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Research Article

SOLUBILITY ENHANCEMENT OF DIACEREIN BY MANNITOL SOLID DISPERSONS

PRASHANT S.WALKE*[1], PRASHANT S.KHAIRNAR[1], M.R.NARKHEDE [1], J.Y.NEHETE[1]

[1]Department of Pharmaceutical Sciences, MGV's Pharmacy College, Panchavati, Nashik - 422 003, Maharashtra, India.
Email: walkeprashant15@gmail.com

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ABSTRACT

Bioavailability can be increased by changing the disintegration and dissolution rate. The aqueous solubility of drugs lesser than 1µg /ml will create a bioavailability problem and thereby affecting the efficacy of the drug. There are numerous reported methods to enhance aqueous solubility of poorly soluble drug among them solid dispersions is one of the effective and accepted technique in the pharmaceutical industry. Therefore in this study attempt is done to improve the physicochemical properties of diacerein, a poorly water soluble drug, by forming dispersion with mannitol as water soluble carrier. The solid dispersions of Diacerein were prepared in ratio 1:1, 1:3 and 1:5 by physical triturating, solvent evaporation and fusion method. The results revealed that dispersions showed marked increase in the saturation solubility and dissolution rate of Diacerein as compaired to pure drug. A mannitol dispersion (1:5) prepared by fusion method showed faster dissolution rate among studied solid dispersion. The FT-IR shows the complexation and there were hydrogen bonding interactions.Solid dispersions also characterized by using DSC and PXRD. Finally, solid dispersions of Diacerein: mannitol prepared as 1:5 ratio by fusion method showed excellent physicochemical characteristics and was found to be described by dissolution kinetics and was selected as the best formulation in the study.The release study findings were well supported by the results of wettability, saturation solubility and permeability studies.

Keywords: Solid Dispersions, Diacerein, Mannitol, PXRD

INTRODUCTION

Diacerein is an anti-inflammatory, analgesic drug used in treatment rheumatoid arthritis, osteoarthiritis1. Diacerein aqueous solubility is 7 to 10 µg /ml at pH 7.0 at 40°C. After oral dosing the peak plasma concentration is reported 2.2 hours with even distribution *in-vivo* and volume of distribution of 13.2 lit. in humans[1,2]. Low bio availability of Diacerein may be due to its larger volume of distribution and lipophilic nature responsible for low aqueous solubility. Different approaches such as use of β-CD,HP-βCD has been tried to improve the solubility of Diacerein.[3] The poor aqueous solubility of the drug gives rise to difficulties in the pharmaceutical formulation of dosage forms and may lead to variable bio availability. The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rates and consequently improve the bio availability of poorly soluble drugs.

The drug is dispersed in molecular form in a pharmacologically inert carrier which freely water soluble with intrinsic rapid dissolution properties. This technique improves the poor aqueous solubility and low dissolution rates by solubilising effect of carriers, reduction in particle size, reduction in aggregation of hydrophobic drugs due to improved humectation[14].Various hydrophilic materials with high surface area can be utilized to deposit the drug on their surface. The selection of carrier and method of preparation are critical factors influencing the properties of the drug incorporated in the solid dispersion. Solid dispersion techniques can be used to increase dissolution and bioavailability of several insoluble drugs.[7] Dissolution rate of griseofulvin was increased by depositing it on the surface of disintagrants such as primogel, starch, Nymcel9. Solvent deposition technique was used to enhance the dissolution rate and anti-inflammatory effect of piroxicam. The drug is dispersed in molecular form in a pharmacologically inert carrier which freely water soluble with intrinsic rapid dissolution properties[16,22].

Several highly soluble substances can be use to accelerate the release of poorly hydrosoluble drugs.In our case Mannitol Selected as vehicle for preparation of Diacerein solid dispersions[10]. It has been chosen on the basis of its low toxicity, high aqueous solubility and physiological acceptance. It is hexahydric alcohol isomer of sorbitol,white odourless crystalline powder that possess exceptionally high thermal stability (165-167°C) and that can be heated upto 250°C without any degradation.[15,16]

MATERIALS AND METHODS

Materials

Diacerein obtained as gift sample from Tristar Formulations Pvt.Ltd, Pondicherry. Mannitol purchased from Nice chemicals Pvt. Ltd,Cochin, potassium Dihydrogen phosphate,Sodium hydroxide are of analytical grade. Methanol, obtained from Qualigens, Mumbai.

