# Studies on Mechanism of Enhanced Dissolution of Albendazole Solid Dispersions with Crystalline Carriers

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The main purpose of this research was to study the mechanism of drug release from solid dispersions of albendazole, giving special emphasis to particle size of the drug in solid dispersions. Solid dispersions were prepared using three different carriers, mixing ratios and methods in an attempt to improve the solubility and dissolution rate of albendazole. The mechanism of enhanced dissolution was investigated by a novel dissolution technique as an adjunct to phase solubility study, wettability test, differential scanning calorimetry, X-ray diffractometry, infrared spectroscopy and scanning electron microscopy. The solubility of albendazole was greater with albendazole-poloxamer 407 system, while polyethylene glycol dispersions showed predominant wettability. Physical mixtures showed enhanced dissolution compared with the pure drug, due to improved wetting and solubilization of drug in the diffusion layer offering carrier-rich microenvironment. Preparation of solid dispersion further improved the dissolution compared to the physical mixture, owing to increased surface area for mass transfer, thermodynamically enhanced dissolution of a higher energy amorphous form from the carrier, in addition to improved wetting and solubilization. All carriers showed comparable degree of drug particle size reduction, whereas mixing ratio and method of preparation substantially affected the particle size. Intermolecular association of drug with the carrier led to inhibition of drug recrystallization.



World health organization has recommended albendazole (ABZ) as an adjunct as well as alternative to surgery for the management of hepatic and pulmonary echinococcosis caused by *Echinococcus granulosus*[1]. Systemic absorption of this drug is warranted also during the treatment of extra-ocular and cerebral cysticercosis, though the most effective treatment for the latter is debated[2–4]. ABZ belongs to biopharmaceutical classification system (BSC) type II (low aqueous solubility with high permeability)[5-6].

Preparation of ABZ solid dispersion (SD) by solvent evaporation method using an amorphous carrier (polyvinylpyrrolidone) at 1:10, 1:20 and 1:40 (drug-carrier) ratios; X-ray diffraction (XRD) patterns; solubility and dissolution profiles of the same have been reported earlier[7]. The aim of the present task was to prepare amorphous dispersion of ABZ in crystalline carriers, namely, urea, polyethylene glycol 6000 (PEG) and poloxamer 407 (PXR), and to study the extent of inhibition of drug recrystallization as well as other mechanisms of improved dissolution of ABZ from SDs.

Adsorbent carriers have been recommended previously for size reduction of drug particles during preparation of SD[8]. Recently, researchers have also reviewed methods for preparing molecular dispersion (solid solution) employing different carriers[9]. However, only few reports include experiments trying to measure or confirm particle size reduction of drug in the SD[10–12]. The present study has been designed to examine the particle size of drug in SD using a novel dissolution technique as an adjunct to routine evaluation methods meant for assessing solubility, wettability, crystallinity, drug-carrier interaction and morphology.

## MATERIALS AND METHODS

The following materials were used: ABZ (gift sample from Juggat Pharma, Bangalore, India), mebendazole (gift sample from Cadila Pharmaceuticals Ltd., Ahmedabad, India), urea and polyethylene glycol 6000 (Qualigens, Mumbai, India), poloxamer 407 (gift sample from BASF India Ltd., Chennai, India). All other materials used were

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of either HPLC or analytical grade.

**Formulations:**
Physical mixture (PM) was prepared by mixing ABZ with urea or PEG or PXR for 5 min at 1:1, 1:3 and 1:5 weight ratios using glass mortar and pestle. Melting method (MM), solvent method (SM) and kneading method (KM) were followed for the preparation of SDs[13-14]. The procedures are given below in the same order:

The PM was heated by stirring at 190-200° in an oil bath to achieve a homogenous dispersion. When the solid was completely dissolved, the hot liquid was shifted to a water bath (99°) with continued stirring. It was then subsequently cooled to 25°. The congealed mass was pulverized, passed through 30 mesh, stored in a vacuum desiccator (12 h) and passed through 60 mesh before packaging in an airtight container.

The PM was dissolved in a minimal volume of anhydrous methanol, and the solvent was removed by slow evaporation under reduced pressure. The dried co-precipitate was passed through 30 mesh, stored in a vacuum desiccator (48 h) and passed through 60 mesh before packaging in an airtight container.

The PM was triturated using a small volume of methanol-water (1:1) solution to give a thick paste, which was kneaded (30 min) and then dried at 45° in an oven. The dried mass was pulverized, passed through 30 mesh, stored in a vacuum desiccator (48 h) and passed through 60 mesh before packaging in an airtight container. When methanol alone was used for kneading, the thick paste got dried immediately. To avoid drying of the solvent during kneading, methanol was previously mixed with water (1:1) and then used for the kneading process. The SDs blocked the 60 mesh screen unless passed previously through 30 mesh and dried in a vacuum desiccator.

**Assay of drug content:**
The drug content of SD or PM was determined spectrophotometrically by dissolving the sample in glacial acetic acid, followed by sufficient dilution with water to measure the absorbance at 291 nm (UV-1601PC, Shimadzu)[15].

**Phase solubility study:**
Phase solubility study for ABZ was performed as described by Higuchi and Connors[16]. Excess amount of ABZ was added to aqueous solutions containing the carrier at various concentrations and shaken for 96 h at 25 and 37°. Samples were withdrawn, filtered through a membrane filter (0.45 µm), diluted with water and analyzed in a spectrophotometer (UV-1601PC, Shimadzu) at 291 nm.

