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Original Research Article

Albendazole Microparticles Prepared by Spray Drying Technique: Improvement of Drug Dissolution

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Abstract

Purpose: *To enhance the dissolution of albendazole (ABZ) using spray-drying technique.*
Method: *ABZ binary mixtures with Kollicoat IR® (KL) and polyvinyl pyrrolidone (PVP) in various drug to polymer ratios (1: 1, 1: 2 and 1; 4) were prepared by spray-drying. The spray-dried particles were characterized for particle shape, and dissolution rate as well as by differential scanning calorimetry(DSC) and Fourier transform infrared (FTIR).*
Results: *Scanning electron micrographs showed a homogeneous distribution of ABZ in the polymer matrix for ABZ-PVP spray-dried system in ratios of 1: 2 and 1: 4, while it was observed only upon using a ratio of ABZ: KL 1: 4 in case of ABZ-KL systems. FT-IR spectra of both physical mixtures and spray-dried mixtures did not show any change for all ABZ-polymer systems, thus indicating the compatibility of the carriers with ABZ. ABZ exhibited a noticeable enhanced dissolution rate from its spray-dried coacervate with PVP and this was independent of the drug/polymer ratio. Drug release was 78, 81 and 81 % from the spray-dried ABZ-PVP systems of drug: polymer ratio of 1:1, 1:2 and 1: 4, respectively, within 5 min. Drug showed complete dissolution within 15 min. On the other hand, enhancement of dissolution rate varied with ABZ: KI ratio.*
Conclusion: *Enhancement of ABZ dissolution for both types of spray-dried particles is due to the reduction in drug particle sizes, wetting of the dissolution medium by the hydrophilic carriers and the amorphosization of the drug crystals by the carriers.*

Keywords: *Albendazole, Spray-drying, Kollicoat, Polyvinyl pyrrolidone, Dissolution, Amorphous*

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INTRODUCTION

Albendazole (ABZ), methyl [5-(propylthio)-l- H-benzimidazol-2yl] carbamate, is considered as one of the most effective of the broad-spectrum anthelmintic agents [1]. The drug is very effective against systemic cestode infections especially in inoperable or disseminated cases of hydatidosis [2] and neurocysticercosis [3]. Low aqueous solubility may be the biggest problem hindering the systemic use of ABZ [4]. Therefore, it is difficult to use ABZ in the treatment of systemic helminthiasis [5], and so, it is important to enhance its poor aqueous solubility.

Aqueous solubility of the poorly soluble drugs could be enhanced by the application of auxiliary hydrophilic substances or by using new technological possibilities [6]. Solid dispersions of drugs in water-soluble carriers is of a great interest as a means of improving the dissolution

rate, and hence possibly bioavailability, of a wide range of hydrophobic drugs [7].

Spray drying is a widely used technique to enhance drug solubility and dissolution rate [8]. Several drugs showed improved dissolution rates by spray drying of these drugs with hydrophilic polymers, as for example, indomethacin [9] and ketoprofen [10]. Kollicoat IR® (KL) is a graft copolymer of poly (vinyl alcohol)-poly (ethylene glycol) (PVA-PEG) [11]. KL was used to enhance dissolution rates of poorly water-soluble drugs. Kollicoat IR-omeprazole microparticles with increasing its dissolution rate were prepared using spray- and freeze-drying techniques [12].

The aim of the present study is to enhance the dissolution rate of ABZ for systemic absorption using co-spray-drying of ABZ with Kollicoat and PVP in varying ratios.

EXPERIMENTAL

Materials

Albendazole (ABZ) was kindly donated from Saudi Pharmaceutical Industries (Riyadh, KSA). Kollicoat IR® (KL) was obtained from BASF (Ludwigshafen, Germany). Polyvinyl Pyrrolidone (PVP K30) was purchased from Flukachemica (Buch, Switzerland). All used materials were of analytical grades.

Preparation of physical mixtures

Physical mixtures (PMs) were prepared by gentle mixing the weighed amounts of ABZ and each of the carriers (Kollicoat IR®, PVP) in a mortar with a spatula. The ratios of the drug to the carrier used were 1:1, 1: 2and 1:4 by weight.

