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IMPROVEMENT OF SOLUBILITY OF CEFIXIME AND OMEPRAZOLE BY SOLID DISPERSION AND SLUGGING METHOD

M. Lavanya* and A. Deevan Paul

Department of Pharmaceutics, SVU College of Pharmaceutical Sciences, SV University.

Abstract

In fact, it has been estimated that 40% of new chemical entities currently being discovered are poorly water-soluble. Unfortunately, many of these potential drugs area bandoned in the early stages of development due to solubility concerns. Cefixime as per BCS classification is a class IV drug with poor solubility and poor permeability. Poor solubility of drugs leads to poor absorption and hence poor bioavailability. Omeprazole as per BCS classification is a class II drug with poor solubility and good permeability. Methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvent(s), and particle size reduction have also been utilized to improve the dissolution properties of poorly water-soluble drugs. Bioavailability of a drug can be increased by increasing the solubility of a drug. The % increase in saturation solubility with PVPK-30 and urea was higher than other polymers and techniques. This shows that solid dispersion using solvent evaporation technique gives a better solubility of drug when compared to other techniques. This might be due to the better solubilization effect of drug and polymer with solvent over PEG-6000 and slugging method. Slugging method is next best alternative for solubilization of drug.

Key Words: *Omeprazole, Cefixime, PEG-6000, PVPK-30.*

Corresponding Author:

M. Lavanya

Final semester,M.Pharmacy,
SVU College of Pharmaceutical sciences,
Email: lavanyam7989@gmail.com
Ph. No: +919849243591

QR code

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INTRODUCTION:

The enhancement of oral bioavailability of poor water soluble drugs remains one of the most challenging aspects of drug development [1-5]. Together with the permeability; the solubility behavior of a drug is a key determinant of its oral bioavailability[5-14]. There have always been certain drugs for which solubility has presented a challenge to the development of a suitable formulation for oral administration. The formulation of poorly soluble compounds for oral delivery at present is one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry [15-25]. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches. Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of low water soluble drugs [26-30] there are practical limitations of these techniques.

In 1961, SekiguchiandObi developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water soluble drugs can be overcome. This method, which was later, termed solid dispersion which involved the formation of eutectic mixture of drugs with water-soluble carriers by the melting of their physical mixtures [31-34].

Preparation of Solid Dispersions:

Various preparation methods for solid dispersions have been reported in literature. These methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, de-mixing (partially or complete), and formation of different phases is observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted. It was already recognized in one of the first studies on solid dispersions that the extent of phase separation can be minimized by a rapid cooling procedure. Generally, phase separation can be prevented by maintaining a low molecular mobility of matrix and drug during preparation. On the other hand, phase separation is prevented by maintaining the driving force for phase separation low for example by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible.

Analytical Method:

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METHODOLOGY

Slugging of Cefixime and Omeprazole

Drug (cefixime and omeprazole) were mixed with excipient (lactose and sodium chloride) in different ratios (1:1, 1:2and, 1:3)and allowed to slug using single station tablet compressing machine under high pressure. The slugs formed were powdered using mortar and pestle and passed through sieve 80#. The solubility of drug in 10ml water was determined

RESULTS AND DISCUSSION:

The present study was aimed to increase solubility of cefixime and Omeprazole by slugging method.

Preparation of calibration curve for Cefixime

Cefixime was found to be soluble in organic solvents such as ethanol. A simple reproducible method of estimation was carried out in ethanol ranging from 2-26 µ/ml solutions at 234nm (Table **1**) against the blank the standard graph obtained was linear,. (Figure **1**) Cefixime is insoluble in water and having poor bioavailability and coming under the category of class 4 of biopharmaceutical classification (BCS) system.

Preparation of calibration curve for Omeprazole

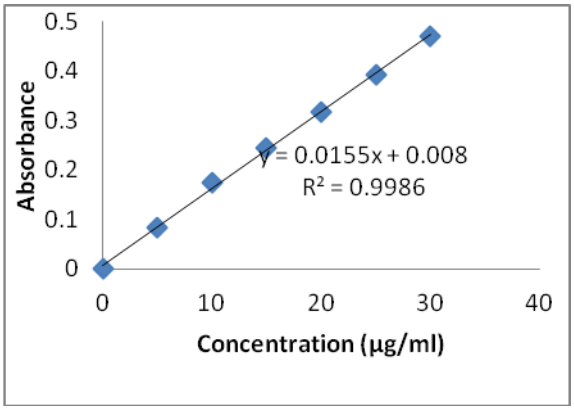
Omeprazole was found to be soluble in organic solvents such as ethanol. A simple reproducible method of estimation was carried out in ethanol ranging from 2-26 µ/ml solutions at 302 nm (Table **2**) against the blank the standard graph obtained was linear.. (Figure **2**) Omeprazole is very slightly soluble in water and having poor bioavailability and coming under the category of class 2 of biopharmaceutical classification (BCS) system

