International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.4, No.3, pp 1159-1166, July-Sept 2012

Different Binary Polymer Mixture For Solubility Enhancement Of Poorly Water Soluble Drug By Solid Dispersion Technique

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Abstract: A solvent evaporation method was used to prepare fluconazole solid dispersions in the presence of various carriers. The amount of ethanol used to prepare solid dispersions did not have a significant effect on the dissolution rate of fluconazole. The results of X-ray diffraction and thermal analysis indicated that the drug was in the amorphous state when PVP, HPMC, were used as carriers. The dissolution rates of fluconazole in PVP, HPMC, However, dissolution profiles were found to depend on the carrier used; the dissolution rate of fluconazole increased slowly for solid dispersions prepared using HPMC, whereas rapid initial dissolution rates were observed for solid dispersions prepared using PVP.Increases in dissolution rates were partly dependent on the ratios of fluconazole to carrier. The results of DSC and XRD studies showed that fluconazole in solid dispersions exists in the amorphous state in PVP, HPMC. These results confirm that the solvent evaporation method could be used to prepare fluconazole solid dispersions using PVP, HPMC,as carriers, as a means of enhancing fluconazole dissolution rates.
Keywords:-binary mixture,fluconazole,Solvent evaporation method,DSC,In vitro study.

1. INTRODUCTION

In pharmaceutical technology there exist numerous drug substances, including new chemical entities, that in spite of their high therapeutic effectiveness, are characterized by poor water solubility. The latter limits their potential uses in formulating bioavailable pharmaceutical products. In all those cases, the rate limiting factor for drug absorption becomes the dissolution rate of the active ingredient in the gastro-intestinal liquids (20,21,22) Therefore, the enhancement of oral bioavailability of such poor water-soluble drugs and the preparation of solid oral dosage forms is currently one of major objectives and greatest challenges in the area of new formulations development. 'Solid dispersion' is one of the earlier, yet still favorable, approaches for overcoming this limitation. Owing to its simplicity from the manufacturing and process scalability standpoints, solid dispersion has become one of the most active and promising research areas of great interest to pharmaceutical companies. Furthermore,

such formulations possess considerable advantages over other commonly used techniques, especially micronization. Hence it is expected that the popularity of solid dispersions will grow rapidly (). The term solid dispersion refers to solid state mixtures, prepared through the dispersion, typically by solvent evaporation or melt mixing, of one or more active ingredients in an inert carrier matrix (16,17,18). In these dispersions, the drug can be present in a fully crystalline state (in the form of coarse drug particles), in a semicrystalline state, and in fully amorphous state (in the form of a fine particle dispersion, ormolecularly distributed within the carrier). Such systems prove to be very effective for enhancing the dissolution rate of low solubility drugs. Poly(ethylene glycol) (PEG) and polyvinylpyrrolidone (PVP) are the most used drug carriers for solid dispersion preparations (10,11,12) due to their strong hydrophilic properties and their capability to form molecular adducts with many compounds. The presence of hydroxyl or carbonyl groups in the repeat units of these polymers tend to increase the water solubility () of the drug and also improve its bioavailability (18,19,20). The enhanced dissolution rate characteristic of solid dispersions can generally be accounted for by one of the following mechanisms; eutectic formation, increased surface area of the drug due to precipitation in the carrier, solid solution formation, improved wettability due to intimate contact with a hydrophilic carrier, precipitation as a metastable crystalline form or a decrease in substance crystallinity. Both the properties of the carrier-drug combination and the method of manufacture will influence the type of solid dispersion formed, and thus the subsequent behaviour of the solid dispersion (24,25). Solid dispersions are generally prepared by one of two methods, co-melting of drug carrier mixtures or dissolving drug and carrier in a mutual solvent followed by solvent removal. For example, direct extrusion of melts into hard gelatin capsules, or the compression moulding of transdermal patches, could be possibilities for large scale manufacturing. Hydrophilic synthetic polymers have been widely investigated as carrier substances for solid dispersions. In this paper, a solvent wetting method was used to prepare solid dispersions of flucoazole. This method requires the minimal amount of solvent in dissolving the drug.We used various polymeric carriers in this study. Polyvinylpyrrolidone (PVP), was chosen as water-soluble polymers. Hydroxypropylmethylcellulose (HPMC) was chosen as a swelling and eroding polymer in water. The physicochemical properties of fluconazole in solid dispersions were characterized by differential scanning calorimetry and powder X-ray diffraction, and the effects of various hydrophilic solid dispersion carriers on its dissolution properties were investigated. Another was to explore the additional influence of blending some of these polymers. Finally,by comparing the properties of the solid dispersions made by this method with those made using the more standard solvent evaporation method.