**Contact angle:**
Sample powder from pure drug or PM or SD (300 mg) was compressed into a pellet by a hydraulic press at 5000 kg/cm$^2$ pressure (1 min) (KP 462, Kimaya Engineering, Thane, India). Water (20 µl) was placed from a micro syringe on the pellet surface, and the drop was photographed after 3 s for the determination of contact angle as described preveously[17-18].

**Thermal analyses:**
Thermal analyses were carried out as reported previously[13-14]. Differential scanning calorimetry (DSC) for all powder samples was performed on a differential scanning calorimeter (DSC-60, Shimadzu, Japan) using 2-4 mg of sample in a closed aluminium pan at a heating rate of 5°/min from 35 to 300° under a nitrogen purge of 40 ml/min. TA 60WS software (version 1.4, Shimadzu, Japan) was used.

In order to evaluate the presence of residual solvent in the SDs, thermogravimetric analysis (TGA) was performed. Samples (10-12 mg) were placed in open pans and heated at a rate of 10°/min under nitrogen purge (40 ml/min) from room temperature to 110°. Subsequently, the samples were kept isothermally (5 min) at 110°. Weight loss occurring between ambient temperature and 110° was considered to be the weight of residual solvent.

**Powder X-ray diffraction:**
XRD was carried out for all preparations and pure drug employing a $CuK_\alpha$ source operating at 40 kV, 20 mA, 3°/min scanning rate and 3° to 40° (2θ) range (JDX 8030, Jeol, Japan). The positions and intensities of diffraction peaks were considered for the identification and comparison of crystallinity of the drug or carrier[18].

**Infrared spectroscopy:**
Fourier transform infrared (FTIR) spectra were obtained on a Perkin-Elmer Fourier transform infrared spectrophotometer (Spectrum one B 68718, USA) with a resolution of 2 cm$^{-1}$ from 4000 to 400 cm$^{-1}$. KBr pellets were prepared by gently mixing the sample with KBr (1:100 ratio).

**Particle size analysis and scanning electron microscopy:**
Particle size and size distribution of the pure drug sample

was determined using a laser scattering particle size analyzer (Horiba LA - 910, Japan). The morphology of pure drug, PM and SDs was studied using a scanning electron microscope (JSM-5610 LV, Jeol, Japan). Images were recorded at 800 times magnification.

**Dissolution study:**

*In vitro* dissolution studies for all preparations and pure drug equivalent to 20 mg of ABZ were carried out in 900 ml of distilled water at 37° using USP XXIII type 2 dissolution apparatus (TDT-06P, Electrolab, Mumbai, India) with an agitation of 50 rpm for 2 or 8 h. To avoid floating, the sample was clamped between infusion filter paper pieces and immersed in the dissolution medium. The sample (2 ml) withdrawn at different time intervals was filtered through a membrane filter (0.45 µm) and processed as described previously[19]. The filtered sample (0.5 ml) in a 15 ml test tube was mixed with 3 ml of borate buffer (pH 10.5) (5 min) and chloroform (4 ml) using a vortex mixer. It was then centrifuged at 2500 rpm (10 min). Chloroform layer (2 ml) was transferred to another test tube, and the solvent was evaporated to dryness in vacuum at 40°. The residue in the tube was reconstituted with acetonitrile (0.1-0.2 ml) containing mebendazole as an internal standard (1 µg/ml) and injected (20 µl) into an HPLC system.

The samples were analyzed following HPLC method reported previously[19]. A liquid chromatograph (LC-10ADVP, Shimadzu, Japan) equipped with a variable wavelength UV detector (SPD-10A, Shimadzu), a Rheodyne injector valve (model 7125) and a Supelcosil ODS analytical column (5 µm, 0.46 cm × 25 i.d.) was used. The mobile phase consisted of a 0.05 M phosphate buffer (pH 7.0)-acetonitrile (55:45), and the pH of the same was adjusted to 6.5 using phosphoric acid. The flow rate was 1.0 ml/min, and the detection was at 310 nm.

## RESULTS AND DISCUSSION

Fig. 1 shows solubility profile of ABZ influenced by carrier material concentrations at two different temperatures. Both PEG and urea exhibited similar effect on the solubility, while PXR showed an enormous improvement. There was a requirement of minimum concentration of PXR (0.75%) to exhibit the solubility enhancement. This might be attributed to its surface-active property and critical micelle concentration. PXR is a polyoxyethylene-polypropylene block copolymer (structurally related to PEG) non-ionic surfactant with a hydrophilic-lipophilic balance value of 18-23 used as

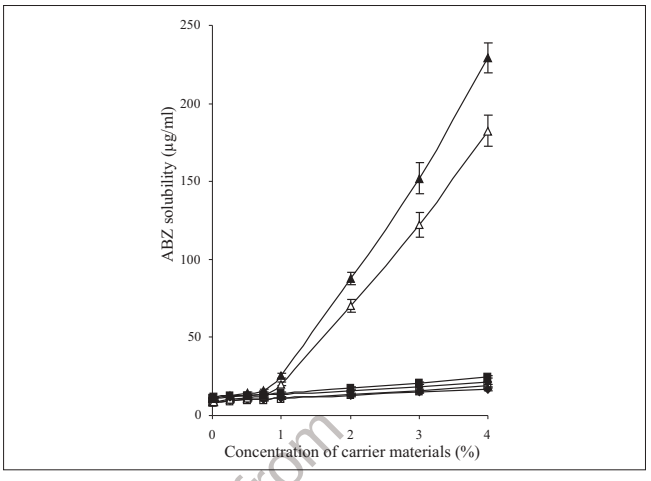


**Fig. 1: Phase solubility diagram of ABZ**
**Phase solubility of ABZ at 37° (open symbols) and 25° (closed symbols) in presence of urea (•), PEG (□) and PXR (△)**