Spray-dried binary systems using Kollicoat IR® and PVP

Appropriate mass ratios (1:1, 1:2, and 1:4) of ABZ with either KL or PVP were prepared in water/ethanol (2: 1 mixture), where the drug was completely dissolved in ethanol, and KL or PVP was dissolved in distilled water. The aqueous solution was added gradually to the ethanolic drug solution with subsequent vigorous stirring for 1 h during spray-drying procedure to assure equilibrium. The resultant dispersion was spray-dried in a Mini Spray-Dryer B-290 (BüchiLabortechnik AG, Flawil, Switzerland) with the following conditions: inlet temperature 140 °C, outlet temperature 70 – 75 °C, the flow rate 5 mL/min, air flow rate 40 – 50 m^3/h, and atomizing air pressure 1.0 – 1.1 bar. The batch size of the prepared ratios was about 5 g each.

Drug loading

The entrapment efficiency of ABZ in the spray-drying particles was determined as the mass ratio of the entrapped drug to the theoretical amount of ABZ used in the preparation. Spray-dried particles equivalent to 5 mg of drug were accurately weighed and dissolved in a suitable quantity of ethanol. The drug content was determined spectrophotometrically at 290 nm.

Morphological assessment

The morphological characteristics of spray-dried particles were observed by scanning electron microscopy. The samples were sputter-coated with a thin gold palladium layer under an argon atmosphere using a sputter module in a high-vacuum evaporator. The coated samples were then scanned and photomicrographs were taken with a JSM-1600 scanning electron microscope (Jeol, Tokyo, Japan).

Differential scanning calorimetry (DSC)

DSC studies of the drug and the spray-dried particles containing ABZ in the matrices of KL and PVP, as well as single components, were performed using a DSC-60 (Shimadzu, Kyoto, Japan). Samples (3 – 5 mg) were placed in hermetically sealed aluminum pans. A scanning rate of 10 °C/min was used over the 25 – 200 °C temperature range. Indium was used as the temperature and enthalpy standard.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of ABZ and ABZ binary systems with KL and PVP compared with the individual components were recorded using FTIR Perkin Elmer spectrophotometer (Spectrum BX). Samples were mixed with KBr and compressed into disks using hydraulic press before scanning from 4000 to 600 cm^{-1}. The data were analyzed using Perkin Elmer software (Spectrum V5.3.1).

In vitro dissolution studies

The *in vitro* dissolution rate of ABZ from its spray-dried systems in the matrices of KL and PVP was investigated in a USP dissolution test apparatus (Caleva Ltd., Model 85T, Philips, UK). The dissolution profiles of ABZ from spray-dried systems were studied in 0.1 N HCl (pH = 1.2). The drug-loaded particles equivalent to 20 mg of ABZ were placed in the dissolution vessel

containing 500 ml of the dissolution medium, which was rotated at 100 rpm and temperature was kept constant at 37 ± 0.5 ^{o}C. At pre-determined time intervals, the samples (5 ml) were withdrawn, filtered and replaced immediately with fresh dissolution medium. The amount of drug dissolved was assayed spectrophotometrically at 290 nm.

Dissolution efficiency after 15 min ($DE\%_{15}$) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100 % dissolution in the same time [13]. Also, the relative dissolution rate (RDR_{15}) data of the different samples were calculated by determining the amount of ABZ dissolved from a particular sample and normalizing for the amount of drug dissolved from pure drug sample over the same time interval (15 minutes).

Statistical analysis

The results were analyzed by using the software graph pad software (CA 92037 USA). Differences between formulations were considered to be significant at $p \leq 0.05$.

RESULTS

Scanning electron microscopy (SEM)

Scanning electron micrographs of ABZ, KL, spray-dried ABZ-KL and spray-dried ABZ-PVP systems in weight ratios of 1:1 and 1:4 compared to the corresponding physical mixtures are displayed in Fig. 1A and B ABZ exhibits irregularly shaped crystals, while KL particles appear highly spherical. In case of ABZ-physical mixtures with KL and PVP, drug crystals appear as lumpy aggregates surrounding the large polymer spheres.