2 EXPERIMENTAL METHODS

2.1. CHEMICALS AND REAGENTS

FLU (fluconazole) was a generous gift from Cipla India Pvt. Ltd. (Mumbai, India). Polyvinyl - pyrrolidone (Kollidon_K30) and Hydroxypropyl methylcellulose (HPMC) was provided by were provided by BASF (Ludwigshafen, Germany). All other chemicals were of reagent grade and were used without further purification.

2.2 PREPARATION OF FLUCANAZOLE SOLID DISPERSIONS WITH HYDROPHILIC POLYMERS BY SOLVENT EVAPORATION METHOD:-

The solid dispersions were prepared by dissolving the mixture of flucanazole at the weight ratios of which given below table with the aid of a minimal volume of ethanol in which hydrophilic adsorbent carrier lactose was suspended in constant ratio added init.[8,10] The solvent was removed by evaporation under reduced pressure at 37^{o}C (Veggo Vacuum oven,India). Solid mass obtained was passed through the # 80 and stored in vacuum desiccator until use.

Batch No.	Drug	PVPK30	HPMC	Lactose
B-1	1	1	1	1
B-2	1	2	1	1
B-3	1	2	2	1
B-4	1	1	2	1

PHYSICOCHEMICAL CHARACTERIZATION:

1. SOLUBILITY MEASUREMENTS:-

The saturation solubility of drug and SD with PVPK30 and HPMC in distilled water and phosphate buffer saline (PBS pH 7.4) was determined by adding an excess of drug and SD to 10 ml distilled water or PBS in glass stoppered tubes. The stoppered tubes were rotated for 24 h in water bath shaker at 37^{o}C. The saturated solutions were filtered through a 0.45 µm membrane filter, suitably diluted with water and analyzed by UV spectrophotometer, UV-1601PC, Shimadzu, Japan .

2. DRUG CONTENT:-

Drug Content and Percent Yield Solid dispersions equivalent to 60 mg of fluconazole were weighed accurately and dissolved in a suitable quantity of ethanol. The solutions were filtered through a membrane filter (0.45 μm). The drug content was determined at 262 nm by UV spectrophotometer (UV-1601PC, Shimadzu, Japan,) after suitable dilution. Analysis of data were done using Disso v 2.08 software. The percentage yield of each formulation was also calculated.

SOLID STATE CHARACTERIZATION:-

DRIFTS STUDY:-

The DRIFTS spectra of pure fluconazole, spray-dried fluconazole physical mixtures, and solid dispersions were obtained, after appropriate background subtraction, using an FTIR spectrometer (FTIR-8400, Shimadzu Corp) equipped with a diffuse reflectance accessory (DRS-8000, Shimadzu Corp) and a data station. About 2 to 3 mg of the sample was mixed with dry potassium bromide, and the sample was scanned from 4,000 to 400 cm-1.

XRPD STUDY

The XRPD patterns were recorded on a radiograph diffractometer (PW 1729, Philips, Eindhoven, The Netherlands). The samples were irradiated with monochromatized Cu Ka radiation (1.542_ A) and analyzed between 2 and 50_ (2u). The voltage and current used were 30 kV and 30 mA, respectively. The range and the chart speed were 5 3 103 CPS and 10 mm/_ (2u), respectively.

DSC STUDY:-

DSC studies were conducted using a Mettler-Toledo DSC 821e instrument equipped with an intracooler (Mettler- Toledo, Greifensee, Switzerland). Indium/zinc standards were used to calibrate the DSC temperature and enthalpy scale. The samples were hermetically sealed into pierced aluminum pans and heated at a constant rate of 10^0C/min over a temperature range of 25 to 170^0C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 mL/min.

SHAPE AND SURFACE MORPHOLOGY

The shape and surface morphology of the solid dispersion was studied by scanning electron. microscopy (SEM), JEOL, JSM 50A, Tokyo, Japan. The samples were mounted on double-sided adhesive tape that has previously been secured on copper stubs and then analyzed. The accelerating voltage was 5 kV.