potential emulsifier and solubilizer in pharmaceutical preparations[20]. Recently this polymer has also been used as a solid dispersion carrier[14,21]. There was a rise in the solubility when the study temperature was reduced from 37 to 25°. The exothermic nature of the solubility enhancement predicted hydrogen bond formation between drug and carrier, since a rise in temperature disfavours hydrogen bonding. This finding was also supporting the choice of these carriers in situations where they would prevent the mobility of drug molecules to reunite and recrystallize during formation of SD. Similar hydrogen bonding is possible in the SD also when the drug is molecularly dispersed in a carrier (solid solution). Wettability was significantly improved in all SDs compared to pure drug (fig. 2). Mixing ratio and method of preparation had only a slight effect on the contact angle. PEG systems showed the best wettability, whereas PXR systems had relatively less wettability among the dispersions prepared.

Fig. 3 shows DSC thermograms. Pure drug, PM and SDs of 1:1 drug:carrier ratio had an endothermic peak at 195-200°, corresponding to melting of ABZ. Such melting peak with ABZ-PXR dispersions of 1:1 ratio was not as sharp as observed with ABZ-urea or ABZ-PEG systems, signifying that drug solubility in PXR is relatively high. SDs in urea or PEG or PXR of 1:3 ratio, regardless of the method of preparation, showed a broad endotherm (not shown) at a temperature lower than the melting point of ABZ. The SDs of 1:5 drug:carrier ratio, irrespective of the method of preparation, showed almost disappearance of drug peak, suggesting two possibilities - namely, amorphous precipitation of the drug and better solubilization in the carrier.

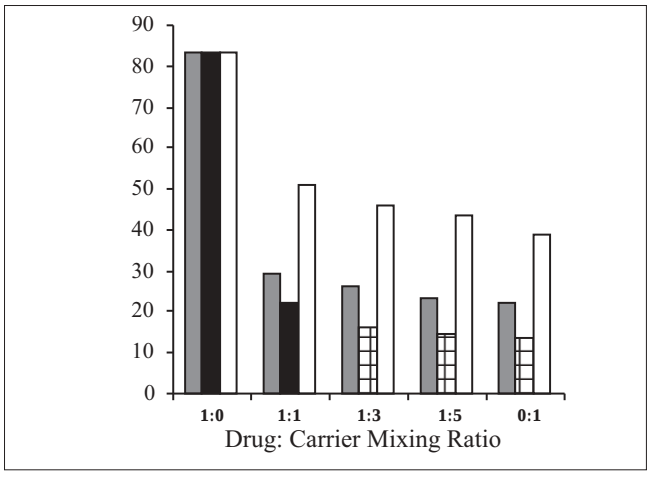


**Fig. 2: Wettability of solid dispersion**
**Contact angle of ABZ and its SDs with urea (▒), PEG (■) and PXR (□) prepared by solvent method**

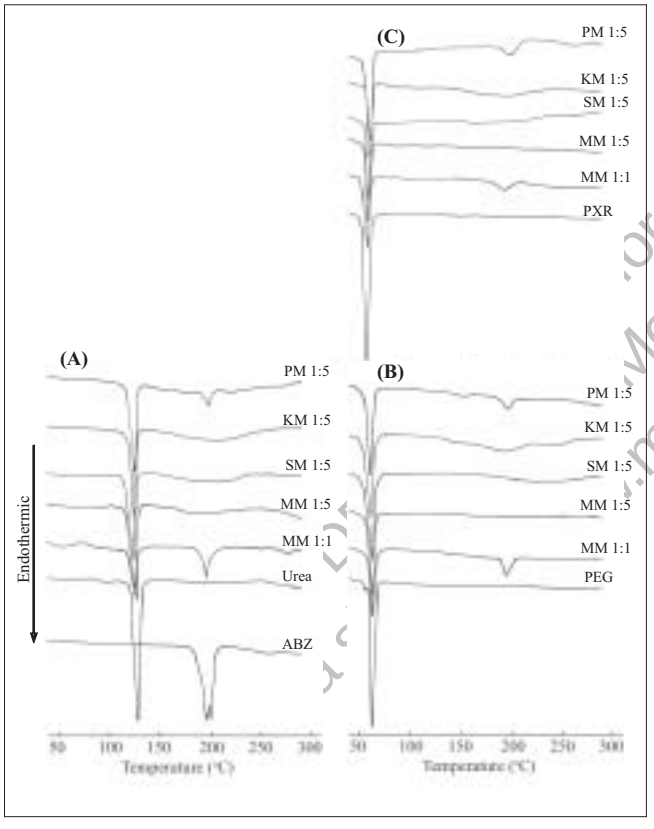


**Fig. 3: DSC thermograms of ABZ and solid dispersions with different carriers**
**DSC thermograms of ABZ and its SDs with urea (A), PEG (B) and PXR (C) prepared by melting method (MM), solvent method (SM) and kneading method (KM) compared to physical mixture (PM)**

The TGA was performed to determine the amount of residual methanol to assure the safe use of products, because of the fact that ABZ is used for a prolonged time period over several weeks in the treatment of echinococcosis[22]. The weight percentage of residual solvent was determined to be less than 0.2% for the products of SM and 0.3-0.2% for KM. The solvent was thought to consist mainly of water, as the thermograms showed no sign of methanol evaporation at 65° and PMs themselves showed a loss of weight (less than 0.1%) during the analysis. Samples passed the residual solvent test recommended for methanol (Class 2 solvent)[23].