Regarding the spray-dried drug-KL (1:2) mixture, the drug crystals began to appear as spherical and smaller and some of the polymer crystals appear large (Fig. 1B). On the other hand, the spray dried ABZ-KL 1:4 revealed the presence of very small spheres of both drug and polymer that are seen homogeneous dispersed. In case of scanning electron images of spray-dried ABZ-PVP (1:1 and 1:4), the images showed that the drug crystals were homogeneously embedded - as small-sized spheres- between the spherical polymer crystals (Fig. 1A).

Thermal analysis

The DSC thermogram of pure ABZ (Fig. 2 A) shows an endothermic peak at 218 ºC with a shoulder at 198 ^{o}C due to drug melting [15], while KL exhibits a broad endotherm at 213.14 ^{o}C with a thaw point of 207.5 ^{o}C. The drug's melting shoulder was shallow and broad and its melting endotherm disappeared in case of its-KL physical mixtures in weight ratios of 1:1 and 1:4. On the other hand, ABZ endotherm has been no longer detected in case of the drug-KL spray-dried mixtures at the studied ratios (1:1 and 1:4) and the drug melting shoulder was seen broad in case of 1:1 ratio.

The DSC thermograms of ABZ-PVP binary systems are illustrated in Fig. 2B. It was clear that PVP showed a shallow, broad endothermic peak around 81 ^{o}C, which represents the vaporization of moisture from the PVP sample. DSC scan of ABZ-PVP 1:1 physical mixture showed that the endothermic peak of the drug existed at the same position compared to the untreated drug but it lost its distinct sharpness, while in the case of ABZ-PVP 1:1 physical mixture, the drug melting endotherm has been no longer seen.

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of ABZ binary systems with KL and PVP compared with the individual components are displayed in Figs 3 A and B. The spectrum of the ABZ shows an absorption peak of stretching vibration, characteristic of the NH bond as a band of medium intensity at 3323 cm^{-1} and a bending vibration at 1525 cm^{-1}. In addition, stretching bands and deformation characteristics of aliphatic carbons were seen at 2958 cm^{-1} and 1450 cm^{-1}, respectively. Moreover, a stretching band of the aromatic ring double bonds appeared at 1590 cm^{-1}, in addition to a strong peak of stretching vibration corresponding to the C = O group at 1634 cm^{-1}. The FTIR spectrum of KL showed a characteristic broad band at 3421 cm^{-1}, which is assigned for OH stretching and a stretching vibration band of C=O at 1637 cm^{-1} as well as a C-H stretching vibration peak at 2915 cm^{-1}. PVP showed a characteristic stretching C=O band at 1673 cm^{-1}.

In vitro dissolution profiles of ABZ from KL and PVP binary systems

Fig. 4 shows the *in vitro* dissolution profiles of ABZ from its-KL spray-dried systems using

