Enhancement of Solubility and Bioavailability of Hydrochlorothiazide Using Solid Dispersion Technique

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ABSTRACT

Objective: The variable aqueous solubility of Hydrochlorothiazide (HCTZ) is the major factor limiting its oral bioavailability. The objective of the study is to enhance of the solubility of HCTZ by using solid dispersion technique.

Methods: The polymers used were PVP K30, PVP S630, HPMC & PEG 6000 and solid dispersions were prepared by solvent evaporation method in different ratios of 1:0.5, 1:1, 1:3, 1:5 respectively. The prepared solid dispersions were characterized by DSC and FTIR. The equilibrium solubility was determined in water to study the effect of polymers on solubility of HCTZ. In vitro dissolution studies were conducted in distilled water from solid dispersions equivalent to 12.5 mg of HCTZ. How the solid dispersions affect the permeation of the drug across membranes was evaluated by measuring the in vitro permeation of Drug PVP and Drug HPMC across cellophane membrane using the vertical Franz diffusion cell.

Results: Successful conversion of the crystalline Hydrochlorothiazide to amorphous solid dispersion was achieved at 1:1, 1:3 & 1:5 levels of drug to HPMC E 15 & drug to PVP and with PVP S630 it was achieved at 1:3 & 1:5 level. Amorphous conversion was not observed in case of PEG 6000 at any level. The solid dispersion prepared with HPMC E 15 & PVP K30 at 1:5 level showed a 98% and 66.3% drug release at 5min respectively. The enhancements in case of 1:5 Plasdone s630 and PEG 6000 were not significant. The results of equilibrium solubility studies indicates that the solvent evaporated solid dispersions of HPMC E 15 & PVP K30 were the best. Permeation studies indicate that a 3 to 4 fold increase in the solubility of the drug results in 10 fold increase in permeation. Thus enhancement in solubility also results in enhancement in the permeation across artificial membranes.

Conclusion: The above study shows that solid dispersion of HCTZ

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offers a simple and attractive solution to increasing the solubility of the poorly water soluble drug and thereby improve its oral bioavailability.

**Keywords:** Hydrochlorothiazide (HCTZ), Solid dispersions (SD), Permeation studies.

**INTRODUCTION**

The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability.

Hydrochlorothiazide \(^{1,2}\) is a diuretic drug belonging to the chemical class of benzoxazole derivative. It acts orally and the dosage used for treatment of congestive heart failure and hypertension ranges from 25 to 50 mg daily alone or combination with other antihypertensive drugs up to 100 mg if necessary. HCTZ is a poorly water soluble drug which has a reported bioavailability of <65%. Therefore lots of efforts have been made to increase dissolution of drug. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion \(^{3-6}\) (SD) is one of such methods and involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method. The formulation of having low aqueous solubility using solid technology has been an active area of research since 1960. Among the various approaches to improve solubility, the SD technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous.

The aim of the present work was to improve the aqueous solubility of the drug by using solid dispersion technique. Ethanol was determined to be the solvent choice. The polymers used were PVP K30, PVP S630, HPMC & PEG 6000 and solid dispersions were prepared by solvent evaporation method in different ratios. The effect was evaluated by measuring the *in vitro* dissolution in water and permeation studies.

**MATERIALS AND METHODS**

Chemical and Reagents

HCTZ USP (EMCO Industries), HPMC E 15 CPS (Dow Chemical’s), PVP K30 (Ashland specialty), Plasdone S630 (Ashland specialty), PEG 6000 (Merck India), Ethanol (Merck India). All other reagents and chemicals used were of analytical reagent grade and were used as such without any further purification. Purified water USP was used where ever required.

**EXPERIMENTAL**

Solid dispersions were prepared by solvent evaporation technique \(^{7}\). The formulation composition details are given in table1. All batches were evaluated for assay and uniformity of content. Each sample (approximately 2.5 mg) was subjected to differential scanning calorimetry over a range of 50°C to 300°C. Samples were heated under nitrogen atmosphere (Flow rate of N\(_2\)-
50ml/min). Equilibrium solubility studies (about 30 mg equivalent weight of SD) were carried out in purified water.

Each batch of SDs (at n=3) was subjected to dissolution in purified water using USP type I apparatus at 50rpm. Samples were withdrawn at 5, 10, 15, 30, 45, 60 and 75 minutes interval and analyzed for % drug dissolved using UV spectrophotometric method.

