INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY

Volume: 2: Issue-2: April-June -2011 IJABPT ISSN 0976-4550

# SOLUBILITY ENHANCEMENT OF ORAL HYPOGLYCEMIC AGENT BY SOLID DISPERSION TECHNIQUE

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**ABSTRACT :** The present study was aimed to increase the solubility of the poorly water soluble drug (Gliclazide) by using hydrophilic polymers (PVP K-30 and HPMC E4). Solid dispersions were prepared by kneading method. Phase solubility study, *in-vitro* dissolution of pure drug, physical mixtures and solid dispersions were carried out. PVP and HPMC were found to be effective in increasing the dissolution of Gliclazide in solid dispersions when compared to pure drug. FT-IR spectroscopy, differential scanning calorimetry and X-ray diffractometry studies were carried out in order to characterize the drug and solid dispersion.

**Key words-** Solid dispersion, Gliclazide, PVP K-30, HPMC, Kneading method.

## INTRODUCTION

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be rate determining step for appearance of medicinal effect, therefore efforts to increase dissolution of drug with limited water solubility is often needed. Many methods are available to improve these characteristics, including salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of these methods and involved a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method. (Chiou, et.al., 1971)

Gliclazide is N-[[( hexahydrocyclopenta [c]pyrrol-2(1H)-yl) amino]-carbonyl]-4-methyl benzene Sulfonamide or 1- (hexahydrocyclopenta [c] pyrrol-2-(1H)-yl)-3-(p-tolylsulfonyl) urea or N-(4-methylbenzene sulfonyl)-N'-(3-azabicyclo [3.3.0] oct-3-yl) urea or 1-(3-azabicyclo[3.3.0] oct-3-yl)-3-p-tolylsulfonyl urea $C_{15}H_{21}N_3O_3S$, molecular weight 323.4 is a white or almost white crystalline powder, odorless, tasteless, M.P. 165-170$^{o}$C.( British Pharmacopoeia, 1998)

It is readily absorbed in gastrointestinal tract and transported through bound plasma proteins. It treats diabetes mellitus by reducing the platelet adhesiveness and aggregation by antagonizing the abnormal fibrin deposition on the vessel wall and by reducing the excessive response of the diabetic microvessel. It is practically insoluble in water, sparingly soluble in acetone, slightly soluble in ethanol (96%) and freely soluble in dichloromethane.(Saeed, et.al., 2003).

There are several reports available on solid dispersions of Pharmaceuticals with polyvinylpyrrolidone which revealed that with increase in PVP content, crystallization was inhibited while solubility was enhanced.( Ansari, et.al., 2008).

HPMC is a water-soluble polymer and cannot be dissolved in alcohol alone, while HPMC can be easily dissolved in water and the mixtures such as water and alcohol.( Kumar, et.al., 2009).

## Experimental

### Materials

A gift sample of Gliclazide was received from Aurochem Pharma, PVP K-30 and HPMC E4 was obtained from S.D. fine chemical (India).

## METHODS

### Physical mixture of Gliclazide

Physical mixtures of Gliclazide at three different mass ratios (1:1, 1:2, 1:3 and 1:4) were prepared. The mixtures were passed through a sieve no. 80. The prepared mixtures were then filled in glass bottles, sealed and stored in a dessicator until further use.

### Solid dispersion of Gliclazide

A mixture of drug and polymers in three different mass ratios were wetted with water and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried in hot air oven at 50°C for 24 hours. It was then scrapped, dried and was passed through sieve no. 40 and stored in a dessicator until further evaluation. (Chaulang, et.al., 2008)

### Drug content

The drug content in each solid dispersion and physical mixture was determined by the UV-spectroscopic method. An accurately weighed quantity of solid dispersion or physical mixture, equivalent to 40 mg of Gliclazide, was transferred to a 100 ml volumetric flask containing 10 ml of methanol and dissolved. The volume was made up to 100 ml with NaOH. The solution was filtered through 0.45 mm membrane filter paper and from the same solution 1ml was diluted 100 times with NaOH to achieve 4 mmol $l^{-1}$ and the absorbance was measured at 226 nm. (Patil et al., 2008).

### Phase Solubility Studies

The phase solubility studies were carried out according to the method reported by Higuchi and Connors. Excess amount of Gliclazide was added to the screw capped vials containing 20 ml of aqueous carrier solution (PVP K-30 and HPMC) at various concentrations and placed on a rotatory shaker and agitated at room temperature for 48 hours. After equilibrium, the solutions were carefully filtered through Whatman No.41 filter paper and after appropriate dilution; solutions were analyzed at 226 nm by using UV- visible spectrophotometry.

### Dissolution study

The dissolution study of pure drug, physical mixture and solid dispersion was carried out by using USP dissolution apparatus (type 2) at 100 RPM at temperature of 37 ± 0.5°C using 900 ml volume of ml pH 1.2 and pH 7.4 used as the medium, equivalent 40 mg of drug were taken. Samples of 10 ml were withdrawn at regular intervals. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The filtered samples were analyzed spectrophotometrically at 226 nm and the drug release was determined.