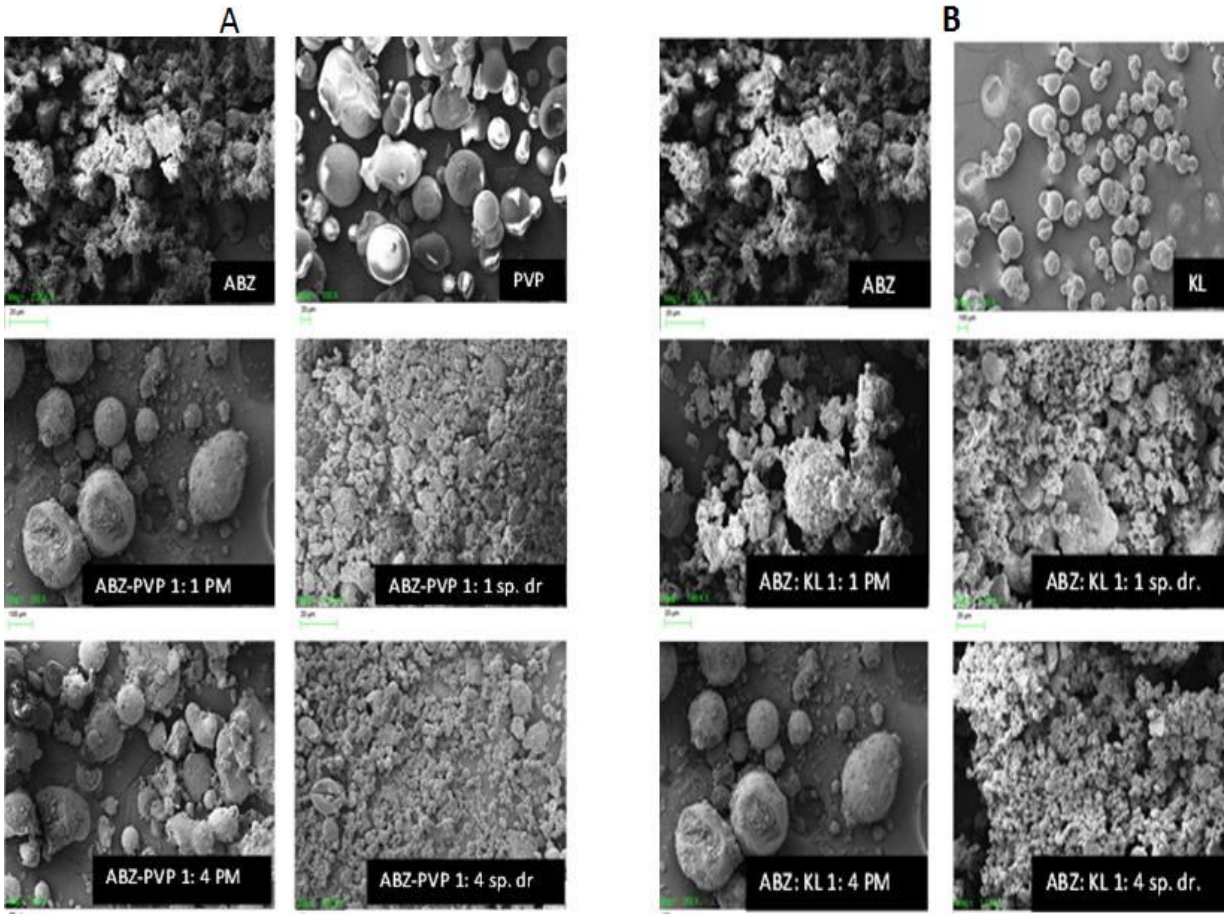

Fig 1: A = SE micrographs of ABZ-KL spray dried and physical mixtures in drug: polymer ratios 1: 1 and 1: 4 compared to the individual components; **B =** SE micrographs of ABZ-PVP spray dried and physical mixtures in drug: polymer ratios 1: 1 and 1: 4 compared to the individual components

