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Dissolution Enhancement of Poorly Water Soluble Diacerein by Solid Dispersion Technique

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ABSTRACT

Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. In the present investigation, an attempt was made to improve the solubility and dissolution rate of a poorly soluble drug, Diacerein by solid dispersion method using PVP K-30 and HPMC E4 as carriers. Four different formulations were prepared by solvent evaporation method with varying drug: carrier ratios viz.1:1, 1:2 1:3 and 1:4 and the corresponding physical mixtures were also prepared. The formulations were characterized for solubility parameters, drug release studies and drug-polymer interactions by using phase solubility studies, DSC, XRD analysis, FTIR spectrum. All the formulations showed marked improvement in the solubility behavior and improved drug release. Formulation containing drug: polymer ratio of 1:4 with PVP K-30 showed the best release 101.22% in 70 min as compared to the pure drug i.e. 63.48% in 120 min. The interaction studies showed no interaction between the drug and the carrier. It was concluded that PVP K-30 as a carrier can be well utilized to improve the solubility of poorly soluble drugs.

Key Words: *Diacerein, Dissolution, HPMC E4, PVP K-30, Solid dispersion and Solubility.*

INTRODUCTION

Discovering a way to increase the solubility of poorly soluble drugs in order to improve their Pharmaceutical and biological availability still remains one of the major technological problems[1]. The current status of scientific development having highly variable oral bioavailability of drugs due to low solubility and dissolution rate in the gastrointestinal absorption of many new drugs. Even though there are many methods intended to solve the problem in which the formulation of solid dispersion is one of the ideal methods to dissolution enhancement. The solid dispersions as a dispersion of one or more active ingredients in an inert carrier or matrix, prepared by the melting, solvent, or melting solvent method[2]. Solid dispersions have been explored as potential delivery systems for many poorly water soluble drugs such as Griseofulvin, Indomethacin and Oxazepam. The ability of solid dispersions to afford drug release as fine, dispersed particles has resulted in improvements in dissolution rates of poorly water soluble drugs which have also been reflected in increases in oral bioavailability[3]. The increase in dissolution rate and solubility provided by solid dispersions can be explained by the mechanisms described by the Noyes–whitney equation. A significant particle size reduction can be obtained by manufacturing solid dispersions and in many cases the drug is molecularly dispersed in the carrier. Conversion of the physicochemical state of the drug, e.g. from crystalline to amorphous, as well as solubilization and supersaturation by the carrier, can cause an increase in the kinetic solubility and the dissolution rate[4].

Diacerein is an anthroquinone derivative 9, 10-dihydro-4, 5 bis (acetyl)-9, 10-dioxo-2-anthracene carboxylic acid, mainly used in osteoarthritis. From the anthronoid, Diacerein and its metabolites Rhine brake both the production of zylokine (IL-1, IL-6, IL-16 TNFa) which at the point of the inflammation cascade and proteolytic enzyme. Additionally, Diacerein stimulates the synthesis of cartilage components such as proteoglycane, glykosaminoglycane and hyaluronsa ure1-2. Molecular formula of Diacerein is $C_{19}H_{12}O_8$, Molecular weight is: 368.29 and is pale yellow crystalline powder. Diacerein is very sparingly soluble in water (0.01 mg/ml). The poor solubility and wettability of Diacerein give rise to difficulties in Pharmaceutical formulation

meant for oral or parental use, which may lead to variation in bioavailability[5].

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 i.e. Felodipine, Valdecoxib, Carbamazepine, Artemisinin , Flunarizine, Piroxicam and Diflunisal[6].

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 or alcohol and chlorohydrocarbon[7].

MATERIALS AND METHODS

Materials:

Diacerein was a gift sample from a Cipla Pharmaceuticals (Mumbai), PVP K-30 and HPMC E4 from a FDC (Goa). All other reagents and solvents were of AR grade.

