International Journal of Drug Delivery 5 (2013) 323-330

http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Solid Dispersions of Poorly Water Soluble Drug Using Spray Drying Technique

Shinde Sunita S*[1] , Patil Manisha V[1] Amol Shete S[2] , Disouza JI[1] Atpadikar Pranit[1]

***Corresponding author:**

Shinde Sunita S.

[1]Department Of Pharmaceutics, Tatayasaheb Kore College of Pharmacy[1], Warananagar, India
[2]Department of Pharmacognosy, Ashokrao Mane College of Pharmacy[2],Pethvadgaon, India

Abstract

The basic objectives of this study were to prepare and characterize solid dispersions of poorly water-soluble drug fluconazole using hydrophilic carriers by spray drying technique.

In the present study, a spray drying technique has been used to prepare solid dispersions with hydrophilic carriers, mainly PVP K30and porous carrier Aerosil 200 are used

Solid dispersions in the form of spray dried powder were characterized in comparison with pure drug and corresponding physical mixtures in the same ratios by SEM, IR, DSC, and XRPD studies.

The absence of fluconazole peaks in XRPD profiles of solid dispersions suggests the transformation of crystalline fluconazole into an amorphous form. the absence of fluconazole peak in DSC curves of solid dispersions. The DRIFTS spectra revealed the presence of hydrogen bonding in solid dispersions. The in vitro dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure fluconazole, spray-dried fluconazole, and physical mixtures of drug with hydrophilic carriers.

It may be concluded that solid dispersions of the purely water-soluble drug fluconazole were successfully prepared by spray drying using hydrophilic carriers

Keywords: Fluconazole; PVP; Spray drying; Solid dispersion; Dissolution enhancement.

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 [14]. 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 stand points, 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 [11]. To enhance the dissolution rate, increasing the drug solubility is necessary according to the Noyes–Whitney equation. Various studies have been done in attempt to improve solubilities of poorly water soluble drugs; they include micronization, solid dispersion, solvent deposition, ordered mixture, roll-mixing and complexation. Some of the dissolution- enhancing methods have been applied for the production of pharmaceutical preparations. Among these, a solid dispersion is one of the effective methods for enhancing the drug dissolution rates. 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 [13]. In these dispersions, the drug can be present in a fully crystalline state (in the form of coarse drug particles), in a semi crystalline state, and in fully amorphous state (in the form of a fine particle dispersion, or molecularly distributed within the carrier). Such systems prove to be very effective for enhancing the dissolution rate of low solubility drugs. [12] Pharmaceutical materials that are processed by high energy processes such as spray drying, spray drying, jet milling, melt extrusion and so forth are often rendered at least partially amorphous. This occurs by virtue of that these processes create conditions that can prevent crystallinization or mechanically disrupt the structure of an existing crystalline material .The high internal energy and specific volume of the amorphous state to relative the crystalline state can lead to enhanced dissolution and bioavailability, but can also create a possibility that is may spontaneously convert back to the more stable crystalline state during processing or storage .As stated earlier ,the application of spray drying technique to obtain amorphous form of the drug substances either alone or in combination with a hydrophilic polymer is now known .The technique has desirable characteristics that the resultant particles

are spherical and free flowing The method also offers advantage that granulation and drying are completed in one step[5]
Fluconazole is antifungal drug, which is often administered orally. Fluconazole exhibits very slightly soluble and as a consequence it exhibits low bioavailibity after oral administration. Therefore the improvement of fluconazole dissolution from its oral solid dosage forms is an important issue for enhancing its therapeutic efficiency. Fluconazole is insoluble in water which leads to poor dissolution rate and subsequent decrease in its gastrointestinal (GI) absorption [6]. Results of several investigations revealed that the absorption of Fluconazole was limited by its dissolution rate. The formation of amorphous forms to increase drug solubility and the reduction of particle size to expand surface area for dissolution and decrease the interfacial tension with the aid of a water-soluble carrier are among the possible mechanisms for increasing dissolution rates there by improving bioavailability of poor water-soluble drugs. The most commonly used hydrophilic carriers for solid dispersions include PEG, PVP, colloidal silicon dioxide, and lipids, such as polyglycolized glycerides (Gelucire) [4]. The solvent evaporation, melt adsorption, fusion, spray drying, spray freezing, spray congealing, melt extrusion, and supercritical fluid precipitation are the techniques reported for the preparation of solid dispersions. [7]. in the present work, spray drying techniques was used to prepare Fluconazole solid dispersions. Hydrophilic carriers like PVP-K30 using porous carrier Aerosil 200 are used to prepare solid dispersions of Fluconazole with different ratios of drug to carrier. The pure drug (PD), physical mixture and Solid Dispersion (SD) were subjected to DSC, IR and X- Ray Diffraction (XRD) spectroscopic studies to elucidate possible crystal changes in Fluconazole and drug-carrier interactions. Hence the present study was aimed to improve the solubility and/or dissolution rate of poorly water-soluble drug through the solid dispersion approach.