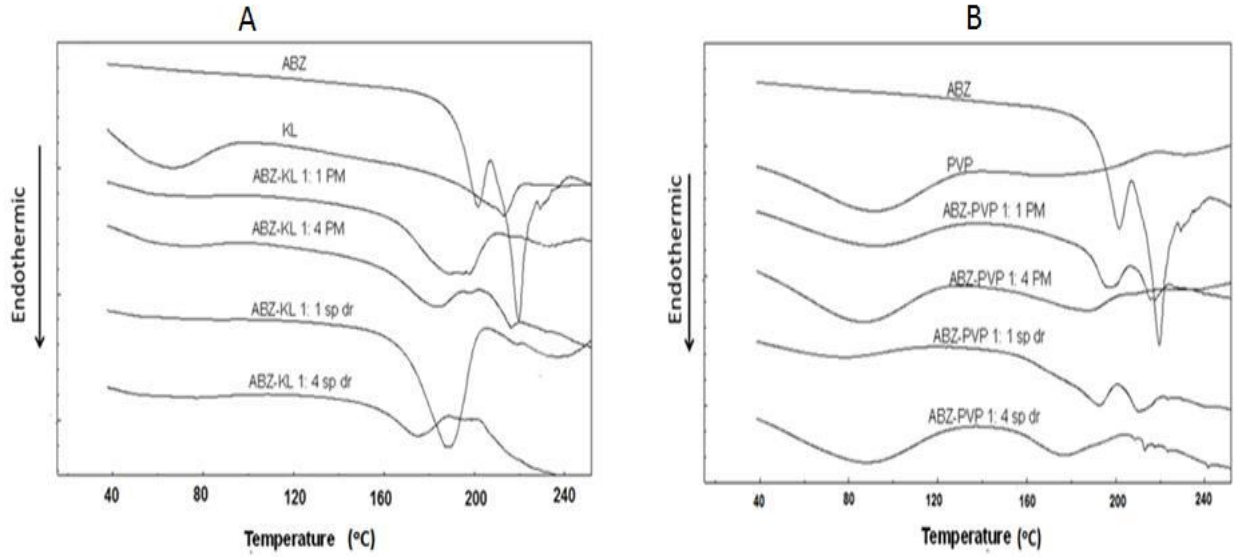

Fig 2: A = DSC thermograms of ABZ-KL spray dried and physical mixtures in drug: polymer ratios 1: 1 and 1: 4 compared to the individual components, and B = DSC thermograms of ABZ-PVP spray dried and physical mixtures in drug: polymer ratios 1: 1 and 1: 4 compared to the individual components

