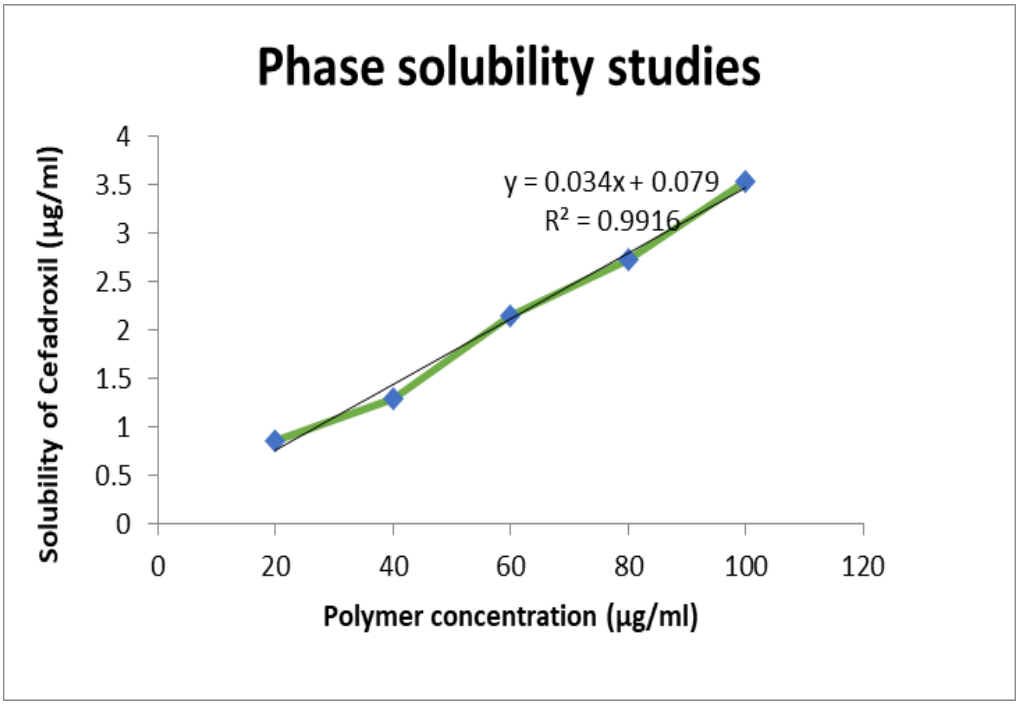

Fig. 2. Phase Solubilities studies of Cefadroxil in different concentration of Polymer

The solubility of Cefadroxil in water was found to be 0.0033 µg/ml. From these phase solubility studies it was concluded that solubility of Cefadroxil increased with increase in concentration of polymer from 2% to 10%. The regression coefficient (r^2) value of Cefadroxil for polymer was 0.991. It was evident from the regression coefficient values that solubility of Cefadroxil in PVP K 30 solution bears the linear relationship. Further, as shown in table no. 4, the values of Gibb's free energy of transfer (ΔG°tr) were negative indicate a spontaneous solubilization process of Cefadroxil in polymer solution. Stability constant value was 0.088 ml/µg.

Entrapment Efficiency

This is the most important measurement for microparticulation system. Scale-up possibilities, Production of drug and most importantly the encapsulation capacity of the drug can be known. The solid dispersion method results in excellent efficiency.

Table 4: The % Yield and Entrapment efficiency of cefadroxil solid dispersion formulas

Formula	% Yield	Entrapment efficiency
F1	80.66%	19.2 %
F2	88.88%	52.53 %
F3	86.83%	65.33 %

Fourier Transform Infrared (FTIR) Spectroscopy of Cefadroxil

The FTIR spectra indicate no difference between the formulated drug and the pure drug peaks. Hence, we can conclude that there is no polymer interaction with the drug [15, 16, 17].