To find out the permeability of the solid dispersion of the HCTZ, *In vitro* permeation studies of solid dispersions (HPMC 1:5, PVP 1:5) and plain drug were carried out in pH 7.4 phosphate buffer. Samples were withdrawn at 1, 2, 3, 4 and 5 hrs interval and analyzed for % drug permeated through artificial membrane using UV spectrophotometric method.

**RESULTS AND DISCUSSION**

The content uniformity and assay values of solid dispersions were within a range of 96.5% to 98.3%. DSC thermograms of samples are shown in fig 1, 2, 3 & 4.

Successful conversion of the crystalline HCTZ to amorphous solid dispersion was achieved at 1:1, 1:3, & 1:5 levels of drug to HPMC E 15 & drug to PVP and with PVP S630 it was achieved at 1:3 & 1:5 level. Amorphous conversion was not observed in case of PEG 6000 at any level. Comparative values of equilibrium solubility studies are shown in fig 5.

Equilibrium solubility data showed that there was no significant enhancement in aqueous solubility for PEG based at all ratios. In case of S 630 based SD, significant enhancement occurred only at 1:5 ratio (approximately 2 fold) at lower ratios the enhancement was not significant. In case of PVP, at 1:1 and 1:3 ratios the enhancement in permeability is four folds while at 1:5 ratio there is a nearly 5 fold enhancement in aqueous solubility.

In case of HPMC significant enhancement is observed at all ratios. Nearly 4 folds enhancement is observed up to 1:3 ratio and 6 to 6.5 folds enhancement is observed at 1:5 ratio. This may be due to the fact that in the DSC graphs no amorphous conversion of the drug is observed for PEG 6000 at any ratios. While in case of HPMC amorphous conversion is observed from 1:0.5 while in case of PVP it was observed from 1:1 ratio. On the other hand S-630 shows amorphous conversion from 1:3 level onwards.

The rank order correlation among the polymers is as follows:

HPMC (1:5)>PVP (1:5)>HPMC (1:0.5)>PVP (1:1)>HPMC (1:3)>PVP (1:3)>HPMC (1:1)

Hence HPMC (1:5) PVP (1:5) were selected as the best polymers and ratios for the further evaluation studies of solid dispersion of HCTZ.

*In vitro* dissolution data of solid dispersions was shown in the table 2 and comparison of drug release from 1:5 SDs at 5 min and 30 min were shown in fig 6.

The solid dispersion prepared with HPMC E 15 & PVP K30 at 1:5 level showed a 98% and 66.3% drug release at 5 min respectively. The enhancement in case of 1:5 Plasdone S630 and PEG 6000 were not significant.

The permeation studies were conducted to F4 and F8 formulations because from the results of dissolution data it is said that only 1:5 formulations were found to the best among all the rest formulations. The comparative values of drug permeated at 1hr and 5hr are shown in fig 7.

From this study it was clear that the permeation increased at about 10 folds with HPMC and 2.5 fold with PVP K 30 when compared to the plain drug.
CONCLUSION

DSC and FTIR studies results indicated that no interaction of drug with the carriers and conversion of crystalline form to amorphous form of drug results in improvement of solubility. SD technique was successfully employed to enhance the aqueous solubility of HCTZ. The enhanced solubility also leads to enhanced permeability across artificial membrane. Further In vivo studies to substantiate these findings are under progress in our laboratory.

ACKNOWLEDGEMENT

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Declaration

This research work entitled “ENHANCEMENT OF SOLUBILITY AND BIOAVAILABILITY OF HYDROCHLOROTHIAZIDE USING SOLID DISPERSION TECHNIQUE” is an original one and carried out by us in Malla Reddy College of Pharmacy, Hyderabad.

REFERENCES


Table 1. SD Formulation Chart

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<th>Ratios</th>
<th>HPMC 1:0.5</th>
<th>HPMC 1:1</th>
<th>HPMC 1:3</th>
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Table 2. In vitro Dissolution data of SDs

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Figure 1. DSC Thermogram of HCTZ SD with HPMC E 15 Cps

Figure 2. DSC Thermogram of HCTZ SD with PVP K 30
Figure 3. DSC Thermogram of HCTZ SD with Plasdone S630

Figure 4. DSC Thermogram of HCTZ SD with PEG 6000
Figure 5. Drug dissolution profile in equilibrium solubility analysis

Figure 6. Comparison of drug release from 1:5 sds at 5 min and 30 min
Figure 7. Comparison of drug permeation through membrane at 1 hr and 5 hr.