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RESEARCH ARTICLE

Solubility Enhancement of Poorly Water Soluble Drug by Solid Dispersion Technique

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ABSTRACT

The objective of the research project is the enhancement of the solubility of Acyclovir by using solid dispersion technique. The polymers used were Polyethylene glycol (PEG 6000) and Mannitol and solid dispersions were prepared by hot melt method and kneading method. The phase solubility study was carried out to study the effect of polymers on solubility of Acyclovir. The prepared solid dispersions were characterized by Fourier transform Infrared spectroscopy (FT-IR) to identify the physicochemical interaction between drug and polymers. The dissolution studies of solid dispersion were performed by using USP II apparatus (paddle type). The dissolution studies were carried out in pH 1.2 and pH 7.4 medium. The two methods were used, the hot melt method (1:3 %w/w) prepared by using PEG6000 showed highest percentage drug release (101.89%) as compared to kneading method in pH 1.2. Thus, the solid dispersion technique can be successfully used for improvement of solubility of Acyclovir.

KEYWORDS

Solid Dispersion, Acyclovir, PEG 6000, Mannitol, Hot Melt Method, Solubility Enhancement

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[1]. Many methods are available to improve these characteristics including salt formation, micronization and addition of solvent or surface active agents[2]. 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[3].

Acyclovir is 2-Amino-1,9-dihydro-9((2-hydroxy-ethoxy)methyl)-6H-purin-6-one $C_8H_{11}N_5O_3$, Molecular weight 225.21 g/mol is white or almost white crystalline powder, odorless, tasteless., M.P 256.5- 257ºC. It is slightly soluble in water, practically in soluble in most organic solvent; soluble in dilute[4].

There are several reports available on solid dispersions of pharmaceuticals with Polyethylene glycol which revealed that with increase in PEG content, crystallization was inhibited while solubility was enhanced. Mannitol It is freely soluble in Water (182 g/L at 25°); slightly soluble in Alkalis and Ethanol, practically

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insoluble in Ether and Glycerine[5].

MATERIAL AND METHODS

Materials

A gift sample of Acyclovir was received from Torrent Pharmaceuticals, PEG 6000 and Mannitol was obtained from S. D. fine chemical (India).

Methods

Physical Mixture of Acyclovir

Physical mixtures of Acyclovir at three different mass ratios (1:1, 1:2, and 1:3) were prepared. The mixtures were passed through a sieve no. 40. The prepared mixtures were then filled in glass bottles, sealed and stored in a desicators until further use[6].

Solid Dispersion of Acyclovir

A mixture of drug and polymers in three different mass ratios are melted at a particular temperature in a china dish and the drug is then dispersed into the molten mixture with a constant stirring. The molted mixture is then poured and cooled immediately to obtain the formed dispersion. The resulting mixture was sieved through a sieve no. 40 and stored in a dessicator until further evaluation.

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 50 mg of Acyclovir, was transferred to a 100 ml volumetric flask containing 0.1N HCL. The solution was filtered through 0.45 mm membrane filter paper and from the same solution 1ml was diluted and the absorbance was measured at 251 nm[7].

Phase Solubility Studies

The phase solubility studies were carried out according to the method reported by Higuchi and Connors. Excess amount of Acyclovir was added to the screw capped vials containing 20 ml of aqueous carrier solution (PEG 6000 and Mannitol) 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 251 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 II) 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 50 mg of drug were taken. Samples of 1 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 251 nm and the drug release was determined[8].

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, PEG 6000 and solid dispersion prepared by Hot melt method.

The FTIR spectra of Acyclovir, PEG 6000 and their solid dispersion are shown in the Figure No. 4 respectively. In IR spectra of Acyclovir the C-H stretching in aromatic ring occurs at 3440.16 cm-1, the N-H stretching in amine occurs at 3188.44 cm-1 and the C=O stretching occurs at 1626.05 cm-1.The peaks showed undisturbed structure in the material characteristics when Acyclovir is used with PEG 6000.

RESULTS AND DISCUSSION

The phase solubility studies were performed to determine stoichiometric proportions of Acyclovir and carriers- PEG 6000 and Mannitol. The effects of polymers concentration at room temperature on solubility are shown in Figure 1.