Method

Solvent evaporation method

Four formulations of Solid dispersions containing Diacerein with PVP K-30 and with HPMC as carriers in ratios of 1:1, 1:2, 1:3 and 1:4 were prepared by solvent evaporation method (SE). The drug and carrier were weighed accordingly to the specified drug: carrier ratio. Diacerein and polymers were dissolved in methanol in porcelain dish. The solution was stirred till slurry was formed. The mass was dried in hot air oven maintained at 45 ^{0}C for 12 hours. Solid mass was pulverized and passed through sieve no.-60 to get uniform sized particles[8].

Physical mixture

Physical mixtures (PM) were obtained by pulverizing in a glass mortar and carefully mixing accurately weighed (1:1 to 1:4 by weight) amounts of Diacerein and Polyvinyl pyrrolidone (K-30) Diacerein and Hydroxy propyl methyl cellulose (E4)[9].

Estimation of Diacerein

Diacerein was estimated at 258 nm using double bean UV-Visible spectrophotometer (Systronics 2201). Standard calibration curve of Diacerein was plotted in pH 7.2 phosphate buffer in concentration range 2-10 µg/ml. In this concentration range good linearity was observed with the correlation coefficient (R) - 0.9998. The graph obeyed Beer-Lambert's law in the concentration range[8].

Phase solubility studies

Phase solubility studies were performed according to method reported by Higuchi and Connors. An excess of Diacerein was added to screw-capped vials containing aqueous polymer solution (1% to 4% *wt/vol* concentration range). Vials were shaken on rotary shaker at room temperature for 24 hours. At equilibrium after 2 days, aliquots were withdrawn, filtered (by Whatman filter paper no. 41) and spectrophotometrically assayed for drug content at 258 nm[10].

Assay of the drug content

Known amounts of the drug–polymer binary systems (SD and PM) were dissolved in pH 7.2 phosphate buffer and then the drug content was evaluated spectrophotometrically at 258nm, value at which the absorbance of the polymers is negligible. The experimental value was the average of three replicates[8].

Characterization of solid dispersion

1) Fourier transforms infrared spectroscopy

Fourier transforms infrared spectroscopy (FTIR) spectra of the Diacerein, PVP K-30, HPMC, their physical mixtures and solid dispersion was recorded using a Fourier Transform Infrared spectrophotometer (Schimadzu, Japan). Samples were prepared using KBr (Spectroscopic grade) disks by means of hydraulic pellet press at a pressure of 5 tons. The samples were scanned from 4000 to 400 cm^{-1}[11].

2) Differential scanning calorimetry

he DSC measurements were performed on a Differential Scanning Calorimetry (Mettler Toledo 820) with a thermal analyzer. All accurately weighed samples (5 mg) were placed in sealed aluminum pans, before heating under nitrogen flow (20 ml/min) at a scanning rate of 10^{0}C/min. from 35^{0}C- 300^{0}C. An empty aluminum pan was used as reference[12].

3) X- ray diffraction

The X-ray powder diffraction patterns were obtained by using Philips PW 1700 with Cu K alpha (Lambda) radiation and crystal monochromator, voltage: 45 mv and current 20 amp. The diffraction patterns run at 2.4^0 /min over the 2θ range of 2-50^{o} [13].

In-vitro drug release

The *in-vitro* drug release of Diacerein, its physical mixture and solid dispersions were studied in pH 7.2 phosphate buffer upto 2 hrs using USP II apparatus (Electrolab 8 station) at the speed of 100 rpm in 900 ml medium at 37±0.5^{o}C. The samples of drug, physical mixtures and solid dispersions were taken in muslin cloth and tied to the paddle. Aliquots of 10 ml, was withdrawn at regular intervals. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The 1 ml of solution was taken and diluted upto 10 ml with phosphate buffer (pH 7.2) and filtered using Whatman filter paper No.1. The filtered samples were analyzed UV-spectrophotometrically at 258 nm[5, 14].