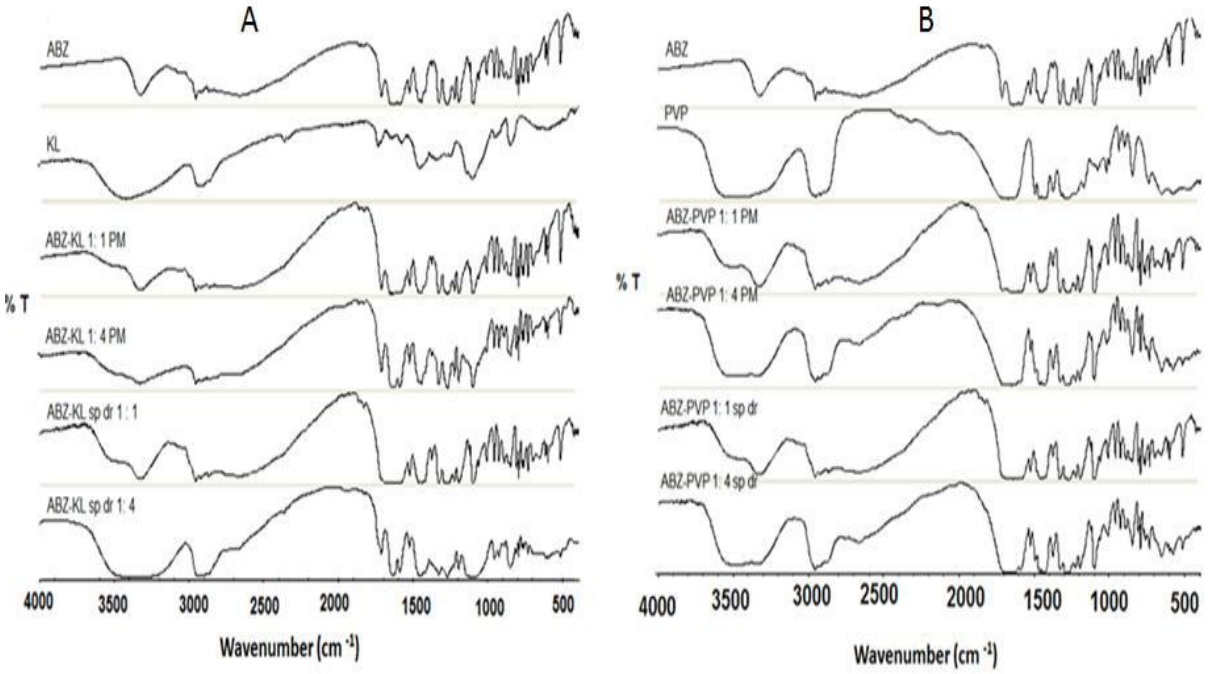

Fig 3: A = FTIR spectra of ABZ-KL spray dried and physical mixtures in drug: polymer ratios 1: 1 and 1: 4 compared to the individual components, and B = FTIR spectra of ABZ-PVP spray dried and physical mixtures in drug: polymer ratios 1: 1 and 1: 4 compared to the individual components

different drug: polymer ratios. ABZ alone exhibited slow dissolution rate, in which only 8.8 % were dissolved within 15 min., and about 25 % were dissolved after 60 min. Spray-drying of the drug in KL matrix caused a noticeable enhancement of its dissolution rate under the influence of ABZ: Kl ratio. Upon using 1:1 ratio, the drug dissolution rate was slightly improved with $D\%_{15}$ and RDR_{15} values of 18.43 and 4.31, respectively (Table 1). These values are not significantly different from the values recorded in case of 1:1 and 1:4 physical mixtures from which the drug exhibited $D\%_{15}$ values of 20.67 and 25.84, respectively and RDR_{15} values of 4.94 and 5.61, respectively. However, in case of increasing the polymer weight ratio (1:2 and 1:4 spray-dried systems), the drug's dissolution was remarkably enhanced. For example, 100 % and 96 % of ABZ was dissolved within 30 min from spray-dried systems using drug: KL ratios of 1:2 and 1:4, respectively, and, in turn, the drug RDR_{15} was increased nine folds in both ratios (Table 1). It is clearly evident that the drug dissolution rate from its-KL spray dried particles (1:2 and 1:4 ratios) was statistically different from that observed in case of using ABZ-KL ratio of 1:1 ($p < 0.05$).

The dissolution patterns of ABZ-PVP spray-dried systems were displayed in Fig. 5. Comparatively, the dissolution enhancement of ABZ from its-PVP spray-dried systems was higher than that observed in case of its-KL systems. In addition, the extent of the dissolution enhancement was not significantly governed by the polymer weight ratio (only the release from ratio 1:1 is significantly different from that obtained from the ratio 1:2 at the first 30 min, $p < 0.05$). The drug was completely dissolved within 15 min from its-PVP spray-dried systems in case of drug: polymer ratios of 1:1 and 1:2, while about 97 % of the drug amount was dissolved after the same time from ABZ-PVP 1:4 ratio. Furthermore, the values of $D\%_{15}$ and RDR_{15} recorded in case of 1:1, 1:2 and 1:4 ABZ: PVP ratios were very close (74.07, 76.29 and 72.66 $D\%_{15}$ values were observed for 1:1, 1:2 and 1:4 ABZ-PVP spray-dried systems, respectively (Table 1). Moreover, a very slight increase in the drug dissolution rate was recorded in case of physical mixtures with PVP using 1:1 and 1:4 ABZ: PVP ratios. However, the release of ABZ from its-PVP spray-dried systems is significantly different from that recorded in case of the corresponding physical mixtures ($p < 0.05$).

Table 1: Dissolution efficiency ($DE\%_{15}$) and relative dissolution rates after 15 minutes (RDR_{15}) of ABZ from its spray-fried KL and PVP systems and some physical mixtures

System	$DE\%_{15}$	RDR_{15}
ABZ	4.44	-
ABZ-KL spray dried (1:1)	18.43	4.31
ABZ-KL spray dried (1:2)	45.24	9.17
ABZ-KL spray dried (1:4)	52.99	9.52
ABZ-KL Physical Mixture (1:1)	20.67	4.94
ABZ-KL Physical Mixture (1:4)	25.84	5.61
ABZ-PVP spray dried (1:1)	74.07	12.05
ABZ-PVP spray dried (1:2)	76.29	12.53
ABZ-PVP spray dried (1:4)	72.66	11.37
ABZ-PVP Physical Mixture (1:1)	14.34	3.08
ABZ-PVP Physical Mixture (1:4)	17.93	3.84