DISSOLUTION STUDY:-

The dissolution studies were performed using a US Pharmacopeia type II dissolution test apparatus (Electrolab TDT-06P, Mumbai, India). The samples equivalent to 60 mg fluconazole were placed in a dissolution vessel containing 900 mL of phosphate buffer (pH 6.8) maintained at 37.6+ 0.5^0C and stirred at 100 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper no. 41, a concentration of fluconazole was determined spectrophotometrically at 232.4 nm. Data were analyzed by PCPDisso software.

Table 1-Various solid dispersion batches with different ratios(w/w) prepared by spray drying(SD) & physical mixture(PM)

Type of formulation with batches	Fluconazole	Aerosil 200	PVPK30
SD-1	1	1	1
SD-2	1	2	2
PM-3	1	1	1
PM-4	1	2	2

Table 2- Solubility studies of drug and solid dispersions Samples

Batch No.	Solubility (μg/ml)	
	Water	PBS
Pure Drug	22.04 + 0.56	57.06 + 0.67
B-1	41.87 + 1.21	52.76 + 1.21
B-2	77.79 + 1.35	81.89 + 2.35
B-3	32.59 + 1.12	63.78 + 1.19
B-4	35.22 + 1.05	55.12 + 1.13

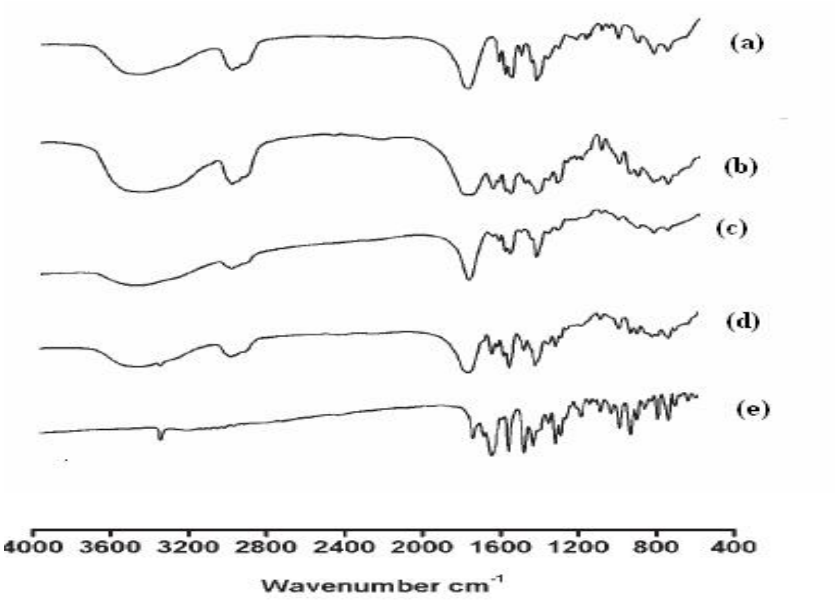

Fig 1. DRIFT spectra's of pure drug(a) B-1(b),B-2(c) B-3(d),B-4(e)

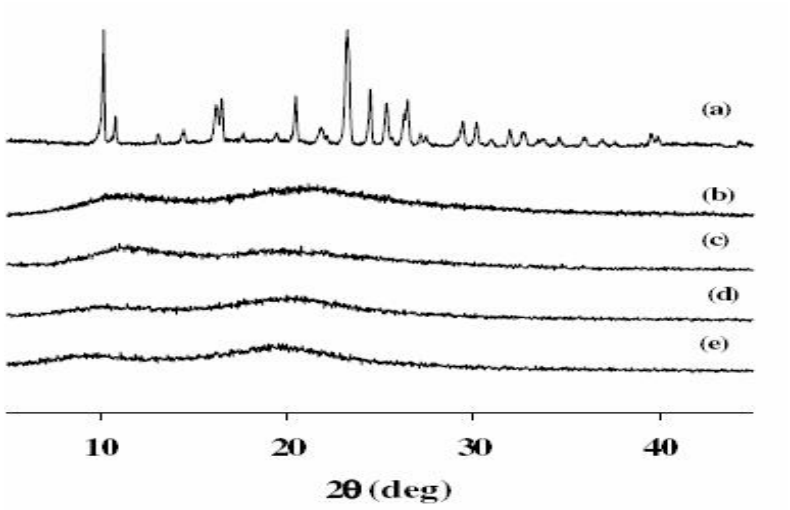

Fig 2. XRD of pure drug(a) B-1(b),B-2(c) B-3(d),B-4(e)