RESULT AND DISCUSSION

Phase solubility studies

Solubility of Diacerein in Distilled water at room temperature was 10.11 µg/ml, at the highest polymer concentration (4% w/v), the solubility increased approximately 6.7 fold and 5.7 fold for PVP K-30 and HPMC at room temperature respectively. The influenced of PVP K-30 and HPMC on solubility of Diacerein is as shown in Figure No.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 A_L type of plot i.e. the solubility of Diacerein increased with increasing carrier concentration.

Drug content

The percentage drug content of physical mixture and solid dispersions prepared with PVP K-30 and HPMC are shown in Table No.1

Table No. 1: Percentage Drug Content of Physical Mixtures and Solid Dispersions

Method	Ratio	Percentage Drug Content in pH 7.2 Phosphate Buffer	
		PVP K-30	HPMC E4
Physical Mixture	1:1	92.54 ±0.08	92.55 ±0.76
	1:2	93.21± 0.42	93.43 ±0.56
	1:3	94.5± 0.43	93.34 ±2.06
	1:4	95.28 0.43	93.64 ±0.2
Solvent Evaporation Method	1:1	97.16± 1.00	98.79 ±1.11
	1:2	100.8± 0.35	100.48 ±1.02
	1:3	99.59 ±0.57	98.73 ±2.73
	1:4	99.51 ±1.26	99.51 ±1.26

(n =3)

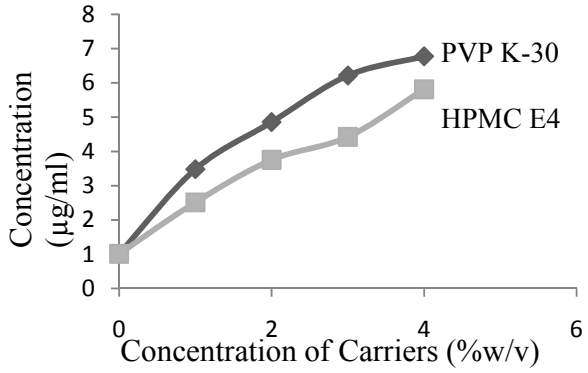

Figure No.1: Results of Concentration of Carriers on Solubility of Diacerein

Characterization of solid dispersion

1).Fourier transforms infra red spectroscopy

FTIR studies carried out to detect the possible interactions between Diacerein, PVP K-30 and HPMC in solid dispersion. The characteristics peak of Diacerein, PVP K-30, HPMC E4, their physical mixture and solid dispersion are shown in Figure No.2. Comparing the spectra of physical mixture and solid dispersion prepared by solvent evaporation method revealed that there were no differences in the position of absorption bands, hence providing no evidence for the absence of hydrogen bonding interactions in the solid state between Diacerein, PVP K-30 and HPMC E4.

2). Differential scanning calorimetry

The DSC thermogram of Diacerein showed the sharp endothermic fusion peak at 258 ^{o}C indicating its melting point and explaining good behavior of crystalline state as shown in Figure No.3A. In solid dispersion prepared by HPMC E4 and PVP K-30, the sharp endothermic peak at 258 ^{o}C is vanished indicating the formation of solid solution which is as shown in Figure No. 3H and 3G respectively.

3). X- ay diffraction

The diffraction pattern of Diacerein, PVP K-30, and HPMC E4 shows sharp peaks indicating crystalline state as shown in Figure No. 4A, 4B and 4C respectively. The solid dispersion prepared by using PVP K-30 and HPMC exhibits characteristics diffraction peaks of Diacerein, PVP K-30 and HPMC but all of reduced intensity indicating conversion of crystalline to microcrystalline state which is as shown in Figure No. 4 F and 4G respectively.