### Characterization of solid dispersion

### Fourier transforms infrared spectroscopy

Fourier transform infrared spectroscopy has been used to assess the interaction between carrier and drug molecule. The FTIR spectrum of pure drug, PVP K-30 and solid dispersion prepared by Kneading method.

The FTIR spectra of Gliclazide, PVP K-30 and their solid dispersion are shown in the Figure No. 4 respectively. In IR spectra of Gliclazide the C-H stretching in aromatic ring occurs at 3055.24 $cm^{-1}$, the N-H stretching in amine occurs at 3363.86 $cm^{-1}$, the C-N stretching in amine occurs at 1317.38 and the C-O stretchin in carbonyl group occurs at 1670 $cm^{-1}$.The peaks showed no significant changes in the material characteristics when Gliclazide is used with PVP K-30.

### Differential Scanning Calorimetry

The DSC thermogram of pure drug, PVP K-30 and its solid dispersion prepared by Kneading method, From the Figure No.5, the pure drug showed the melting point at 173ºC, from Figure No.15 PVP K-30 showed the melting point at 115ºC, the solid dispersion showed the melting point reduced to 98.7ºC from 115ºC and the intensity of the peak in pure drug is reduced. From the Figure No.16 it can be concluded that there is a formation of solid dispersion.

### X-Ray Diffraction

The X-ray diffraction pattern of pure drug, PVP K-30 and its solid dispersion prepared by Kneading method, Gliclazide showed the sharp peak indicating crystalline structure where as PVP K-30 showed diffused pattern. The solid dispersion prepared by Kneading method of Drug and PVP K-30 showed reduction in peak intensity as compared to pure drug indicating conversion of crystalline form to micro crystalline state.

## RESULT AND DISCUSSION

The phase solubility studies were performed to determine stoichimetric proportions of Gliclazide and carriers- PVP K-30 and HPMC. The effects of polymers concentration at room temperature on solubility are shown in Figure 1.

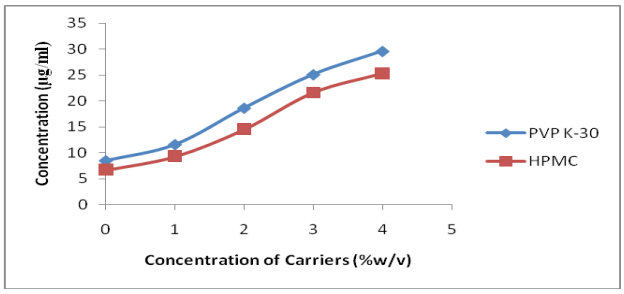


Figure 1: Results of Concentration of Carriers on Solubility of Gliclazide

The plot of drug solubility against polymer concentrations at room temperature indicated a linear relationship between drug and polymer solution. Both the type show $A_L$ type of plot i.e. the solubility of Gliclazide increased with increasing carrier concentration.

Dissolution of the pure drug, physical mixtures as well as solid dispersions of Gliclazide with PVP K-30 (equivalent to 40mg) was tested in acidic buffer (pH 1.2) and phosphate buffer (pH 7.4) for a period of 60 minutes. Dissolution of the pure drug, physical mixture and solid dispersion prepared by kneading method in ratio of 1:4 was found to be 36.63 %, 41.63 and 99.72% in 50 minutes in acid buffer medium. Pure drug and physical mixtures shows almost same release, whereas the solid dispersion (1:4) shows 100% drug release in one hour. The solid dispersion prepared using ratio 1:1, 1:2 and 1:3 showing corresponding drug releases that is 79.29%, 83.30% and 95.12 % in 60 minutes as shown in fig 2.

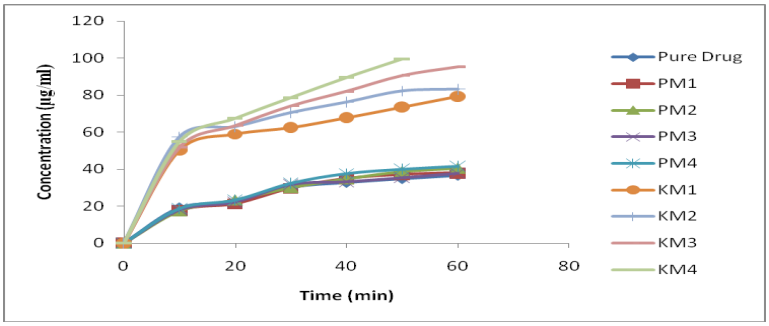


Figure 2: In-vitro Dissolution Profile of Gliclazide, PM and KM with PVP K-30 in pH 1.2

Similar study was carried out by preparing solid dispersion of Gliclazide with the HPMC E4, the dissolution of pure drug, its physical mixture and solid dispersion prepared by kneading method are 36.63%, 39.87% in 60 minutes and 99.65 % in 50 minutes respectively. The solid dispersion prepared in 1:4 ratio show the higher drug release in 50 minutes corresponding to other ratios that is 1:1, 1:2 and 1:3 which are 71.51% 76.58% and 90.88% in 60 minutes respectively in pH 1.2 as shown in Figure 3.