Preparation of Solid Dispersion (SD)

FLU either alone or in combination with PVP (1:1.1:2 parts by weight) was dissolved in sufficient amount ethanol, to clear solution proposed quantity of aerosil200 (Table I), was slowly added to obtain uniform suspension. Spray drying was carried out using laboratory scale spray dryer (LU-20Advanced Model, Labultima,Mumbai, India), under the following set of conditions: inlet temperature 100ºC, outlet temperature, 60 ºC, feed rate–6 ml/min, atomization air pressure 2kg cm/2)and aspiration pressure (_200 mm WC) .Physical mixtures (PMs) in the same ratios were also prepared, shown in Table 1. Physical characterization and dissolution studies of SDs and PMs were performed in comparison with pure drug.

Table1-Various solid dispersion batches with different ratios prepared by spray drying(SD) & physical mixture(PM)

Type of formulation	Fluconazole	Aerosil 200	PVPK30
SD-I	1	1	1
SD-I	1	2	2
PM-III	1	1	1
PM-IV	1	2	2

Physicochemical Characterization
Solubility Measurements

The saturation solubility of drug and SD with PVPK30 (1:1:1: and 1:2:2 w/w) 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 37ºC. 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, .

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

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

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

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^{0}C 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.

Results and Discussion

Table2: Solubility studies of drug and solid dispersions Samples

Solubility studies of drug and solid dispersions Samples	Solubility (µg/ml)	
	Water	PBS
Pure drug	27.04 ± 0.56	57.06 ± 0.67
SD-1	46.87 ± 1.24	72.76 ± 1.21
SD-2	57.79 ± 1.35	81.89 ± 2.35
PM-3	35.59 ± 1.12	63.78 ± 1.19
PM-4	36.22 ± 1.05	65.12 ± 1.13

Solubility Studies and Drug Content

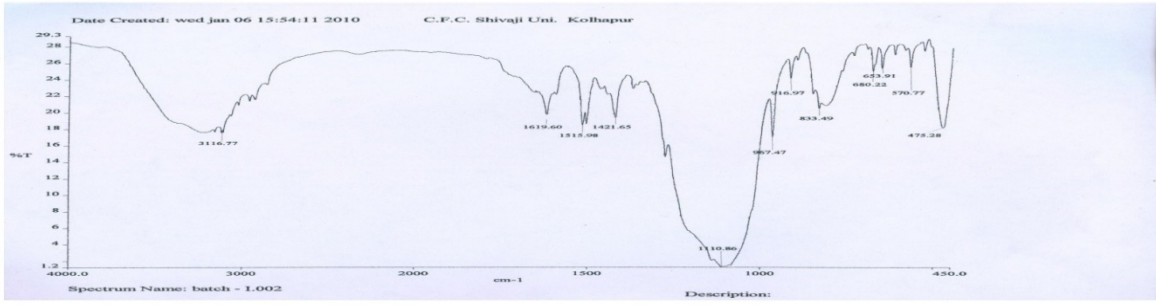
The results of saturation solubility studies are given in Table 2. The solubility of pure drug in water and in PBS (pH 7.4) was found to be 27.04 ± 0.56 and 57.06 ± 0.67 µg/ml. The solubility of SD using PVPK30 (1:1:1: and 1:2:2 w/w) in water was found to be 46.87 ± 1.24, 57.79 ± 1.35µg/ml and in PBS (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 by PVP K30 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 porous carriers.[5,15,17]

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. Figure 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, Only representative spectrum is shown in, to be Influenced of the incorporation of aerosil200, the presence of prominent peak at 1107cm-1, which is hydrogen bonding potential of silonal groups located in local environment of silica is well documented, 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]

