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Improvement of Albendazole Dissolution by Preparing Microparticles Using Spray-Drying Technique

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Abstract

The aim of this work was to improve the dissolution rate of albendazole (ABZ) by preparing its microparticles with certain hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and polyvinyl pyrrolidone (PVP) using spray drying technique. Microparticles of ABZ with these polymers were prepared in different ratios of 1:1, 1:2, and 1:4 by spray drying technique. Morphology and characterization of the prepared ABZ microparticles was studied and photographed using a biological microscope and examined by scanning electron microscope. Smooth surface and spherical microparticles of ABZ were detected by these methods which indicating the coating of drug crystals by the studied polymers. Physicochemical properties of drug alone and its spray dried microparticles were investigated using differential scanning calorimetry (DSC) and powder X-ray diffractometry (PXRD). DSC and PXRD analysis showed that ABZ transformed from the crystalline state to amorphous state by spray drying with these polymers as confirmed by disappearance of its melting peak and characteristic crystalline peaks. Dissolution rate of ABZ from the prepared microparticles was determined and compared to its corresponding physical mixtures. Results have shown that the dissolution rate of ABZ has been enhanced extremely from its spray dried microparticles and reached 100 % as compared to the corresponding physical mixtures. This indicates the success of spray drying technique for improvement of ABZ dissolution. Moreover, it was found that the

dissolution rate of the drug was affected by the polymer type and the ratio of ABZ to polymer. The highest dissolution of ABZ was obtained with HPMC in 1:1 ratio and with both PVA and PVP in ratio of 1: 4 microparticles. The transformation of ABZ from crystalline to amorphous state by spray drying and the hydrophilic coating of drug particles by the polymers are considered among the factors which contributed in improvement of ABZ dissolution.

Keywords

Albendazole, Hydroxypropyl methylcellulose (HPMC), Polyvinyl alcohol (PVA), Polyvinyl pyrrolidone (PVP), Spray drying, Dissolution rate

Introduction

Albendazole (ABZ), methyl[5- (propylthio)-1-*H*-benzimidazol-2yl] carbamate, is a benzimidazol derivative with abroad spectrum of activity against human and animal helminth parasites (Fig 1)[1]. ABZ is effective in the treatment of echinococcosis, hydrated cysts and neurocysticercosis [2]. ABZ is a poorly water-soluble drug (0.2 μg/ ml in water at 25 ^{o}C) [3]. Consequently, it is poorly absorbed from the gastrointestinal tract (< 5%) [4] and it has low oral bioavailability [5]. This property is a major disadvantage for the use of ABZ in the treatment of systemic helminthiasis [6]. Furthermore, the lack of water solubility reduces flexibility for ABZ formulation and administration. Therefore, the overcome of poor aqueous solubility of ABZ is an important goal.

Different efforts have been made to enhance ABZ water solubility and dissolution rate such as preparation of oil in water emulsion [7], incorporation into liposomes [8], complexation with cyclodextrins [9], and preparation of solid dispersions [10]. Moreover, increased systemic bioavailability of albendazole was reported when the drug co-administered with a fatty meal [11], fruit juice [12], cosolvent [13], or with surfactants [14].

Spray drying is a well known technique and is used in food and drug industries. Spray drying has many fields of application in pharmaceutical industry since the

early of 1940s [15]. The method is applicable for drying heat-sensitive materials such as amino acids, antibiotics, ascorbic acid, liver extracts, pepsin and similar enzymes. It is applicable for particle formation; spray dried particles are approximately spherical in shape, nearly uniform in size, frequently hollow, and posses good flowability and a rapid rate of solution. Encapsulation of chemicals can be achieved using spray drying equipment [16]. Another application of spray drying process is in tableting and in coating and its application. Frequently, spray drying is more economical than other processes since it produces a dry powder directly from a liquid and it reduces labor, equipment costs, space requirements and possible contamination of the product.

Examples of successfully tested-drugs which improved their dissolution by spray drying technique are indomethacin [17], tolbutamide [18], carbamazepine [19], and ketoprofen [20].