The XRD patterns of pure drug, PMs and SDs are illustrated in fig. 4. ABZ exhibited characteristic intense diffractions at 2θ of 11.3°, 18.0°, 19.5°, 25.2° in addition to a hallow pattern at 5°-11°. Urea had a more intense peak at 22.3° in addition to relatively less intense peaks at 24.6°, 31.5°, 35.4° and a hallow pattern at 5°-12°. The XRD patterns of PEG showed two characteristic peaks of high intensity at 19.2° and 22.1°, while PXR showed similar peaks at 19.0° and 23.1°. In all SDs, the carrier was present in a highly crystalline state, as evidenced by its diffraction lines of intensity similar to those lines in the corresponding PM. PMs possessed the diffraction peaks of both drug and carrier, indicating that ABZ was in the crystalline state. The XRD patterns of ABZ-urea dispersion of 1:5 mixing ratio prepared by MM and SM showed absence of ABZ peaks. This indicated that ABZ was converted to amorphous form in the crystalline urea. However, the kneaded product showed weak diffraction peaks corresponding to ABZ. Nearly similar observations were obtained with ABZ-PEG and ABZ-PXR systems. As the solid dispersions of MM and SM at 1:5 mixing ratio were X-ray amorphous, further increase in the carrier proportion was not tried. With lower mixing ratios, SDs showed weak to moderately weak diffraction peaks of ABZ, assuming that a portion of ABZ might have recrystallized during the processing and existed having size at submicron level[14]. Degree of recrystallization was relatively high with KM, as noticed in the XRD pattern of the dispersions in all carriers used. The lower intensity of the drug peaks in the PM with high carrier content is due to the dilution effect[24].

FTIR spectra of different formulations are shown in fig. 5. The spectrum for ABZ showed N-H stretching vibration at 3323 $cm^{-1}$, bending vibration at 1525-1630 $cm^{-1}$ and aliphatic C-H at 2958 $cm^{-1}$. Urea showed a doublet band of N-H stretch at 3350-3450 $cm^{-1}$. Two intense bands at 1680 and 1626 $cm^{-1}$ occurred due to carbonyl absorption (amide I band) and $NH_2$ scissoring vibrations respectively. SDs of 1:1 ratio and the corresponding PMs showed superimposed spectra of ABZ and urea. A slight reduction in the carbonyl frequency of urea was noticed as the proportion of urea was increased in ABZ-urea dispersions compared to corresponding PMs. This