Infra-Red spectroscopy(IR)

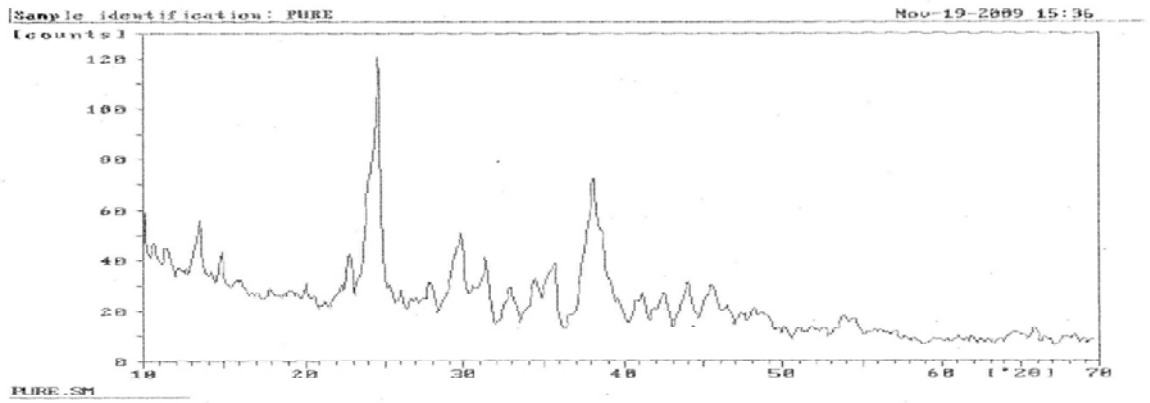
Batch-I = Pure drug+PVP K30+Aerosil (1:1:1)



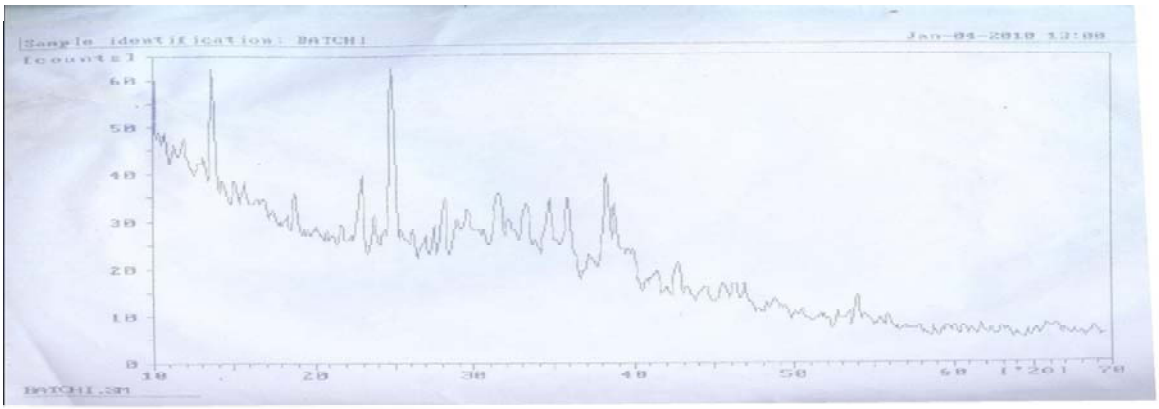
Batch-II =Pure drug+PVP K30+Aerosil (1:2:2)

Figure 1. DRIFT spectras of pure drug(a) SD-1(b),SD-2(c) PM-3(d),PM-4(e)

Batch-III = Pure drug



Batch-I = drug +PVP K30+Aerosil (1:1:1)



Batch-II = drug+PVP K30+Aerosil (1:2:2)