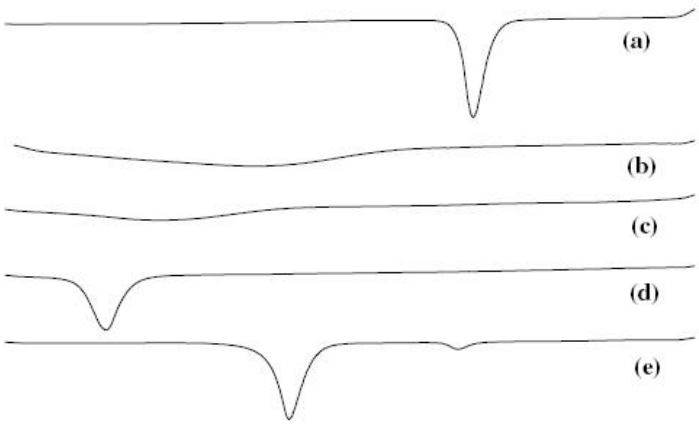

Fig 3. DSC pure drug(a) B-1(b),B-2(c) B-3(d),B-4(e)

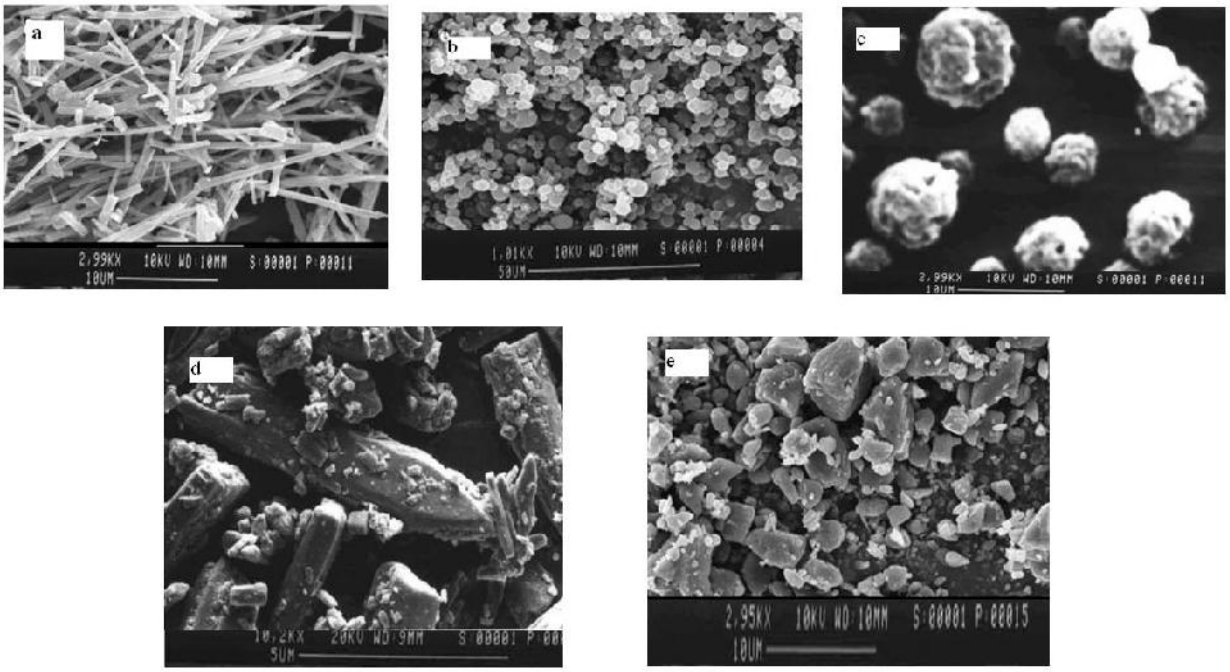

Fig 4. SEM of pure drug(a) B-1(b),B-2(c) B-3(d),B-4(e)