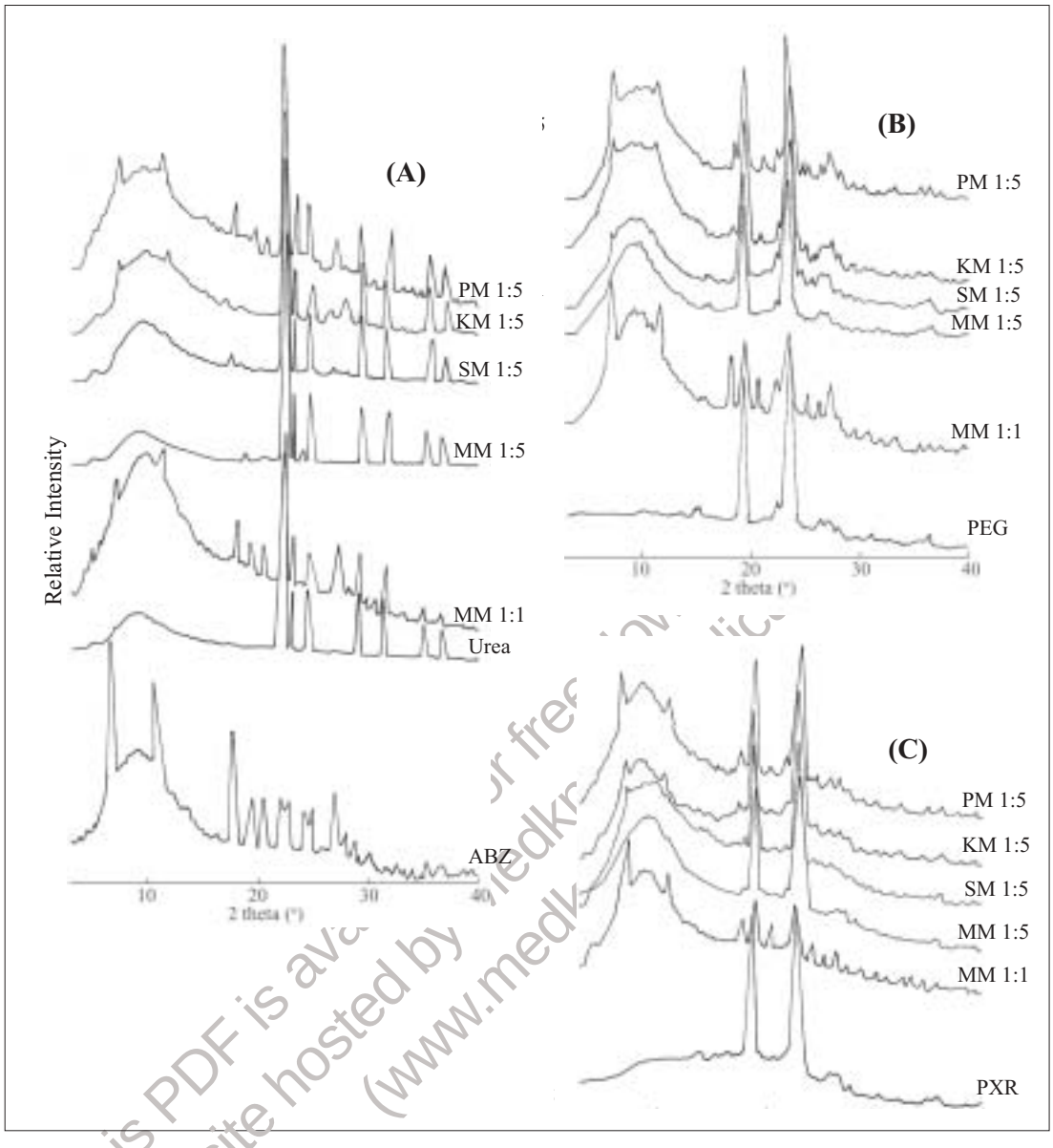


**Fig. 4: XRD patterns of ABZ and solid dispersions with different carriers**
**XRD patterns of ABZ and its SDs with urea (A), PEG (B) and PXR (C) prepared by melting method (MM), solvent method (SM) and kneading method (KM) compared to physical mixture (PM).**

observation suggested possible hydrogen bonding between N-H group of ABZ and carbonyl group of urea[25]. Changes in intensity or frequency of N-H band of drug could not be distinguished due to its overlapping with N-H (doublet) vibration of urea. PEG exhibited a broad O-H stretching vibration from 3300 to 3650 $cm^{-1}$, C-H stretching of $OC_2H_5$ groups from 2800 to 2900 $cm^{-1}$. SDs of 1:1 ratio and the corresponding PMs showed superimposed spectra of ABZ and PEG. The transmittance intensities of N-H stretching band of ABZ were reduced markedly and shifted to 3340 $cm^{-1}$ in SDs with PEG of 1:3 and 1:5 mixing ratios, while the same band was also disappearing with MM at 1:5 ratio. The broad OH stretching band of PEG slightly shifted to lower frequency in these products. Reduction in intensity of transmittance occurred also for NH bending vibrations of ABZ (1525-1630 $cm^{-1}$) in 1:3 and 1:5 ABZ-PEG dispersions. Similar observations were also obtained with PXR dispersions, which might be due to similarity of the groups of polymers[14,20]. From these results, it can be speculated that drug-carrier hydrogen bonding existed in these SDs, causing reduced drug recrystallization[26].

The mean particle size of pure drug sample was calculated to be 10.3 μm. Scanning electron micrographs of pure drug, PXR, ABZ-PXR PM (1:5) and the melt are shown in fig. 6. Pure drug particles were very small in

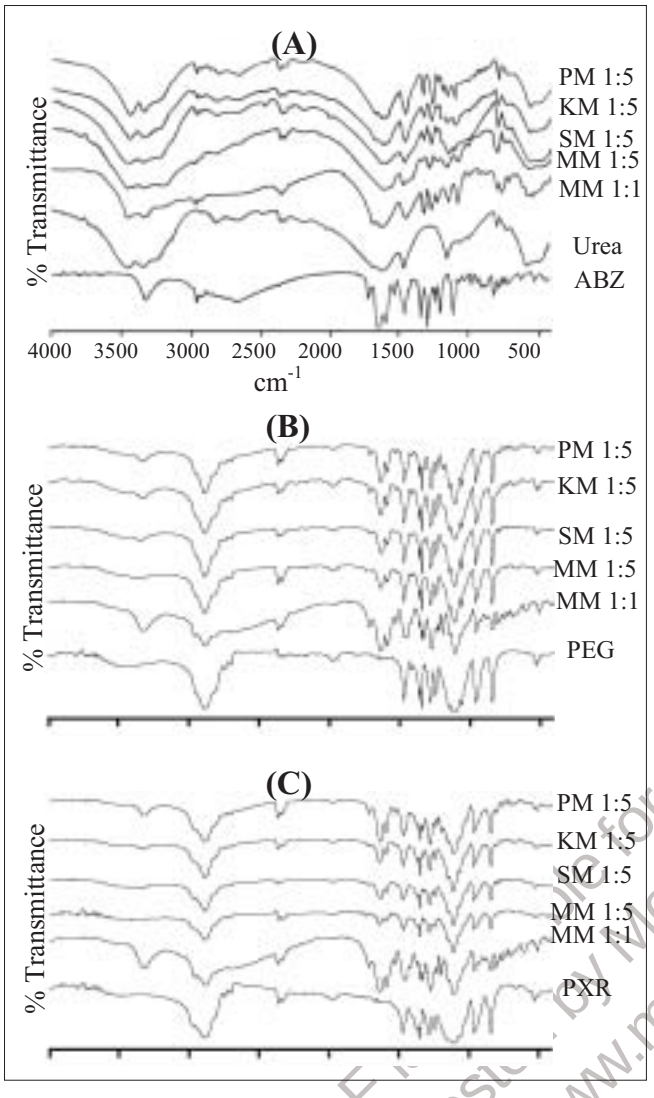


**Fig. 5: FTIR spectra of ABZ and solid dispersions with different carriers**

**FTIR spectra of ABZ and its SDs with urea (A), PEG (B) and PXR (C) prepared by melting method (MM), solvent method (SM) and kneading method (KM) compared to physical mixture (PM)**