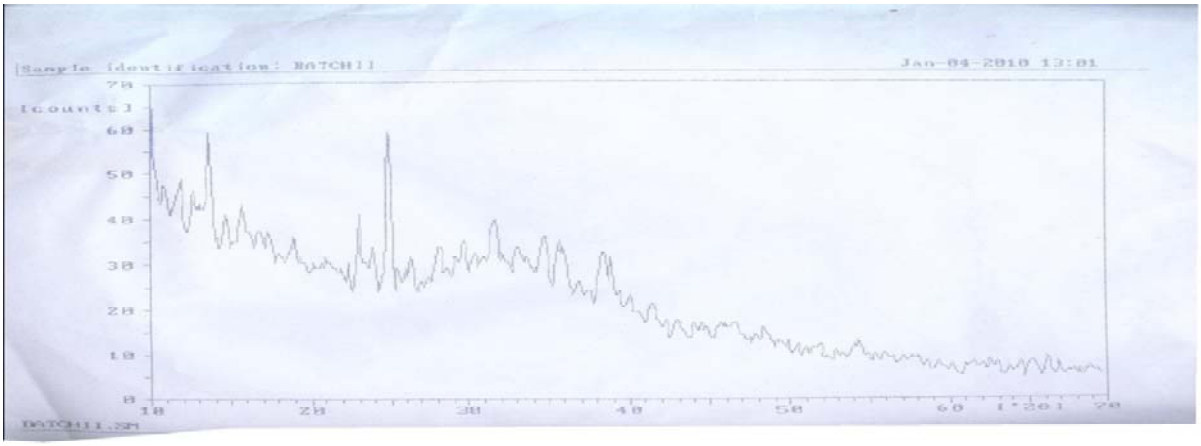


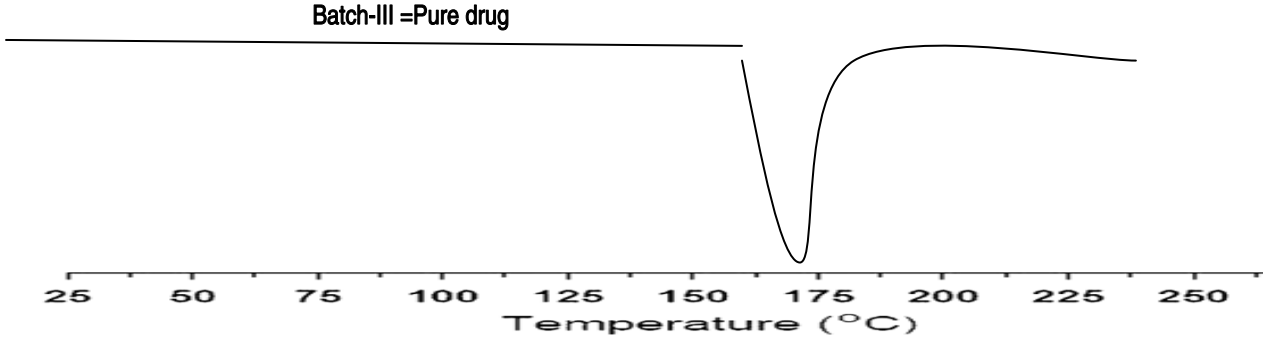
Figure. 2. PXRD diffractograms for pure drug(a) SD-1(b),SD-2(c) PM-3(d),PM-4(e)