Preparation of solid dispersions

Physical mixture[16]

Physical mixtures, Diacerein and mannitol in 1:1,1:3,1:5 W/W ratios, were prepared by homogeneous blending of previously sieved and weighed quantities in mortar and pestle. The physical mixtures were subsequently stored at room temperature in desiccator over anhydrous $CaCl_2$ until use.

Solvent evaporation[8,21,22]

Diacerein and mannitol in1:1,1:3,1:5W/W ratios were dissolved in methanol and allowed to stand overnight. The solvent removed at 60°C until the solid dispersion get dried, pulverized, passed through 44 sieve and stored in a desiccator over anhydrous CaCl2 till its use.

Fusion method[17,22]

The solid dispersions containing 1:1,1:3,1:5W/W Diacerein were prepared by hot melt method. Corresponding physical mixtures were heated at 230°C until they melted. Solidification was reached by cooling to room temperature under ambient conditions. Afterwards, the mixture was pulverised, sieved, and stored in a desiccator over anhydrous CaCl2 till its use.

Evaluation of Solid Dispersions

Phase solubility studies[6]

Phase solubility studies were performed according to the method reported by Higuchi and Connors6. Solubility studies on pure drug, physical mixture and solid dispersions were conducted in thermostatic shaker bath (Labline, Chennai) for 48 hrs at 37° C ± 5° C, finally the solutions were filtered using whatmann filter paper (grade 41 Himedia), suitably diluted and absorbance measured spectrophotometrically (Shimadzu), at 257.6 nm.

All experiments were repeated in triplicate.

Drug content analysis[3]

Solid dispersion equivalent to 50 mg of DIA was dissolved in DMSO. 5ml Aliquot withdrawn, adjusted upto 100ml using 1 % w/v sodium lauryl sulphate solution and assayed UV spectrophotometrically at 257.6 nm.

***In-vitro* release[4, 5]**

Pure drug and solid dispersion equivalent to 50mg filled in suitable capsule. Dissolution studies of diacerein were performed in 900 ml of pH 6.8 Phosphate buffer solution using the USP XXV paddle method with a stirring speed of 50 rpm. At appropriate time intervals, aliquots of 1ml were withdrawn and measured spectrophotometrically (UVSpectrophotometer8453, Hewlett Packard, Germany) at λ = 257.6 nm. Experiments were carried out in triplicate, therefore only mean values with S.D.error bars are reported.

Wettability study [18,19]

Pure drug and solid dispersion, selected on basis of highest percent dissolution rate, equivalent to 50 mg of diacerein weighed and placed in a Buchner funnel. On the surface of the powder, Methylene blue powder (50mg) was layered uniformly and plunged into a beaker containing water at the same level as that of powder. The time required for wetting the methylene blue powder was taken as the wetting time.

Permeation study[20]

Pure drug and solid dispersions permeation studies were carried out in a Franz diffusion cell using Egg membrane. At predetermined time intervals drug diffusion through the membrane were determined spectrophotometrically at λ = 257.6 nm.

FT-IR spectroscopy[13]

IR spectrum of Pure drug and its solid dispersions, containing drug and Mannitol in 1:1, 1:3 and 1:5 W/W ratios , were recorded using Shimadzu FT/IR 5300,infrared spectrophotometer in scanning range 450 to 4000 cm^{-1} , by KBr disc method.

Differential Scanning Calorimetric analy*sis*

A differential scanning calorimeter (DSC 60, Shimadzu) was used to obtain the DSC curves of DIA solid dispersions and its physical mixtures representing the rates of heat uptake. About 10 mg of sample was weighed in a standard open aluminum pans, were scanned from 20-300 °C, at a heating rate of 10 °C/minute while being purged with dry nitrogen.

Powder X-ray diffractometry

Powder X-ray diffraction (PXRD) patterns were traced employing X-ray diffractometer Bruker AXS, DH Advance, Germany for the all samples, using Ni filter, CuK (α) radiation, a voltage of kV, a current of 20 mA and receiving slit of 0.2 in. The samples were analyzed over 2θ range of 5° to 60°, with scan step size of 0.020° (2θ) and scan step time of 1 second.