The aim of this study was to improve the rate of dissolution of ABZ, by using spray-drying technique utilizing different hydrophilic polymers namely; hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), and polyvinyl pyrrolidone (PVP). The influence of drug to polymer ratio on the dissolution profile of ABZ from its spray dried microparticles using the previously hydrophilic polymers was conducted. The physical properties of the prepared microparticles of ABZ were characterized by differential scanning calorimetry (DSC), powder X-ray diffractometry (PXRD), and scanning electron microscopy (SEM).

Results and Discussion

Characteristics of formulation systems of ABZ microparticles are presented in Table 1. The theoretical value of drug loading in the microparticles ranged from 20 to 50% (w/w). The spray drying technique produced the entrapment efficiency (EE) of drug in microparticles ranged from 60.1 to 78.8 % and the highest EE was achieved at drug: polymer ratio 1:1. The yield percent of spray dried microparticles ranged from 45.1 to 55.3 % and no specific trends were identified between the

studied ratios or the type of the polymers and yield %. The prepared spray dried microparticles containing ABZ appeared to be white-fine fluffy powder.

Tab. 1. Characteristics of the prepared ABZ microparticles.

Formulation	ABZ: Polymer Ratio	ABZ %	Polymer %	Yield %	EE %
ABZ:HMPC 1:1	1:1	50	50	50.1	78.8
ABZ:PVA 1:1	1:1	50	50	50 .3	73.7
ABZ:PVP 1:1	1:1	50	50	45.1	70.1
ABZ:HMPC 1:2	1:2	33.3	66.7	48.2	68.2
ABZ:PVA 1:2	1:2	33.3	66.7	55.3	60.1
ABZ:PVP 1:2	1:2	33.3	66.7	48.2	63.7
ABZ:HMPC 1:4	1:4	20	80	54.1	70.3
ABZ:PVA 1:4	1:4	20	80	50.5	73.5
ABZ:PVP 1:4	1:4	20	80	51.73	67.5

The shape and morphology of the microparticles prepared by spray-drying method was examined by digital optical microscopy and scanning electron microscope. Under optical digital microscopy, the microparticles appeared spherical and no free ABZ crystals were observed (Fig 1). Scanning electron microscope (SEM) of the prepared ABZ microparticles is shown in Fig 2. ABZ powder has an irregular crystalline shape (Fig 2-A). All spray-dried microparticles of ABZ-polymers were spherical products (Fig 2-B, 2-C, and 2-D). SEM showed smooth surface of ABZ microparticles with lack of pores which indicated the complete coating of ABZ with polymer particles. The insolubility of the ABZ microparticles in the liquid paraffin during microscopic examination was confirmed by their appearance under SEM which proofed their hydrophilic surface as a result of coating with the used hydrophilic polymers. Moreover spherical shape provides the largest surface area among the geometric shapes which is considered advantageous to enhance the dissolution rate of the studied drug.

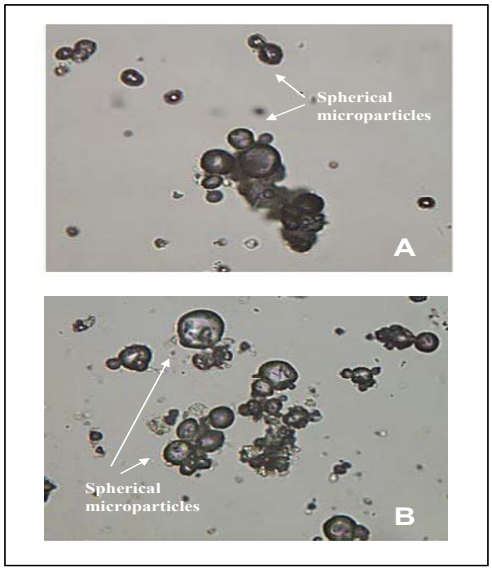

Fig. 1. Morphology of ABZ microparticles prepared by spraydrying and observed by digital optical microscopy (X40). Thedifferent microparticles used were: (A) PVA-ABZ F 1:4(B) HPMC-ABZ F 1:1