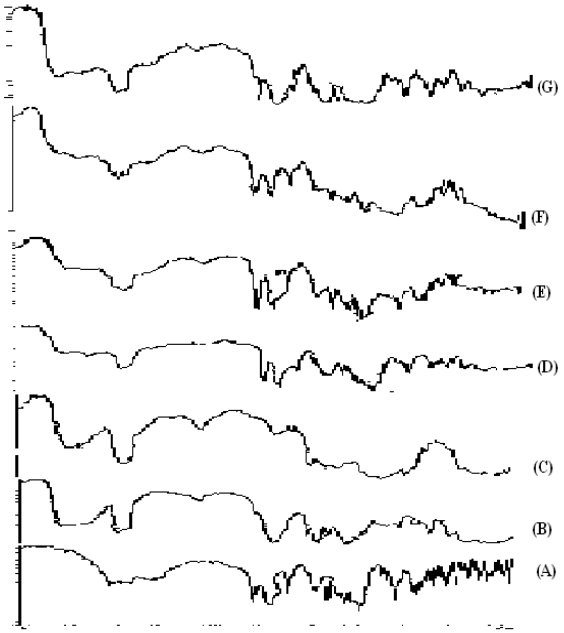

Figure No. 2 FTIR Spectrum:
(A) Pure Drug
(B) PVP K-30
(C) HPMC E4
(D) PM with PVP K-30
(E) PM with HPMC E4
(F) SD with HPMC E4
(G) SD with PVP K-30

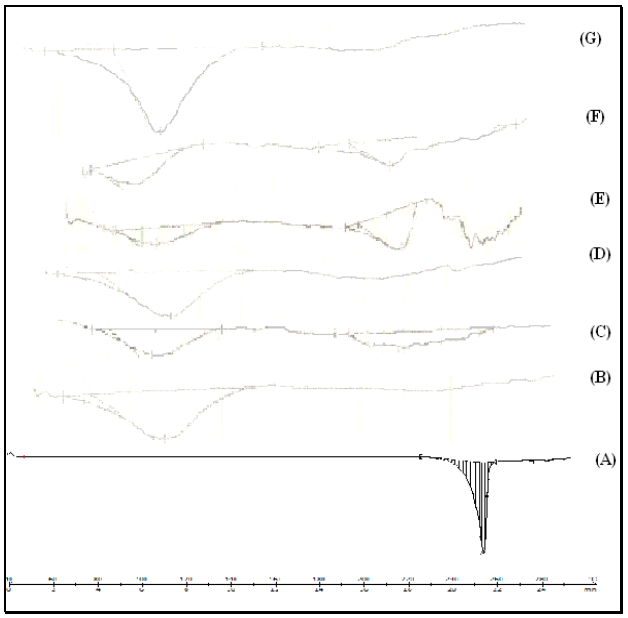

Figure No.3 DSC Thermogram:
(A) Diacerein (B) PVP K-30 (C) HPMC E4
(D) PM with PVP K-30
(E) PM with HPMC E4
(F) SD with HPMC E4
(G) SD with PVP K-30

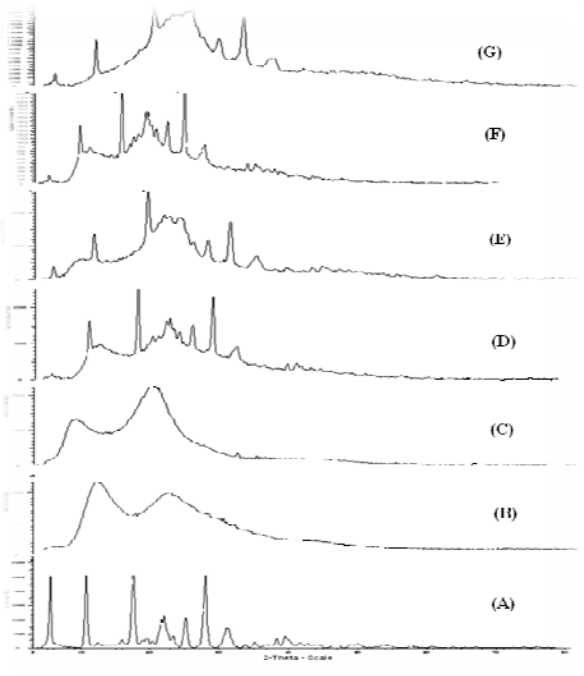

Figure No. 4 XRD Pattern: (A) Pure Drug (B) PVP K-30 (C) HPMC E4 (D) PM with PVP K-30 (E) PM with HPMC E4 (F) SD with HPMC E4 (G) SD with PVP K-30