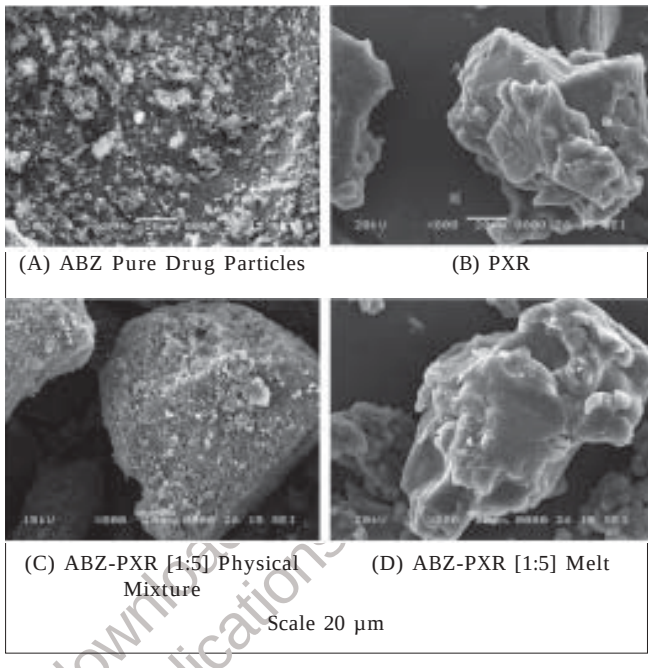


**Fig. 6: SEM images of ABZ and ABZ-PXR products**

**SEM images (× 800) of ABZ, physical mixture (1:5 ratio) and solid dispersion of ABZ-PXR prepared by melting method**



size compared to the carrier particles, and they remained agglomerated with reduced effective surface area. They remained dispersed and physically adsorbed on the surface of carrier particles in the PM. The micrograph of the ABZ-PXR melt (1:5 ratio) showed a homogeneity, hinting ABZ molecules could be dispersed uniformly in the carrier matrices of SDs prepared by melting method at 1:5 ratio, assuming amorphous solid dispersion state.

In the dissolution study, clamping of powder samples between filter paper means that in the case of PM, the carrier would stay close to and dissolve in contact with the drug particles almost to the same extent as that of SD. Wettability and solubilization of drug are improved in the PM also due to the presence of diffusion layer of high carrier concentration around the drug particles[27]. The solubilized drug diffuses to and gets diluted in the bulk of the dissolution medium. This experimental setup offers the possibility to verify the drug particle size reduction in an SD by comparing its dissolution profile to that of corresponding PM with the same drug content and known particle size[27]. The higher the dissolution of SD, the higher must be the size reduction of the dispersed drug. The combined effect of particle size reduction, solubilization and wettability on dissolution can be understood by comparing the dissolution profile of SD with that of pure drug. Though hot-stage microscopy has been used recently for the drug particle size examination in SD, it is not superior to the above-mentioned method in confirming the particle size reduction. The microscopic analysis involves heating of SD to reduce the carrier viscosity, improving its transparency leading to visibility of dispersed particles; but this would also allow the smaller particles to dissolve in the hot carrier, leaving only the coarser ones to be analyzed[12]. In the present study, the sample enclosed in the filter paper did not float in the dissolution medium and hence the rotating paddle apparatus was used for the dissolution studies.

Dissolution followed first-order kinetics during the period of 0-45 min. Fig. 7 illustrates the dissolution rate constant ($K_1$) and dissolution efficiency ($DE_{120}$) calculated as per

the method of Khan[28]. Since the $DE_{120}$ value can be related to area under the plasma level curve of an orally administered drug, this parameter is expressed in conjunction with the rate constant of dissolution[28]. With all carriers, SDs had greater dissolution rates and efficiencies than the corresponding PMs and pure drug, for which the dissolution rate constant and $DE_{120}$ were 0.000713 $min^{-1}$ and 3.844% respectively. Both dissolution rate and dissolution efficiency depended on the method of preparation and mixing ratio.

The drug crystallinity was reduced in kneaded mass at 1:1 drug:carrier ratio as per the XRD report. But this reduction did not result in any important dissolution improvement, probably due to insignificant size reduction. To clarify the differences in dissolution rate and dissolution efficiency, a two-way analysis of variance (ANOVA) was performed. The melts, as well as the co-precipitates with all