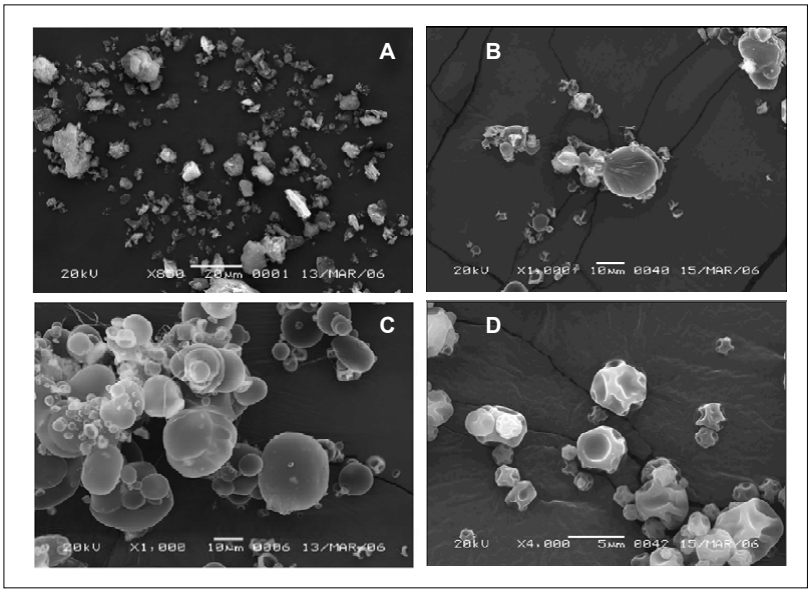

Fig. 2. Photomicrography taken by scanning electron microscopy (SEM) for ABZ particles (A), ABZ:HPMC 1:1 (B), ABZ: PVA 1:4 (C), ABZ:PVP 1:4 (D).

The thermal behavior of ABZ alone and its spray dried microparticles as well as its physical mixtures with the studied polymers are shown in Figs. 3 and 4. The DSC traces of pure ABZ (Fig 3) show an endothermic peak at 218 ^{o}C with a shoulder at 198 ^{o}C which is due to the melting of the drug.

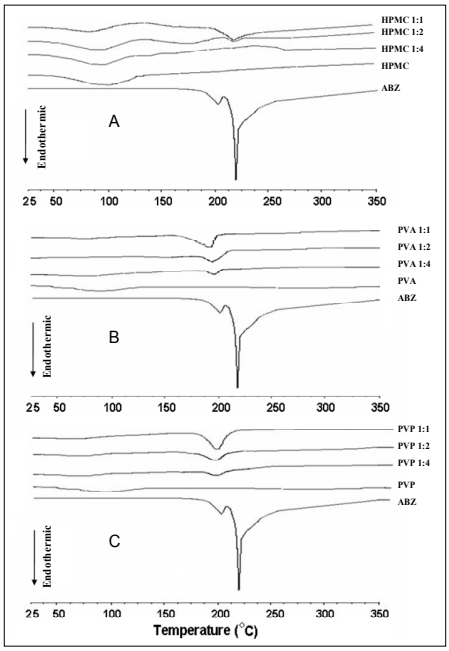

Fig. 3. DSC thermograms of albendazole as well as HPMC microparticles(A), PVA microparticles (B), and PVP microparticles (C)

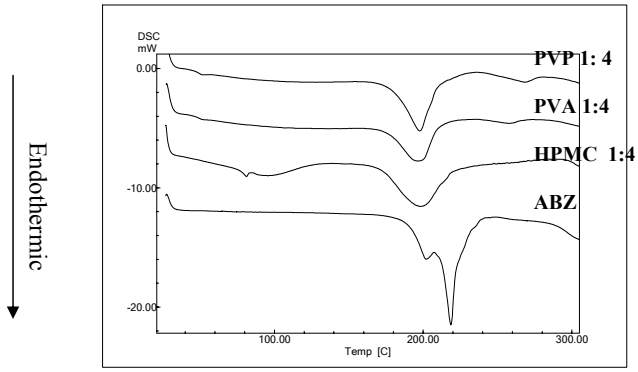

Fig: 4. DSC curves of ABZ alone and its physical mixtures with HPMC, PVA, and PVP in 1:4 ratios