RESULTS AND DISCUSSION

Solubility studies

The solubility of different concentrations of drug and polymer was observed that the prepared with mannitol 1:5 presented higher dissolution concentration as compared with other formulations 1:1,1:3. When mannitol concentration was increased, the solubility was also increased in fusion and solvent evaporation method. But maximum solubility was in fusion method, 1:5 (drug: Mannitol) (276µg /ml) when compared with pure drug (10µg /ml) Table 1.

Table1: Phase solubility study of Diacerein

Methods	Drug: Mannitol(Conc. µg /ml) % W/W		
	1:1	1:3	1:5
Physical Mixture	207	215	222
Solvent Evaporation	231	244	264
Fusion	251	263	276

Drug content analysis

The drug content of different concentrations of drug and polymer was estimated spectrophotometrically at 257.6 nm as was tabulated in Table 2

Table 2: Effect of concentration of Drug: Carrier ratio on %drug content of Diacerein From prepared solid dispersion

Method	1:1 (50%w/w)	1:3(33.33%w/w)	1:5(20%w/w)
Physical mixture	97.99	98.13	99.14
Solvent Evaporation	99.23	99.19	99.79
Fusion Method	99.03	99.14	101.46

In vitro Release studies

The dissolution parameters of the samples and profiles compared with the pure drug are shown in Table.3 and Fig.1 respectively.

Table 3: Invitro dissolution parameter of Diacerein-Mannitol solid dispersions

Time(Min)	% Release			
	Pure drug	PM	SE	FM
0	0	0	0	0
10	10.11	13.8	52.54	30.08
20	15.88	30.77	68.73	64.07
30	29.44	68.32	87.06	78.19
40	42.56	88.12	90.96	85.09
50	49.98	93.85	93.06	93.831
60	55.48	95.33	86.783	99.77

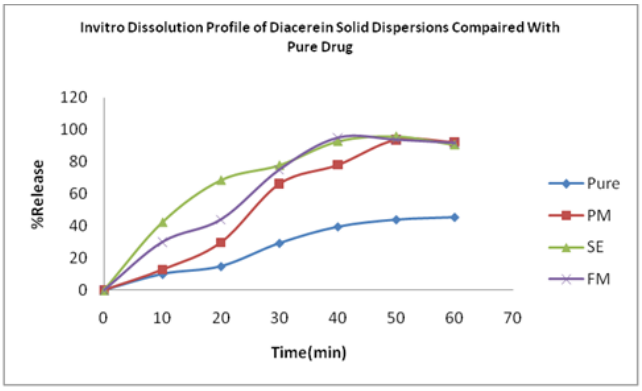

Fig. 1: Invitro Release profile of Diacerein-Mannitol Solid dispersions with pure drug, PM: Physical mixture, SE: Solvent Evaporation, FM: Fusion Method

Wettability studies

The wetting time of the pure drug was found to be 80 mins and the water absorption ratio 3.904, which clearly indicates its poor wettability. The wetting time of the selected Samples was found to be much less and the water absorption ratio was higher than for the pure drug. ($p > 0.05$). This behavior may be attributed to an increased wettability due to presence of hydrophilic carriers in the samples. Table 4

Permeation studies

It was noted that, the amount of drug that permeated through the membranes was found to be higher than the pure drug ($p>0.05$) these findings can be considered as being evidence for an increased release rate of Diacerein from solid dispersions.Table 4

Table 4: Evaluation Parameters for Formulations

Formulation	Saturation Solubility (mg/ml)	Permeability (mg/ml/hr)	Wettability
		Egg Membrane	Buchner Funnel Method (Min)
Pure drug	10	0.022	82
Solvent evaporation	25	0.055	36
Physical Mixture	32	0.040	44
Fusion Method	52	0.061	26

Spectroscopy Study

IR spectra of pure drug and solid Dispersions were compared to confirm the presence of drug. Absorbance at 1190 cm^{-1} and 1207 cm^{-1}showed the presence of drug. These bands were Shifted in the solid dispersion method(fusion method)due to possible hydrogen bonding between the carrier and drug which showed that complex has been formed and indicates that the drug was not degraded in the presence of mannitol or solid dispersions or in complex.