Table 1: Standard graph of Cefixime

S.No	Concentration (µg / ml)	Absorbance
1.	0	0.0000
2.	5	0.106
3.	10	0.209
4.	15	0.316
5.	20	0.423
6.	25	0.502

Table 2: Standard graph of Cefixime

S.No	Concentration (µg / ml)	Absorbance
1.	0	0.0000
2.	5	0.0847
3.	10	0.1750
4.	15	0.2443
5.	20	0.3163
6.	25	0.3940
7.	30	0.4707



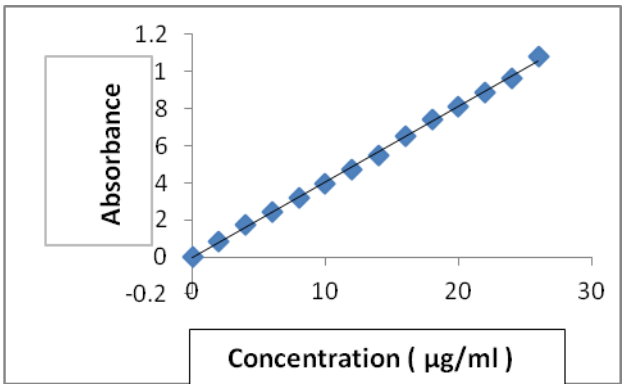


Fig 1: Standard graph of Cefixime **Fig 2: Standard graph of Omeprazole**

Saturation solubility:

Table3: Solubility of cefixime in water

S.No	Solid dispersion formulations	Ratio	Absorbance (nm)	Saturation solubility in distilled water (µg/ml)
1.	Cefixime + I water		0.876	50.0 (100%)
2.	Cefixime + water		0.197	11.2 (22%)
3.	Cefixime +PVP K-30	1:1	0.778	44.0 (88%)
4.	Cefixime +PVP K-30	1:2	0.860	49.1(97%)
5.	Cefixime +PVP K-30	1:3	0.875	49.9 (98%)
7	Cefixime +Urea	1:1	0.820	46.8 (93%)
8	Cefixime + Urea	1:2	0.875	37.6(99%)
9	Cefixime + Urea	1:3	0.875	37.6(99%)
7.	Cefixime + PEG-6000	1:1	0.542	30.9(62 %)
8.	Cefixime + PEG -6000	1:2	0.562	32.1 (64%)
9.	Cefixime + PEG-6000	1:3	0.564	32.2 (64%)
13	Cefixime + lactose	1:1	0.688	43.8 (79%)
14	Cefixime + lactose	1:2	0.702	40.1 (80 %)
15	Cefixime + lactose	1:3	0.702	40.1 (80 %)
16	Cefixime + sodium chloride	1:1	0.684	39.0 (78%)
17	Cefixime + sodium chloride	1:2	0.634	36.2 (81%)
18	Cefixime + sodium chloride	1:3	0.602	34.4 (53%)

Table 4: Solubility of Omeprazole in water

S.No	Solid dispersion formulations	Ratio	Absorbance (nm)	Saturation solubility in distilled water (µg/ml)
1.	Omeprazole + ethanol		0.576	50.0 (100%)
2.	Omeprazole + water		0.197	17.1 (34%)
3.	Omeprazole +PVP K-30	1:1	0.496	43.0 (86%)
4.	Omeprazole +PVP K-30	1:2	0.558	48.4(97%)
5.	Omeprazole +PVP K-30	1:3	0.563	48.9 (98%)
6	Omeprazole +Urea	1:1	0.500	43.0 (86%)
7	Omeprazole + Urea	1:2	0.545	47.0 (97%)
8	Omeprazole + Urea	1:3	0.565	49.0 (98%)
9.	Omeprazole + PEG-6000	1:1	0.274	23.8 (48%)
8.	Omeprazole + PEG -6000	1:2	0.398	34.5 (69%)
9.	Omeprazole + PEG-6000	1:3	0.400	34.7 (69%)
10	Omeprazole + Lactose	1:1	0.380	32.9 (66%)
11	Omeprazole + Lactose	1:2	0.480	41.7 (83%)
12	Omeprazole + Lactose	1:3	0.484	41.8 (83%)
13	Omeprazole + Sodium chloride	1:1	0.440	38.1 (76%)
14	Omeprazole + Sodium chloride	1:2	0.400	34.7 (69%)
15	Omeprazole + Sodium chloride	1:3	0.358	31.0 (62%)

Amongst all, drug solubility (cefixime and omeprazole) was maximum in case of solid dispersion formulation of PVPK-30 and Urea at ratio Drug: PVPK-30 in 1:2 and .1:3.

Slugging method was next better alternative to improve solubilzation.