XRD

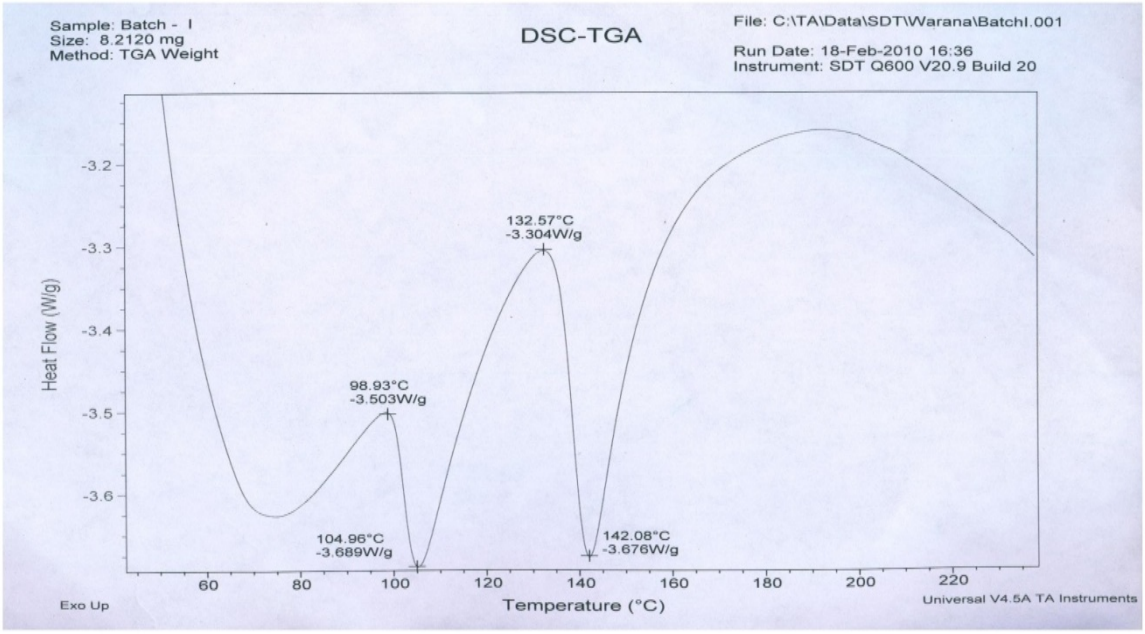
The diffraction spectra of fluconazole showed numerous distinct peaks indicating presence of high crystalline state. From the X-Ray diffraction profile, the characteristic fluconazole peaks with high intensity were found to be 2θ at 13.490 14.80, 22.86, 23.98, 24.70, 26.04, 29.85, 31.42, 32.9. The XRD pattern of solid dispersion of sample SD-2 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. Various studies have shown that PVP K30 inhibits crystallinity of drugs and resulting in amorphous nature of drug in the solid dispersions. 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. The solvent was removed during the preparation of solid dispersions, viscosity of the system increased very rapidly leading to a decrease in drug mobility. When the solvent was evaporated completely, drug molecules were frozen in the polymer matrix. (Figure. 2) In SDs the characteristic peaks of drug disappeared with significant elevation of the diffractograms in lower ratios.[5,15] In PMs, the carrier appeared as an elevated baseline and the drug produced characteristic diffraction peaks.

Thermal Analysis

Batch-III =Pure drug



Batch-I =Pure drug+PVP K30+Aerosil (1:1:1)



Batch-II =Pure drug+PVP K30+Aerosil (1:2:2)

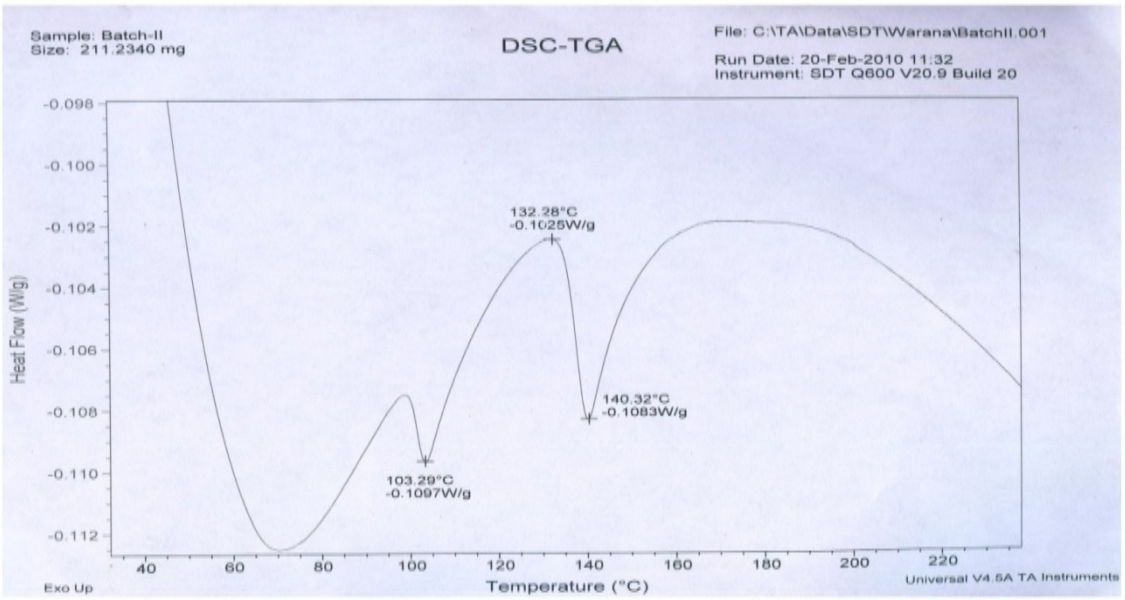
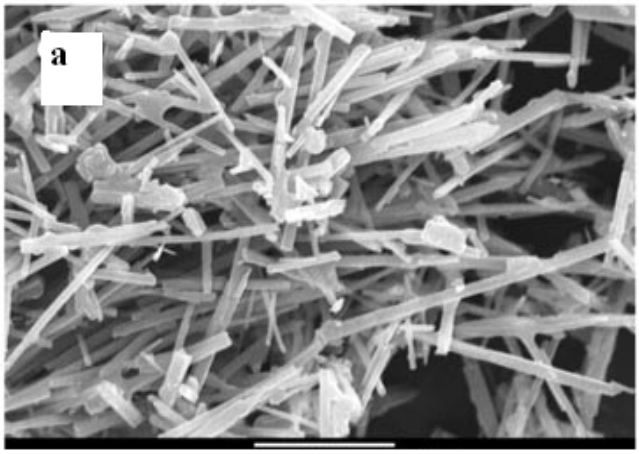