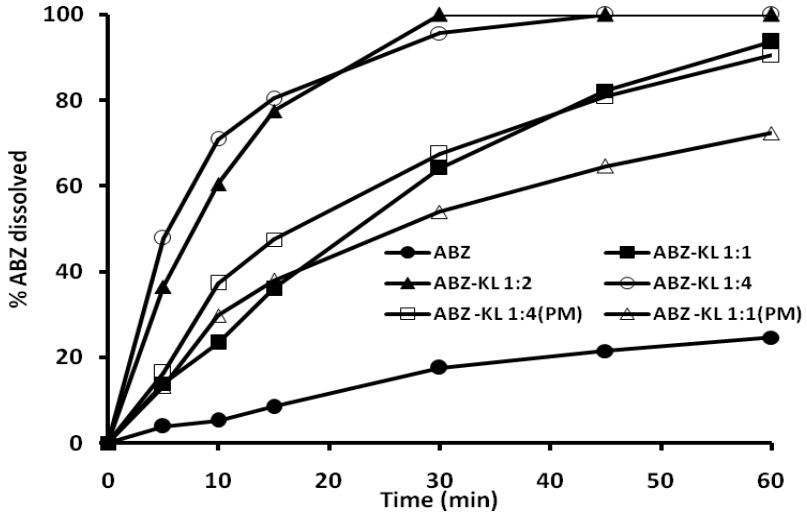

Fig 4: Dissolution profiles of ABZ-KL spray-dried systems compared to the corresponding physical mixtures (PM)

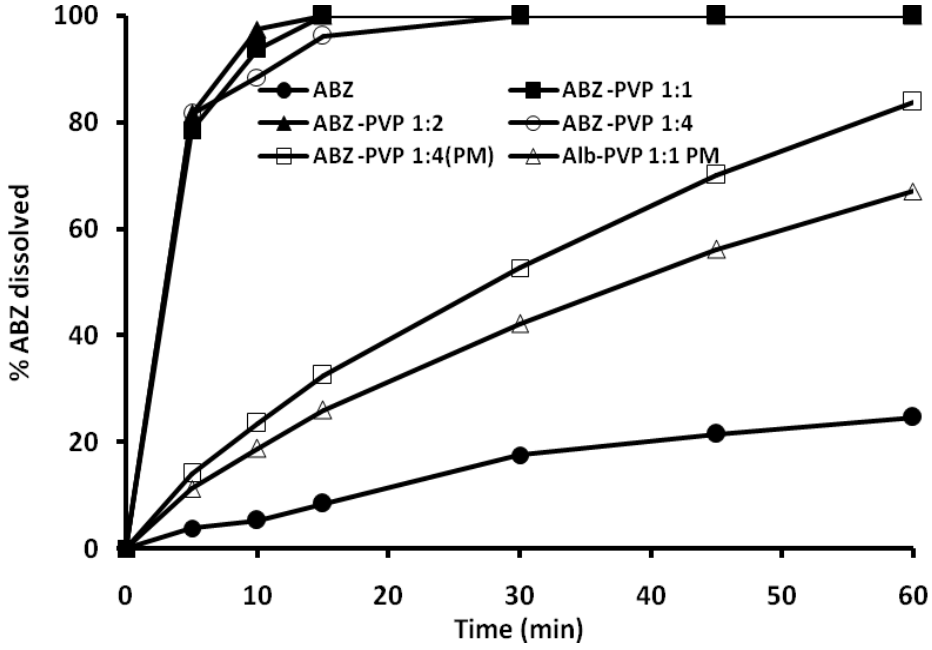

Fig 5: Dissolution profiles of ABZ-PVP spray-dried systems, and physical mixtures (PM)

DISCUSSION

The DSC thermograms of spray-dried ABZ with either KL or PVP at high polymer ratios showed disappearance of the melting endotherm of the drug, indicating homogenous drug dispersion in the polymeric matrices [14]. In addition, some drug-polymer physical mixtures showed the disappearance of the melting endotherm, and this could be attributed to the solubility of ABZ in the molten polymers. Same findings were observed by Ibrahim and Al-Anazi [15], who found that the disappearance of ABZ melting endotherm in case of the drug-physical mixtures with lactose and microcrystalline cellulose and they attributed this finding to the solubility of ABZ in the molten polymers.