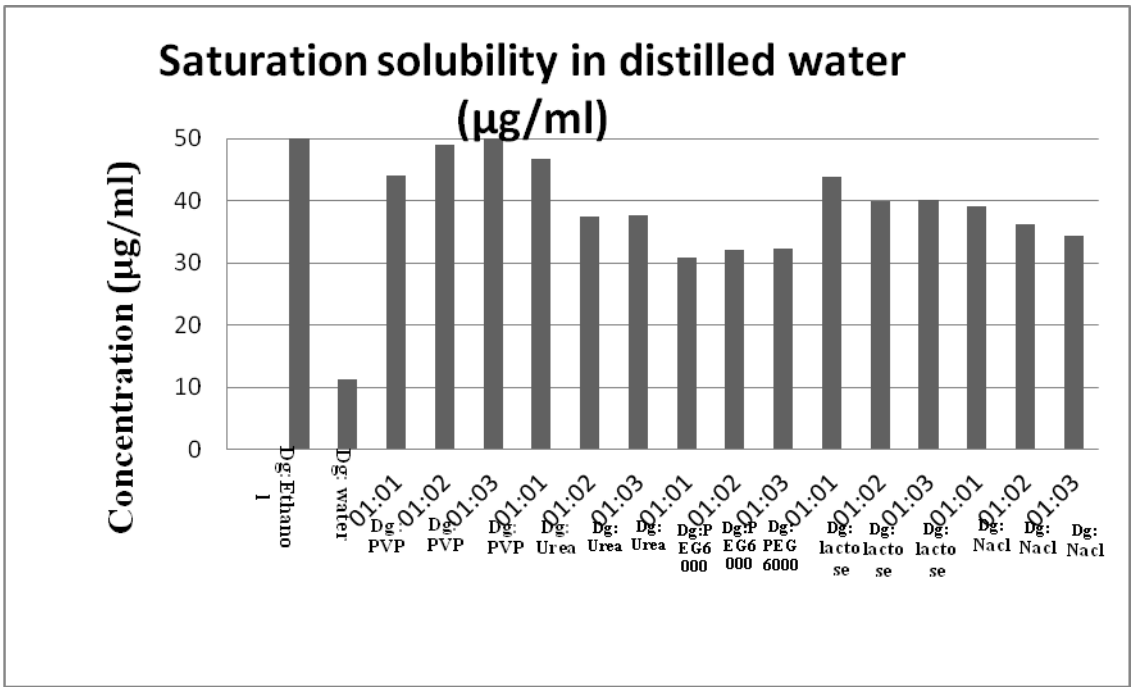


Fig 3: Saturation Solubility graph of Cefixime in water

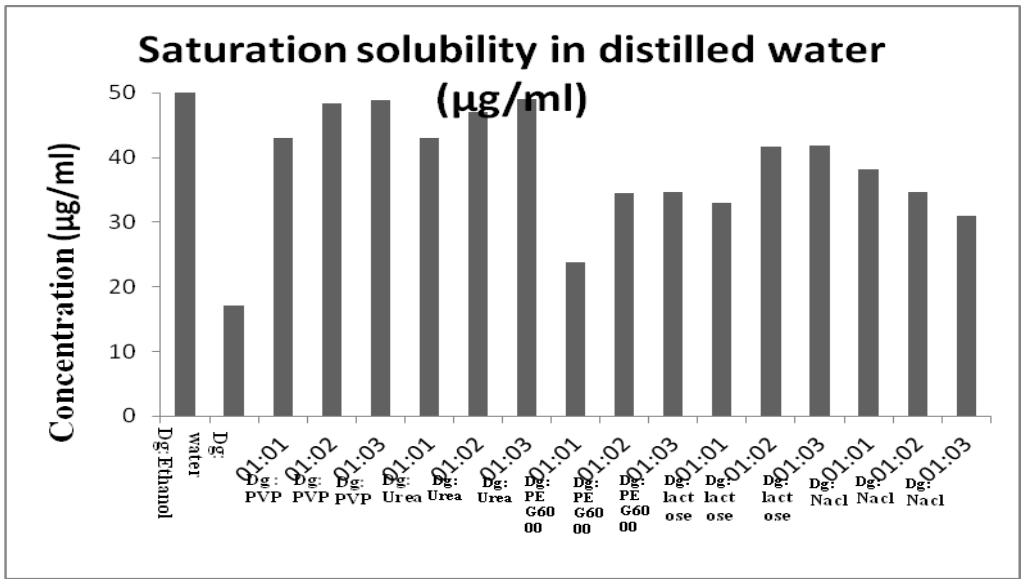


Fig 4: Saturation Solubility graph of Omeprazole in water

DISCUSSION:

The % increase in saturation solubility with PVPK-30 and urea was higher than other polymers and techniques. This shows that solid dispersion using solvent evaporation technique gives a better solubility of drug when compared to other techniques.

This might be due to the better solubilization effect of drug and polymer with solvent over PEG-6000 and slugging method.

Slugging method is next best alternative for solubilization of drug.

CONCLUSION:

In the present research work improvement of solubility of Cefixime and Omeprazole by solid dispersion and slugging method were prepared using various grades of polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations., flow properties and all the formulations were found to be good. solid dispersion of Cefixime and Omeprazole with solvent evaporation technique showed higher drug solubility in comparison to other technique like hot melt and slugging method. Hence this solid dispersion technique can be used to improve the dissolution and hence bioavailability of given dosage forms

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