Figure 3 Differential scanning calorimetry thermograms of Pure drug(a),SD-1(b),SD-2(c) PM-3(d),PM-4(e)

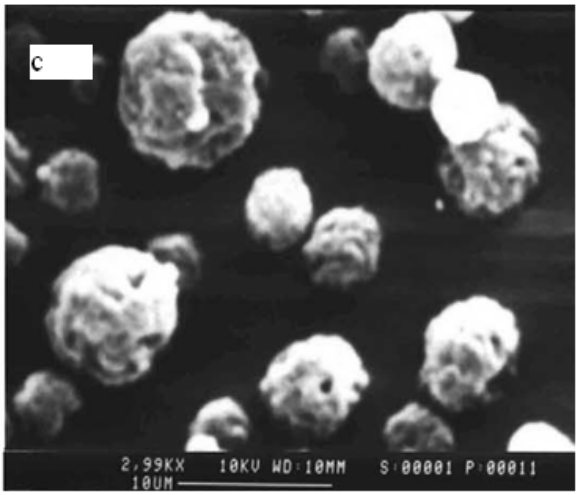
DSC curves of fluconazole, their physical mixture, and spray-dried samples to the amorphicity or crystallinity of fluconazole in the solid dispersions are shown in Figure.3. Pure fluconazole gave melting endotherms at around indicating that the drug is in cubic crystalline form. DSC thermograms of physical mixtures and solid dispersions showed the broad endotherms due to water removal at about 100–140.80C. Melting of fluconazole could be observed between 170 and 180.80C with the physical mixture Figure.3 Melting of fluconazole solid dispersions prepared by spray drying processing fluconazole not is observed when the ratio of drug to PVP was lower than 1:4, which is compatible with their PXRD observations. The similarity in DSC curves and PXRD patterns with spray-dried samples indicated that fluconazole was amorphously dispersed in PVP K30. Because the interaction between fluconazole and PVP could be induced during the heating process in DSC programs as reported [15,16].



DSC Studies

Shape and Surface Morphology

The SEM results are shown in Figure 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, 15.17]