The plot of drug solubility against polymer concentrations at room temperature indicated a linear relationship between drug and polymer

solution. Both the type show AL type of plot i.e. the solubility of Acyclovir increased with increasing carrier concentration.

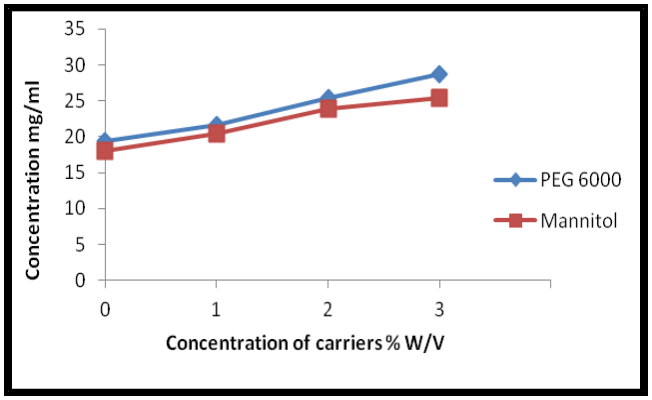

Figure 1: Results of Concentration of Carriers on Solubility of Acyclovir

Dissolution of the pure drug, physical mixtures as well as solid dispersions of Acyclovir with PEG 6000 (equivalent to 50mg) 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 hot melt method in ratio of 1:3 was found to be 36.63 %, 41.63% in 60 min. and 101.89% in 40 minutes in acid buffer medium. Pure drug and physical mixtures shows almost same release, whereas the solid dispersion (1:3) shows 100% drug release in one hour. The solid dispersion prepared using ratio 1:1 and 1:2 showing corresponding drug releases that is 79.29% and 88.49% in 60 minutes as shown in Figure 2.

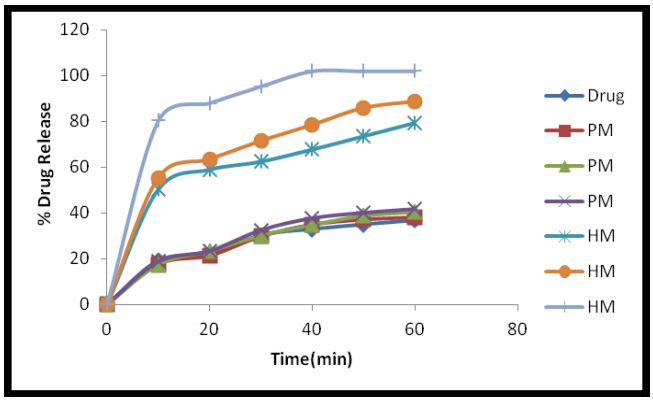

Figure 2: *In-vitro* Dissolution Profile of Acyclovir, PM and HM with PEG 6000 in pH 1.2

Similar study was carried out by preparing solid dispersion of Acyclovir with the Mannitol, the dissolution of pure drug, its physical mixture and solid dispersion prepared by hot melt method are 36.63%, 39.87% in 60 minutes and 100.99 % in 50 minutes respectively. The solid dispersion prepared in 1:3 ratio show the higher drug release in 50 minutes corresponding to other ratios that is 1:1and 1:2 which are 78.55% and 81.59% in 60 minutes respectively in pH 1.2 as shown in Figure 3.

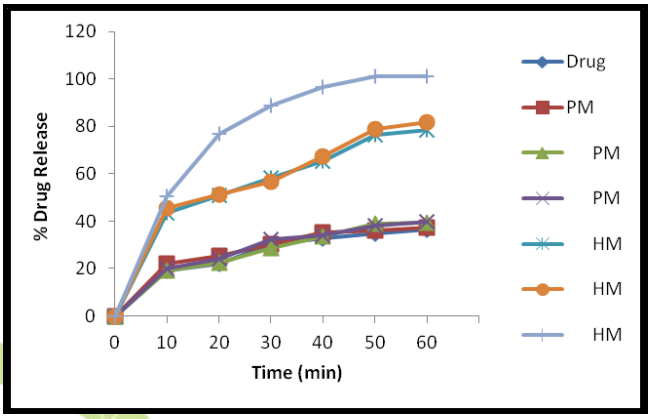

Figure 3: *In-vitro* Dissolution Profile of Acyclovir, PM and HM with Mannitol in pH 1