In the DSC thermograms of pure HPMC (Fig 3-A), PVA (Fig 3-B), PVP (Fig 3-C), a broad endothermic peak ranging from about 65 to 115 ^{o}C was observed. This broad endothermic peak of each polymer may be due to the evaporation of the adsorbed water. The prepared spray dried microparticles of ABZ (Fig 3-A, 3-B, 3-C) show the melting peak of ABZ on their DSC curves but with decrease of its intensity and loss of its sharpness. This became more pronounced as the polymer content increased in the formulated system; as in case of 1:4 ratio of ABZ: HPMC microparticles whereas the melting endothermic of ABZ disappeared. This result might be explained in terms of formation of an amorphous form of drug in microparticles due to the presence of the carrier and the spray drying process. More evidence of transformation of ABZ from crystalline state to amorphous state by spray drying with polymer is the appearance of melting endothermic peak at 198 ^{o}C of ABZ on DSC curve of its physical mixture with the same polymer in the 1:4 ratios as shown in Fig.4. Also, these results mean that HPMC, PVA, and PVP used in this study are not interfered with ABZ.

The powder X-ray diffraction (PXRD) patterns of pure ABZ, pure polymers and spray-dried microparticles are shown in Fig 5. The crystalline peaks located at 7.3^{o,} 11.8^{o,} 18.5^{o} and 24.7^{o} (2θ) corresponding to albendazole crystals were observed [10]. The intensity of crystalline diffraction peaks of the drug in its spray dried products were decreased gradually by increasing the polymer ratio until of crystalline diffraction peaks of the drug in its spray dried products were decreased gradually by increasing the polymer ratio until completely disappeared in the ratio of 1:4 (Fig 5). This indicates that transformation of ABZ from crystalline state to the amorphous state by co-spraying with the studied polymers. This is in good agreement with previous DSC results. It has been known that transforming the crystalline state of the drug to the amorphous state leads to a high-energy state and high disorder, resulting in enhancing solubility and dissolution rate [21]. Accordingly, this will improve the dissolution rate of ABZ noticeably.