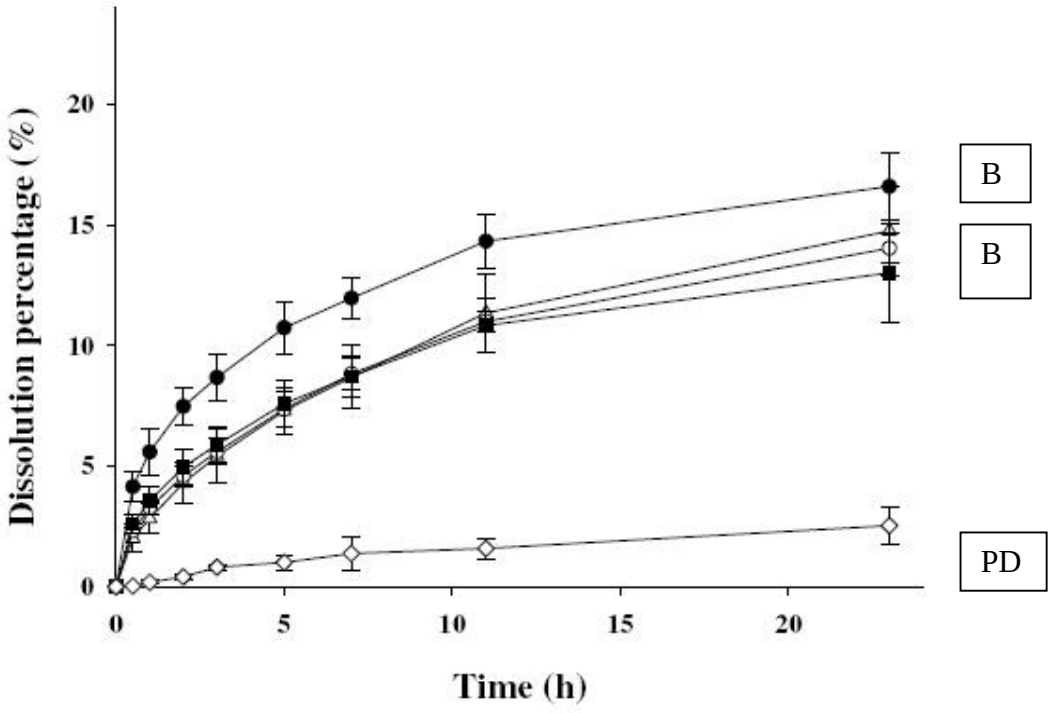

Fig. 5. Dissolution rate of fluconazole from solid dispersions prepared by different polymers ratio

RESULT AND DISCUSSION:-

SOLUBILITY STUDIES AND DRUG CONTENT:-

The results of saturation solubility studies are given in Table 2. The solubility of pure drug in water and in PBS (pH 7.4) was found to be 27.04 ± 0.56 and 57.06 ± 0.67 µg/ml. The solubility of SD using PVPK30 (1:1:1: and 1:2:2 w/w) in water was found to be 46.87 ± 1.24, 57.79 ± 1.35µg/ml and in PBS (pH 7.472.76 ± 1.21, 81.89 ± 2.35 µg/ml respectively. The drug content of solid dispersion with PVPK 30 was found to be in the range of 95 ± 1.45 to 98 ± 2.36% .The increases in solubility of fluconazole in Batch 2 probably may be due to the formation of soluble complexes between water-soluble polymeric carrier and poorly soluble drug. And it might be attributable to an improvement of wetting of drug particles and localized solubilization by the adsorbent carriers.(5,8,9)

FTIR ANALYSIS:-

FTIR is a very powerful technique in detecting presence of interaction in drug-carrier solid dispersions. The appearance or disappearance of peaks and/or the shift of their positions are often indications of interactions such as hydrogen bonding. The intermolecular interaction of complex system was established by FTIR. **Fig 1** shows Fluconazole presenting the characteristic peak of triazole group CH stretching .Fluconazole presented characteristic peak at 3116.77 cm^{-1} was due to CH stretching vibration. In 2.4-Difluorobenzyl group at 1619.34 cm^{-1} presenting C=C stretching vibration , peak at 1421.65cm^{-1} was due to CH_2 scissor stretching vibration and peak at 1110.86cm^{-1} was due to C—C stretching vibration. Due to solvent peak was show at 916.97, In Solid dispersion presented possibility of hydrogen bonding between Fluconazole and PVP due to PVP has two groups =N, =O that can be potentially form hydrogen bond with the drug. At molecular level in SD formulation.However,steric hindrance precludes the involvement of nitrogen atom in intermolecular interaction, thus making the carbonyl group more favorable for hydrogen bonding(5,9,10)