The FTIR spectra of ABZ-KL and ABZ-PVP systems of both physical mixtures and spray-dried mixtures did not show any change of either the drug or the polymer characteristic bands in terms of the position or intensity, which proves the compatibility of the used carriers with ABZ.

In vitro dissolution profiles of ABZ from KL and PVP binary systems

In comparing the dissolution rate of ABZ alone with its spray-dried systems in KL matrix, ABZ alone exhibited slow dissolution rate, while a noticeable enhancement of its dissolution rate was observed under the influence of ABZ: KL ratio. It was found that by increasing the polymer weight ratio, the drug dissolution was remarkably enhanced. The enhancement of dissolution of ABZ was found to be higher in its-PVP spray dried systems compared to KL systems. Moreover, a very slightly increased in the drug's dissolution rate was recorded in case of physical mixtures with PVP using 1:1 and 1:4 ABZ:PVP ratios.

The enhancement of ABZ dissolution rate might be due to improving the wettability of the drug particles and by significantly reducing the drug particle size during the spray-drying with hydrophilic matrices. Fouad *et al* [16] showed that the increased dissolution rate of celecoxib in spray-dried mixtures of KL IR and other excipients was due to improving drug wettability. Also, the inherently higher dissolution rate of the soluble polymer introduces the less-soluble drug as finely divided particles into the dissolution medium [17]. Furthermore, Janssens *et al* [18] explained that a significant decrease of the drug particle size, possibly to the molecular level, in combination with an additional effect of the co-dissolving hydrophilic carrier on the drugs solubility, might decrease the time required for complete dissolution.

It is clearly from the drug dissolution profiles that the drug spray-dried in PVP matrices (in different weight ratios) showed an enhanced drug dissolution rates that were higher than those observed in case of ABZ-KL systems. This finding is in agreement with that of Van den Mooter *et al* [19], who found that PVP was effective in preventing drug crystallization when the drug was formulated as solid dispersions in PVP matrices. They concluded therefore that the physical mechanism of the protective effect of PVP in the case of amorphous ketoconazole is not the consequence of drug–polymer interactions, but mainly due to the polymer anti-plasticizing effect, thereby increasing the viscosity of the binary system and decreasing the diffusion of drug molecules necessary to form a lattice. Moreover, that PVP enhanced ABZ dissolution rate even in low polymer weight ratio (1:1) rather than KL. It could be seen from the SEM images of ABZ-PVP spray-dried system using drug to polymer ratio 1:2 showed homogeneous distribution of both the drug and polymer matrices, while in case of ABZ-KL 1:2 spray-died system, the drug and polymer particles were not seen homogeneous.

The data obtained from DSC, FTIR and SEM studies demonstrated that the spray-drying of ABZ in the matrices of both KL and PVP enhanced its dissolution rate and this enhancement could not be attributed to drug-carries interaction. The hydrophilic polymers improved the drug particles' wettability, by reducing the drug particle size during spray-drying. The action of embedding the finely divided drug particles in the matrices of the soluble component should also be considered. This is in accordance with El Badry *et al* [20], who showed that a total omeprazole amorphosization was induced by spray-drying and freeze-dried processes for both Kollicoat IR® and HP-β-CD confirmed that the drug is no longer present in crystalline form and it was changed to amorphous state.

CONCLUSION

The dissolution rate of ABZ could be enhanced by spray-drying technique using hydrophilic polymers such as KL and PVP. The mechanism of drug dissolution enhancement can be attributed to the hydrophilic nature of the polymers used, production of small-sized spherical particles by spray-drying and change of

the drug crystals embedded in the polymeric matrices to amorphous form.

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