In-vitro drug release

Diacerein release from physical mixtures, solid dispersions alone were studied in pH 7.2 phosphate buffer over the period of 2 hrs. The average percentage release of pure drug was 63.48% and in solid dispersion prepared with PVP K-30 and those prepared with HPMC were shown in Figure No. 5 and Figure No. 6 respectively. The percentage drug release increase with increased in the amount of polymer. The best results were among solid dispersion were obtained with PVP K-30 at 1:4 i.e. 101.22 % in 70 min. as compared to those prepared to HPMC E4 (1:4) i.e. 91.38% in 70 min and this is due to higher solubility of PVP K-30 in dissolution medium as compared to HPMC E4.

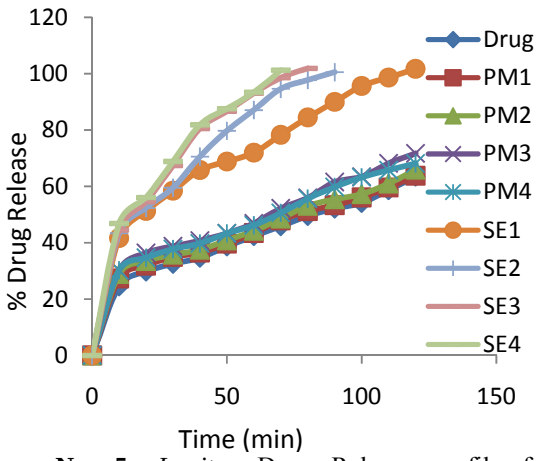

Figure No. 5: *In-vitro* Drug Release profile for Diacerein, Physical Mixtures and Solid Dispersion prepared with PVP K-30

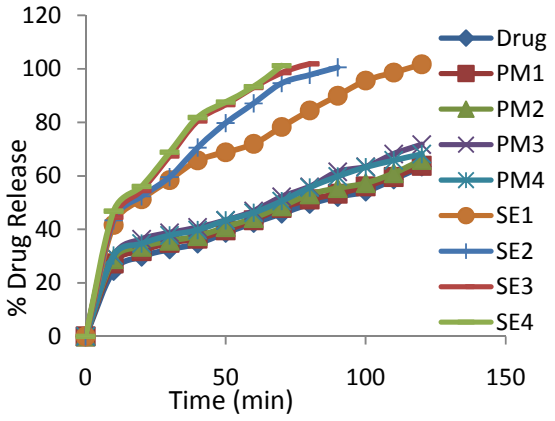

Figure No. 6: *In-vitro* Drug Release profile for Diacerein, Physical Mixtures and Solid Dispersion prepared with HPMC E4

CONCLUSION

From the results, it was observed that the solubility of Diacerein in presence of PVP K-30 and HPMC classified as A_L type. The study shows that the dissolution rate of Diacerein can be enhanced to a great extent by solid dispersion technique using solvent evaporation method due to wetting and solubilization phenomenon. The FTIR spectrum of pure drug, PVP K-30, HPMC E4 and that of solid dispersion shows that there is no chemical interaction between drug and polymers. The XRD pattern revealed that reduction in peak intensity in solid dispersion as compared to drug is due to entrapment of drug in polymers. The solid dispersion prepared by PVP K-30 shows higher dissolution rate as compared to HPMC. The higher drug release rate was found in 1:4 %w/w Diacerein: PVP K-30 i.e. 101.22% in 70 min as compared to pure drug.

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