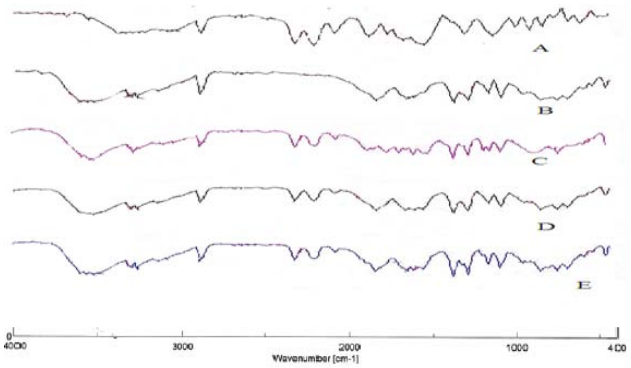

Fig. 2: FT-IR Spectra of Diacerein-Mannitol System FT-IR Spectra Of Diacerein (A),Manitol (B),Melt Agglomeration Method (C),Solvent Evaporation Method(D),Kneading Method (E).

Differential Scanning calorimetric analysis

The DSC curve of DIA exhibited a sharp endothermic peak at 253 ºC due to fusion. Analogously, the thermal curve of Mannitol showed a single endothermic effect with a peak at 170 ºC, corresponding to its melting point. The physical mixture showed an Diacerein and Mannitol derived endothermic peaks with decreased intensity than pure DIA. The thermo grams of both binary systems physical mixture,solvent evaporation and Fusion method showed no endothermic peak corresponding to DIA. It is quite probable that DIA might have dissolved in the molten carrier during DSC scan.

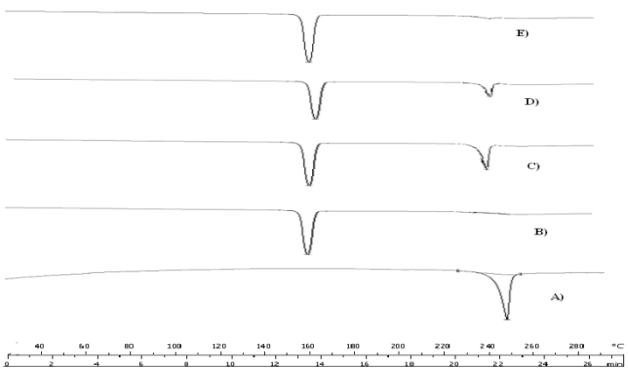

Fig. 3: DSC Thermogram of Diacerein-Mannitol System DSC Thermogram Of Diacerein (A),Mannitol (B), Kneading Method (C),Solvent Evaporation Method(D), Melt Agglomeration Method (E).

Powder X-ray diffractometr

The crystalline nature of the DIA, Mannitol, physical mixture and solid dispersions was determined by PXRD . In the diffractograms, all diffraction peaks were due to carrier crystals and no diffraction peaks of DIA in the physical mixture and solid dispersion was observed. This indicates that the amorphous state of DIA was formed in the solid dispersion system.

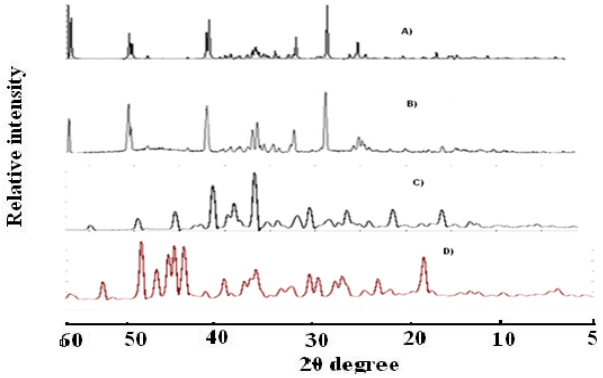

Fig. 4: PXRD of Diacerein-Mannitol System PXRD Of Diacerein (A), Kneading Method (B),Solvent Evaporation Method(C), Melt Agglomeration Method (D)

CONCLUSION

The solid dispersion of DIA was prepared to improve the solubility, dissolution rate, wettability and permeability. Analytical method of IR spectrum was confirmed the drug carrier interaction or complex and showed that the drug was not degraded. A maximum increase in dissolution rates was obtained with the ratio of 1:5 but fusion method showed faster dissolution rate when compared with that of the pure drug and other complexes. The possible mechanisms for an increased release rate from the samples were also postulated and were well supported by study findings, such as in-vitro release, phase solubility, saturation solubility, wettability and permeation study data.Therefore, it can be concluded that the aqueous solubility of poorly soluble drugs can be significantly improved by utilizing the solid dispersion technique, relatively easily.

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