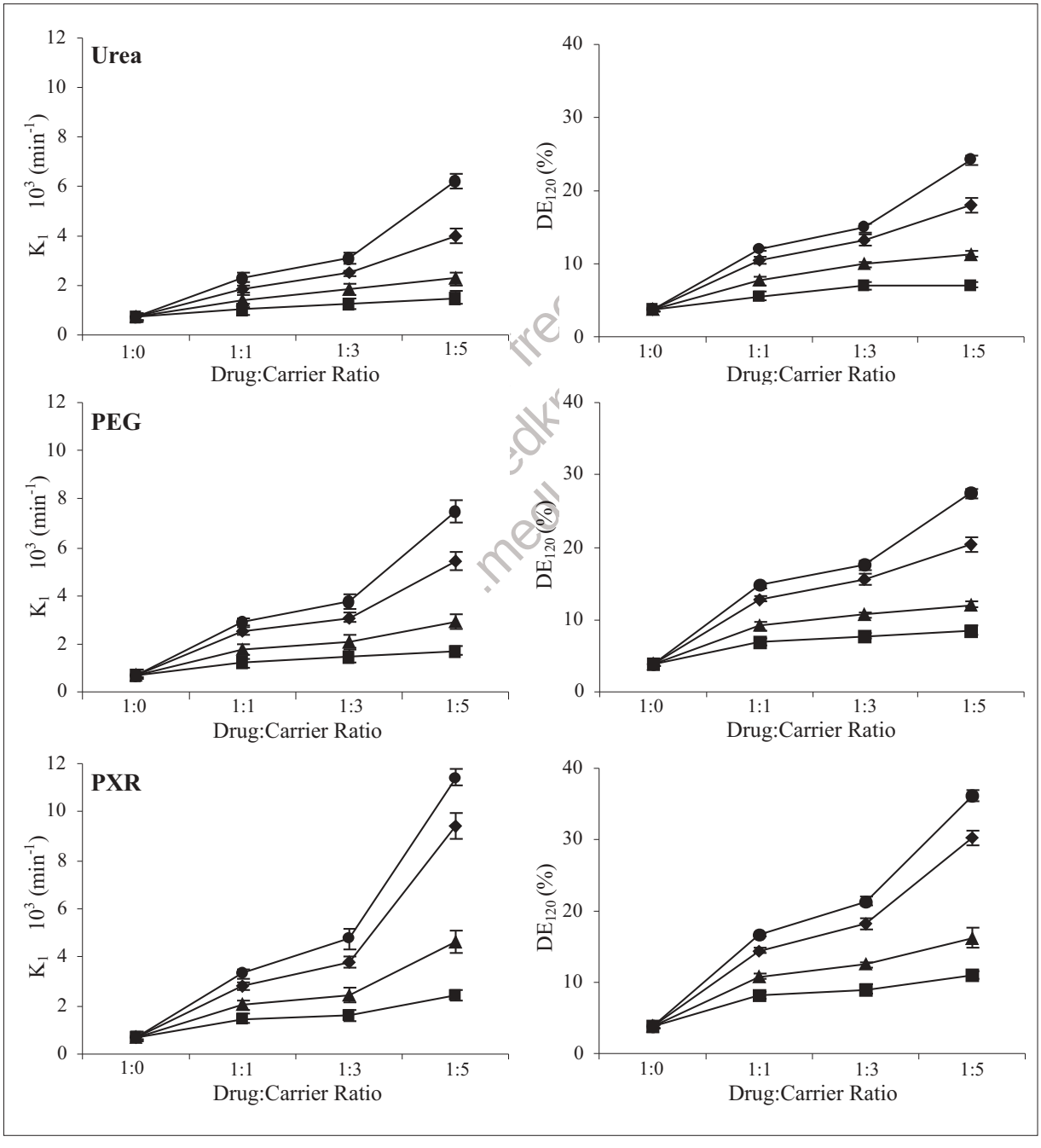


**Fig. 7: Mixing ratio and method of preparation influencing dissolution of solid dispersion**
**Influence of mixing ratio and method of preparation on dissolution rate ($K_1$) and efficiency ($DE_{120}$) of ABZ from SDs prepared by melting (•), solvent (♦) and kneading method (▲) and PM (■)**

the carriers and mixing ratios, had significantly improved dissolution rates than the corresponding PM and pure drug ($P < 0.05$), assuming that size reduction of drug particles in these SDs was significant. Among the three carriers, PXR showed the highest dissolution rate and efficiency with respect to pure drug for all mixing ratios and methods of preparation ($P < 0.05$).

As the 1:5 mixing ratio showed the most significant improvement in dissolution rate and $DE_{120}$ values for all carriers and preparation methods, the profiles are illustrated (fig. 8). The ABZ-PXR melt (1:5 ratio) showed the most remarkable dissolution improvement – 16.1-fold in dissolution rate and 9.4-fold in dissolution efficiency as compared to that of pure drug. Melting method with all the carriers showed around 4-fold improvement in dissolution rate and 3-fold dissolution efficiency compared to the corresponding PM ($P < 0.05$). As the products were similarly superior to the PM, the extent of particle size reduction might also be almost same with all carriers for this mixing ratio and method of preparation. However, with respect to the solvent method, improvement in the dissolution rate and efficiency varied with the carriers used, PXR system showing the fastest dissolution with respect to PM ($P < 0.05$). The kneaded products at the same mixing ratio showed only small improvement (50-80%) relative to PM.