XRD STUDY :-

The diffraction spectra of fluconazole showed numerous distinct peaks indicating presence of high crystalline state. From the X-Ray diffraction profile, the characteristic fluconazole peaks with high intensity were found to be 2θ at 13.490 14.80, 22.86, 23.98, 24.70, 26.04, 29.85, 31.42, 32.9. The XRD pattern of solid dispersion of sample in all batches exhibited all the characteristic diffraction peaks of fluconazole with lower intensity. This study revealed that the crystallinity was reduced to a certain extent in the solid dispersion form. Intensity of peak sharpness was reduced in solid dispersion compared to pure drug was observed in batch B2. In the case of solid dispersions with PVP and HPMC, no characteristic fluconazole peaks were observed. These results are in accord with previous DSC results, confirming that fluconazole was transformed from a crystal to an amorphous form upon dispersion by the solvent evaporation method. Crystallization inhibition was attributed to two effects: interactions, such as hydrogen bonding between the drug and the polymer and the entrapment of the drug molecules in the polymer matrix during solvent evaporation or a combination of both.(Fig. 2) In SDs the characteristic peaks of drug disappeared with significant elevation of the diffractograms in lower ratios.(5,15).

THERMAL ANALYSIS:-

DSC curves of fluconazole, their crystallinity of fluconazole in the solid dispersions are shown in Fig.3. Pure fluconazole gave melting endotherms at around indicating that the drug is in cubic crystalline form. DSC thermograms of solid dispersions batches showed the broad endotherms due to water removal at about 100– 140.8^{0}C. Melting of fluconazole could be observed between 170 and 180.8^{0}C which shown in Fig.3 whereas no such peak was observed in solid dispersions prepared with PVP and HPMC, suggesting that fluconazole was molecularly dispersed and in an amorphous form. The similarity in DSC curves and PXRD patterns with solid dispersion samples indicated that fluconazole was amorphously dispersed in batch B2.Because the interaction between fluconazole and PVP could be induced during the heating process in DSC programs as reported (15,16) .

SHAPE AND SURFACE MORPHOLOGY:-

The SEM results are shown in Fig 4. The surface morphology studies revealed that the solid dispersion was closely compacted into small spherical form. fluconazole existed in exhibited flat broken needles of different sizes, with well-developed edges consisted of large crystalline particles of rather irregular size. On the contrary, the solid dispersions appeared in the form of spherical particles and the original morphology of components disappeared, which supported DSC and XRD data. These results demonstrated that fluconazole in solid dispersion was homogeneously dispersed into PVP K30 at the molecular level.(5,15,22)

DISSOLUTION STUDY

It was also observed that the dissolution rates of fluconazole from solid dispersions were markedly higher than for pure drug. These increases in dissolution rates are attributable to changes in crystal structure, which were demonstrated by the results of DSC and XRD studies. Moreover, as the ratio of HPMC was increased, the dissolution rate of fluconazole increased. Although both HPMC and PVP enhanced significantly the dissolution rate of fluconazole in batch B2, their dissolution profiles were quite different from each other, i.e., PVP solid dispersions showed rapid initial dissolution, whereas HPMC showed gradually increasing dissolution. HPMC is known to form a hydrogel [22,23] and to slowly erode in water, which probably explains this delayed dissolution.Thus, fluconazole can be made with binary mixture with PVP and HPMC to obtain SDs containing amorphous form of fluconazole. Due to anti-plasticizing activity of PVP, viscosity of the binary system increases, which thereby decreases the diffusion of drug molecules necessary to form crystal lattice (5, 11,17)

CONCLUSION:-

Solid dispersions of fluconazole were prepared using the solvent evaporation method and various polymeric carriers. The results of DSC and XRD studies showed that fluconazole in solid dispersions exists in the amorphous state in PVP, HPMC, used as carriers. The dissolution rate of fluconazole from PVP, HPMC solid dispersions was markedly higher than from their corresponding pure drug. These results confirm that the solvent evaporation method could be used to prepare fluconazole solid dispersions using binary mixtures of PVP, HPMC, as carriers, as a means of enhancing fluconazole dissolution rates **.**It may be concluded that solid dispersions of the poorly water-soluble drug fluconazole were successfully prepared by binary system using hydrophilic carriers.

ACKNOWLEDGEMENTS:- The authors are grateful thanks to Shivaji University Kolhapur to Department of physics allowing the X-ray Diffraction,Scanning Eletronic Microscopic and Differential Scanning Calorimetric studies.

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