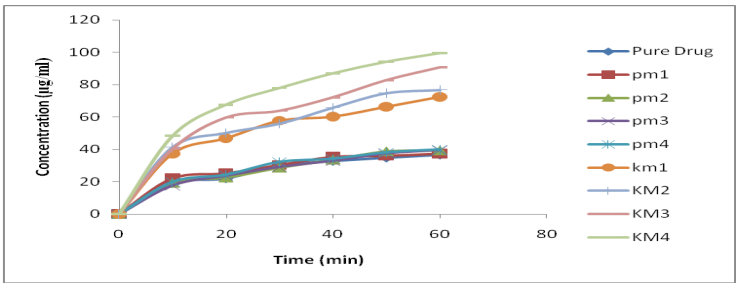


Figure 3: *In-vitro* Dissolution Profile of Gliclazide, PM and KM with HPMC in pH 1.2

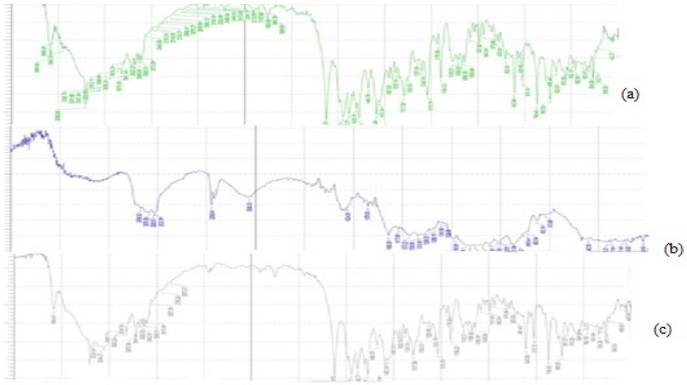


Figure No 4 FTIR Spectrum

1) Gliclazide, 2) PVP K-30, 3) Solid Dispersion

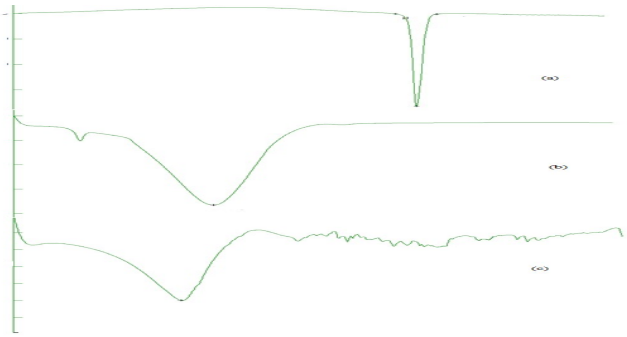

Figure No. 5 XRD Spectrum

1) Gliclazide, 2) PVP K-30, 3) Solid Dispersion

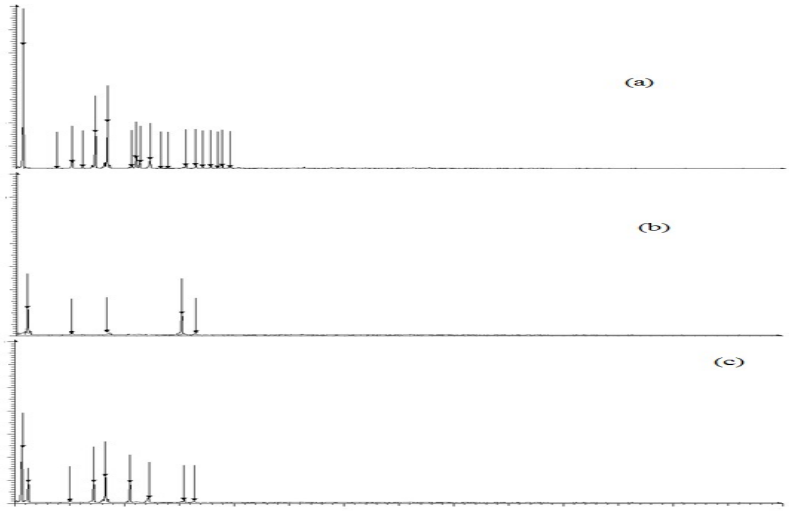


Figure No 6 XRD Spectrum
1) Gliclazide, 2) PVP K-30, 3) Solid Dispersion

The drug content of physical mixture and solid dispersion prepared with PVP K-30 and HPMC E4 are shown in table no.1

Table no. 1 Analysis of Drug Content in PM and SD

| | Drug Content |
|---|---|
| PM ( PVP K-30) | 93.68±0.67 |
| SD (PVP K-30) | 100.50±0.12 |
| PVP K-30 (HPMC) | 92.36±0.07 |
| SD (HPMC) | 100.30±0.32 |

## CONCLUSION

Increasing the drug carrier ratio from 1:1 to 1:4 improved drug release profiles observed in for all formulations in case of Knaeding method with PVP K-30 and HPMC but the drug release rate was higher in 1:4 ratio for both the polymers. The drug release was found to be better in solid dispersions prepared with PVP K-30 as compared to those prepared with HPMC.

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