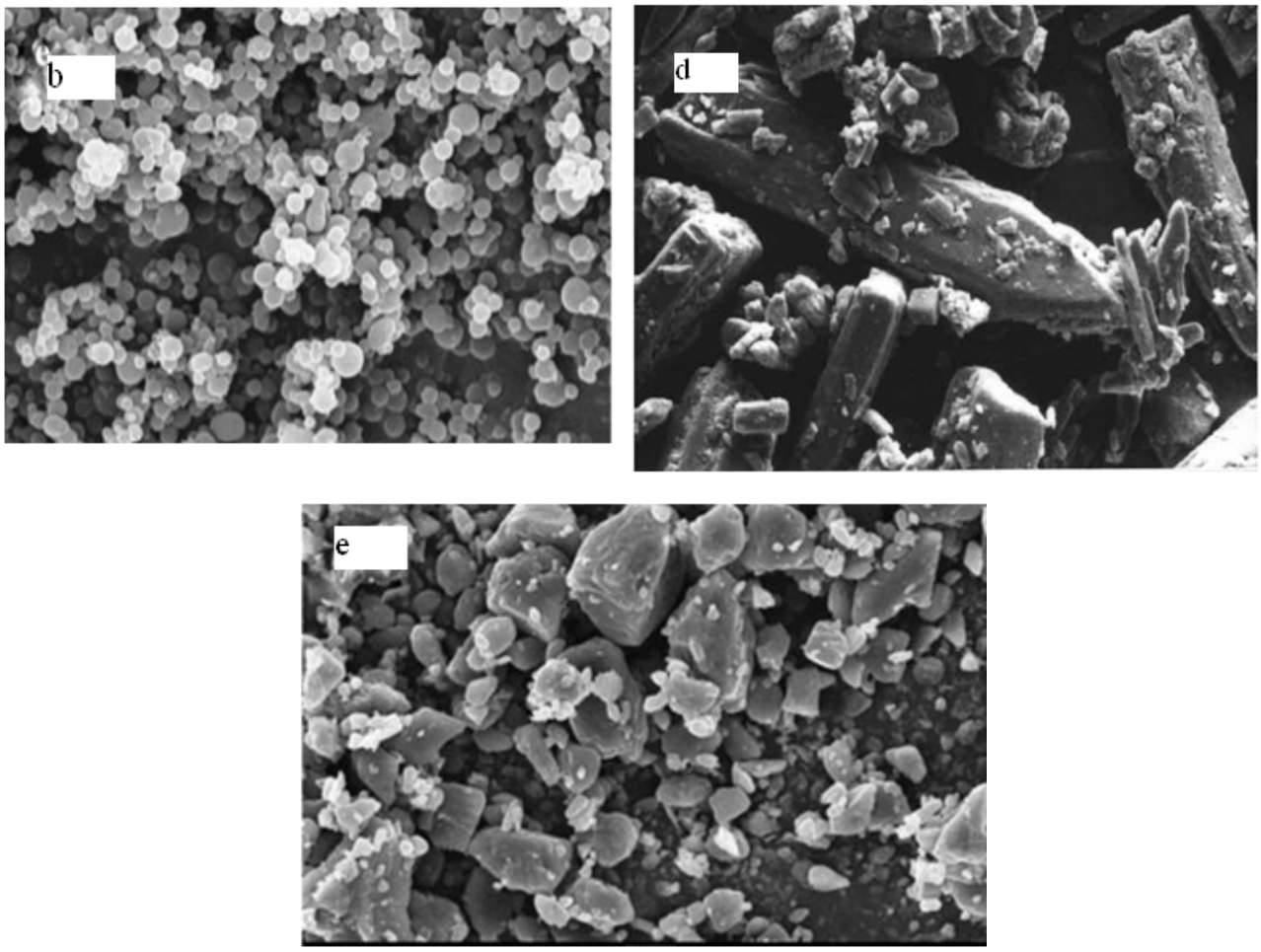


Figure 4.SEM of pure drug(a) SD-1(b),SD-2(c) PM-3(d),PM-4(e)

Dissolution Study

During dissolution study, pure fluconazole and its PMs showed negligible release even after 90 min (Figure.5). Whereas, SDs showed drastic increase in dissolution rate with increasing concentrations of PVP). Increase in dissolution rate of SDs as compared with corresponding PMs was attributed to changes in the solid state during the formation of dispersion. It might be owing to the formation of high-energy amorphous phase as supported by XRPD and DSC data. Thus, fluconazole can be co-spray dried with PVP 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] PMs with PVP did not affect the physical state of drug and hence no improvement in dissolution characteristics was observed.

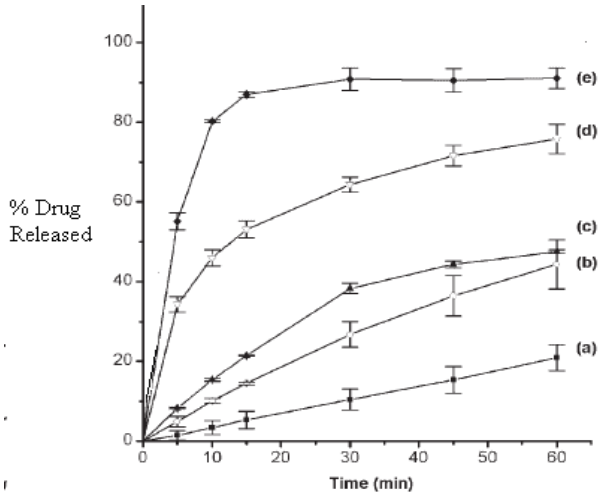


Figure 5. Comparative dissolution profiles of different formulations of fluconazole. Each point refers to mean ± SD(n=3), pure drug(a) SD-1(b),SD-2(c) PM-3(d),PM-4(e)