In all mixing ratios used, melting method exhibited the maximum dissolution rate and efficiency ($P < 0.05$) compared to the PM or pure drug. The relative efficiency of the various methods of preparation with respect to the extent of particle size reduction can be ranked as MM>SM>KM. Such ranking with respect to drug crystallinity using DSC analysis was not possible, especially at 1:5 mixing ratio, presumably due to dissolution of drug particles in the carrier while heating in DSC (fig. 3). The proportion of carrier in the SD had a positive influence on the inhibition of drug recrystallization and extent of particle size reduction. As the carrier concentration increased, the influence of MM and SM on drug particle size got raised and the corresponding change in crystallinity could not be observed with XRD technique due to dilution effect[24]. For the given method of preparation and mixing ratio, the degree of particle size reduction might be similar in all carriers. The relative dissolution potency of the carriers compared to the pure drug might be ranked as PXR>PEG>urea. Though the PXR systems exhibited relatively low wettability, ABZ-PXR melt at 1:5 mixing ratio showed the highest dissolution efficiency among the

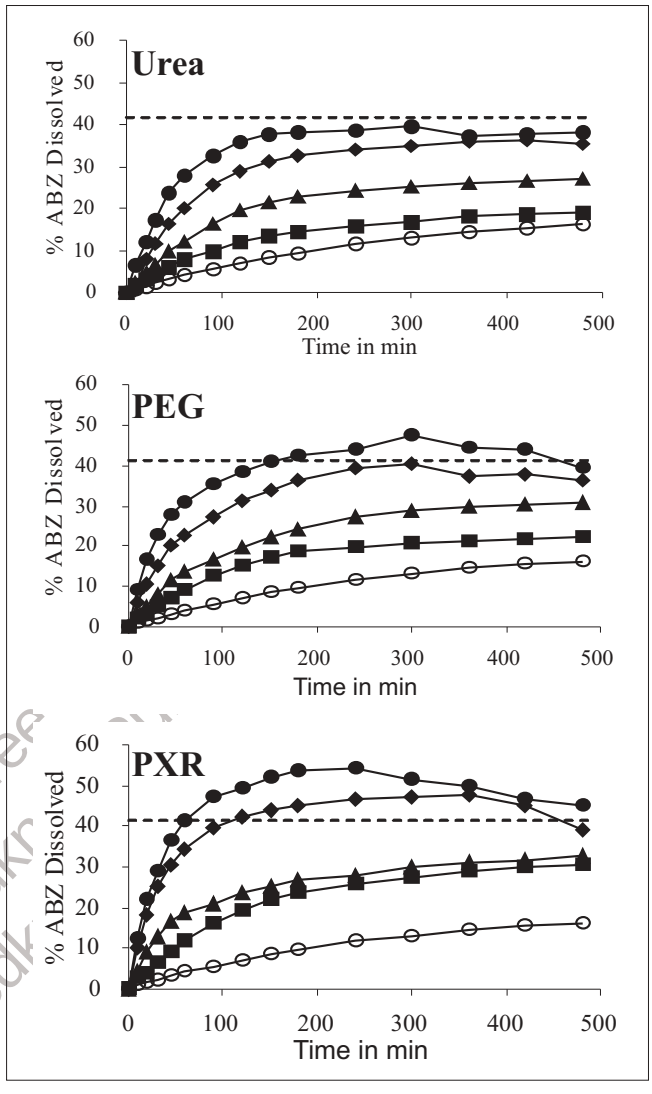


**Fig. 8: Dissolution profiles of solid dispersions**
**Dissolution profiles of SDs of 1:5 (drug-carrier) ratio prepared by melting (•), solvent (♦) and kneading method (▲); physical mixture (■), pure drug (○) and solubility of ABZ in 0.011% carrier solution (- - -)**

carriers used when compared to pure drug ($P < 0.05$). This is because of its highest solubilization effect (in the diffusion layer) as observed in the phase solubility study. Joshi *et al.* recently reported the beneficial effects of the incorporation of a surfactant (Tween 80) into SDs[29]. The improved wettability might be the major contributing factor for the enhanced dissolution of ABZ-PEG system though particle size also played a significant role in dissolution enhancement.

When the dissolution for the products of 1:5 drug:carrier ratio was continued for 8 h, ABZ, from the melt and co-precipitates, was dissolved over its solubility (10.5 µg per ml of distilled water containing 0.01% carrier material). Post-peak decline was noticed due to precipitation of the dissolved

amorphous drug. Such effect was also reported earlier for piroxicam-polyethylene glycol 4000, nifedipine-polyethylene glycol 6000 and nifedipine-hydroxypropylmethyl cellulose dispersions[30-31]. This has been described as supersaturation phenomenon caused by amorphous drug[32-33]. Supersaturation is an event of increase in the drug concentration beyond the solubility level during the dissolution of an amorphous drug, which is well perceptible under nonsink conditions[33]. An initial increase in the solubility followed by crystallization of the dissolved drug confirms the amorphous nature of the drug in the SDs of present investigation.

It could be concluded through the present work that PXR system showed the highest dissolution rate and efficiency with respect to pure drug for all mixing ratios and methods of preparation. However, all carriers showed equivalent efficiency in size reduction of dispersed drug particles. The mixing ratio and method of preparation significantly influenced particle size reduction. Improved wettability and solubilization were mainly contributing to dissolution improvement with the majority of kneaded masses (1:3 and 1:5 ratios), and the reduction in crystallinity was not reflected in dissolution improvement with 1:1 ratio. The mechanisms of enhanced dissolution of melts and co-precipitates with the lowest drug-carrier ratio might be primarily due to increased surface area for mass transfer, though the combined effect of improved wetting (predominant with PEG system), solubilization at the diffusion layer (PXR system) and thermodynamically enhanced dissolution of a higher energy amorphous form (similar in all systems) was also involved. The mean particle size of drug in melts and co-precipitates of 1:5 drug:carrier ratio might be in a range which is many-fold lesser than that of pure drug (10.3 µm). As the ABZ-PXR system exhibited relatively less wettability, further dissolution improvement with the melts and co-precipitates might be achieved by increasing the wettability (by adding a suitable wetting agent while preparing the SD).

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