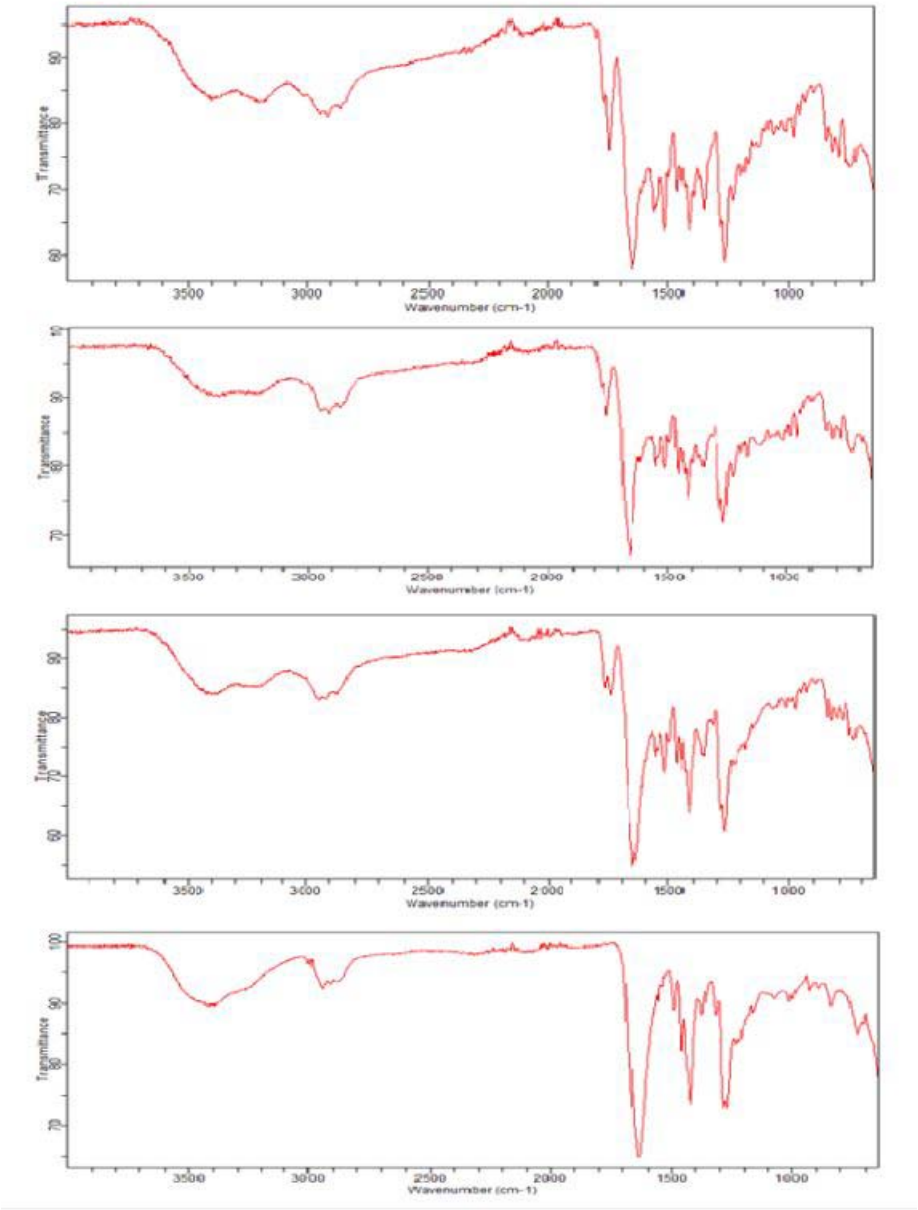

Fig.3. FTIR spectra of Cefadroxil, the polymer and the formulations, as (a) Cefadroxil 1:1 solid dispersion, (b) Cefadroxil 1:2 solid dispersion, (c) Cefadroxil 1:3 solid dispersion (d) PVPK 30 polymer

Modified *in-vitro* Dissolution Studies of Cefadroxil

This study shows the drug release profile of cefadroxil was remarkably increased as solid dispersion formulation when compared with the pure drug. Thus, this means that it has a positive onset of drug action. Hence, the clinical effect of the modified dosage form will be more than the conventional dosage form; it also increases the absorption parameter of the drug due to the network formed by the polymer matrix. As a matter of fact, it does not affect the clinical performance of cefadroxil, earlier it used to get dissolve in stomach and afterwards became ready for the absorption by totally skiping the dissolution phase which is known to be the rate limiting step for Cefadroxil [18].

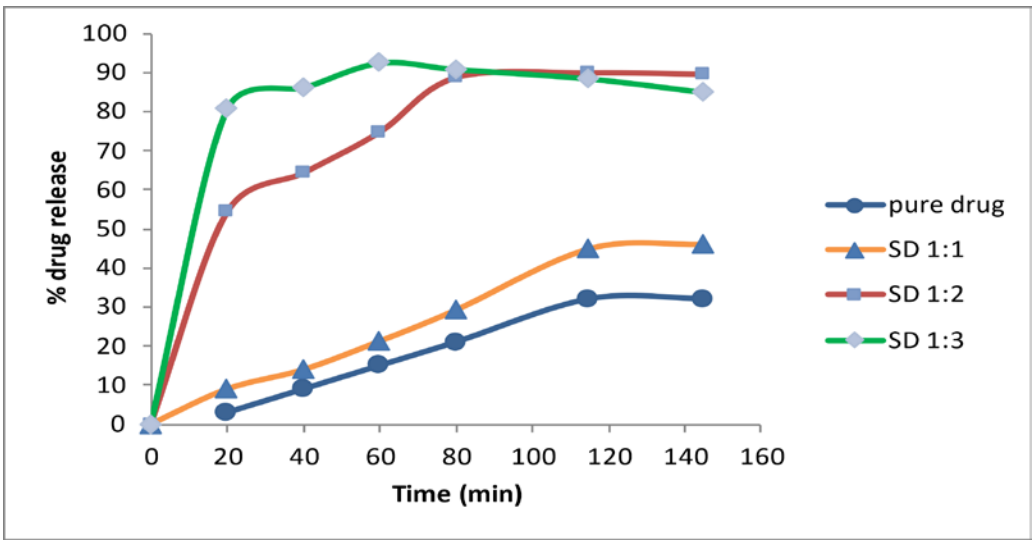

Figure 4: Dissolution study of Cefadroxil pure sample and solid dispersions

CONCLUSION

As the bioavailability of any drug is directly proportional to the absorption of drug at target site. For the absorption of drug, it must be available in solution form. Oral formulations are suffered from this problem if the drug is poorly soluble in water. Various approaches have been utilized for the enhancement of solubility of BCS class II drugs.

Cefadroxil of BCS class II suffers from poor solubility. In our research worked, we have prepared the solid dispersion of cefadroxil using PVP k30 and methanol as solvent. The drug release is remarkably increased when formulated as solid dispersion with respect to pure drug.

Cefadroxil is molecularly dispersed in the formulation structure which contains voids and channels which leads to increase the drug surface area that exposed to the dissolving media. PVP K-30 containing formulations significantly improve the drug solubility. This affects positively on bioavailability and the onset of drug action.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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