Conclusion

It may be concluded that solid dispersions of the purely water-soluble drug fluconazole were successfully prepared by spray drying using hydrophilic carriers. DRIFT spectroscopy revealed the possibility of H-bonding interactions in solid dispersions, which was also supported by DSC and XRPD observations. The in vitro dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure fluconazole, spray-dried fluconazole and physical mixtures of drug with hydrophilic carriers.Therefore, the dissolution rate of the poorly water-soluble drug fluconazole can be significantly enhanced by the preparation of solids using hydrophilic carriers by the spray drying technique.

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.

References

[1]. Patterson JE, James MB. et al. Preparation of glass solutions of three poorly water soluble drugs by spray drying, melt extrusion and ball milling. Int. J. Pharma., 2007, 336: 22–34.

[2]. Hansen T, Holm P. et al. In vivo evaluation of tablets and capsules containing spray-dried o/w-emulsions for oral delivery of poorly soluble drugs Int. J. Pharma., 2005, 293: 203–211.

[3]. Ameye D, Mus D, Foreman P. et al.Spray-dried Amioca® starch/Carbopol® 974P mixtures as buccal bioadhesive carriers., drugs Int. J. Pharma 2005,301: 170–180.

[4]. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. . Eur J Pharm Biopharm; 2000 50: 47-60.

[5]. Ambike A, Mahadik KR.et al spray dried amorphous solid dispersion of simvastatin a low Tg drug in vitro and in vivo evaluation.,Pharmaceutical research; 2005:22:6

[6]. Hong S, Lee S, Chung S, Lee M. et al Accelerated oral absorption of gliclazide in human subjects from a soft gelatin capsule containing a PEG 400 suspension of gliclazide. .J. Control. Rel.; 1998,51:185–192.

[7]. Sapkal NP, Kilor KP, Bhusari AS. et al. Evaluation of some Methods for Preparing

[8]. Gliclazide- β-Cyclodextrin Inclusion Complexes. Trop. J. of Pharma. Res. 2007, 6 (4): 833-840.

[9]. Takeuchi H, Nagira S, Yamamoto H. et al Solid dispersion particles of tolbutamide prepared with fine silica particles by the spray-drying method.; Powder Technology. 2004, 141:1187-1195.

[10]. Taylor LS, Zografi G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm Res. 1997 ,14:1691–1698.

[11]. Mooter V, Augustijns P, Blaton N. et al. Physico-chemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30. Int J Pharm 1998,164:67–80.

[12]. Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems and recent breakthroughs. J. Pharm. Sci. 1999. 88:1058–1066.

[13]. Georgarakis M, Docoslis A. et al Combining SEM, TEM, and micro-Raman techniques to differentiate between the amorphous molecular level dispersions and nanodispersions of a poorly water-soluble drug within a polymer matrix . Int J Pharm32007,40: 76–83

[14]. Chiou WL, Riegelmann S. Pharmaceutical applications of solid dispersion systems.. J. Pharm. Sci. 1971,60:1281–1302.

[15]. H¨orter D Dressman. JB. Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract..Adv. Drug Del. Rev. 2001,46:75–87.

[16]. Paradkar A, Ambike A. Characterization of curcumin–PVP solid dispersion obtained by spray drying ; Int J Pharm 2004,271:281–286

[17]. Chauhan B, Shimpi S, Paradkar A. Preparation and characterization of etoricoxib solid dispersions using lipid carriers by spray drying technique, AAPS Pharm. Sci. Tech. 2005.6: E405–E412.

[18]. Paradkar AR, Chauhan B, Pawar AP. Preparation and characterization of glassy celecoxib.Drug Dev Ind Pharm. 2003,29:739-744

[19]. Gupta MK, Tseng YC, Goldman D. et al. Hydrogen bonding with adsorbent during storage governs drug dissolution from solid-dispersion granules. Pharm Res.2002 ,19:1663-1672.