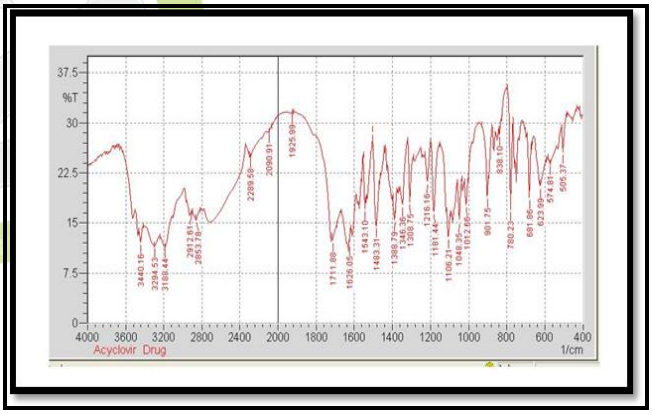

Figure 4 a): FTIR Spectrum Acyclovir

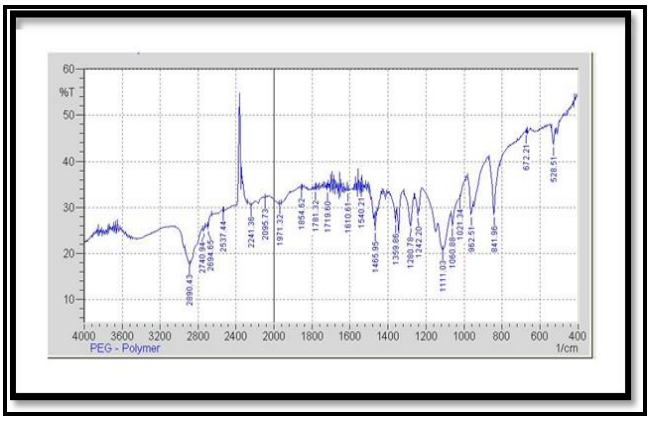

Figure 4 b): FTIR Spectrum PEG 6000

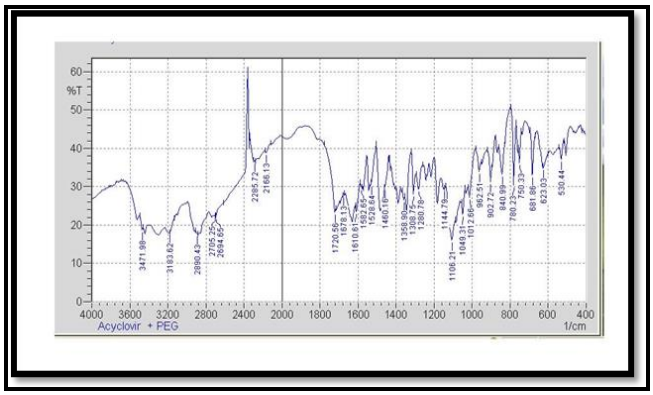

Figure 4 c): FTIR Spectrum Solid Dispersion

The drug content of physical mixture and solid dispersion prepared with PEG 6000 and Mannitol are shown in Table 1.

Table 1: Analysis of Drug Content in PM and SD

Formulation	Drug Content
PM (PEG 6000)	91.25±0.34
SD (PEG 6000)	102.50±0.73
PEG6000 (Mannitol)	93.38 ±0.03
SD (Mannitol)	100.92± 0.11

CONCLUSION

Increasing the drug carrier ratio from 1:1 to 1:3 improved drug release profiles observed in for all formulations in case of Hot melt method with PEG 6000 and Mannitol but the drug release rate was higher in 1:3 ratio for both the polymers. The drug release was found to be better in solid dispersions prepared with PEG 6000 as compared to those prepared with Mannitol.

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