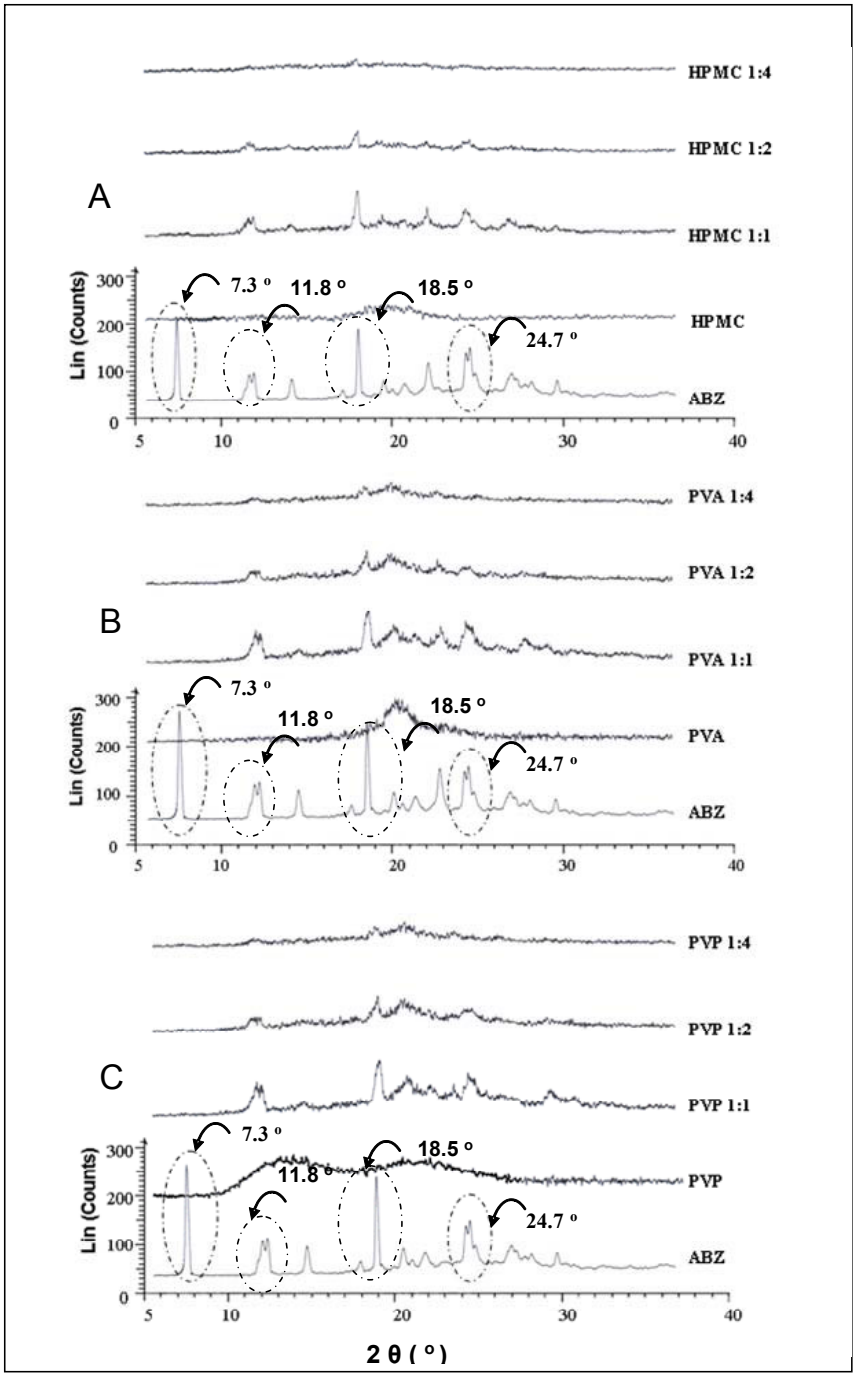

Fig. 5. Powder X-ray diffraction patterns of albendazole as well as HPMC microparticles (A), PVA microparticles (B), and PVP microparticles (C)

Figure 6 represents the effect of HPMC on ABZ dissolution rate from its spray dried microparticles. The percent dissoluted of the drug from its spray dried microparticles with HPMC was 96%, 98% and 100 % after one hour, one and half hour, and two hours respectively, while that from its physical mixture was 28.5 % after two hours. Therefore, the dissolution rate of ABZ has been enhanced remarkably from its microparticles with hydrophilic HPMC prepared by spray drying technique. The improvement of dissolution rate of ABZ could be attributed to amorphization of drug by co-spraying with HPMC as confirmed from DSC and PXRD data. It was noted that the release rate of ABZ is reduced with increasing the HPMC content in the microparticles prepared by spray drying. $T_{50\%}$ (the time required to dissolve 50% drug) of the samples 1:1, 1:2 and 1:4 ratios was 15.55 ± 0.13, 17.62± 0.43, and 21.96± 0.53 mints, respectively. The highest ABZ dissolution rate was achieved from the microparticles of HPMC in 1:1 ratio ($P< 0.05$). This is in agreement with our previous study in which the highest dissolution of indomethacin from its microparticles achieved with the lower HPMC content [17].This finding can be explained by the fact that the microparticles with low polymer content were expected to be more porous than those with high polymer content, which might facilitate the release of the residual drug from the microparticles [22]. Also, the thickness of the hydrogel layer increases with high polymer content due to polymer swelling and forming a gel layer which retarded drug diffusion [23]. Figure 7 shows the effect of PVA on ABZ dissolution rate from the prepared spray-dried microparticles. The percent dissolved of drug from the microparticles of PVA was 90 % after two hour dissolution interval, as compared to 36.4 % from the corresponding physical mixture with PVA in 1:4 ratio after the same time. It is clearly shown that ABZ dissolution rate has been enhanced extremely by spray drying of drug with PVA. It was found that the release rate of ABZ increased concurrent with the polymer content in the microparticels (Fig. 7). The values of $T_{50\%}$ of the drug from microparticles of 1:1, 1:2 and 1:4 ratios were 36.56 ± 0.91, 30.26 ± 0.43, and 14.68 ± 0.53 min., respectively. The highest dissolution rate of ABZ was achieved from its microparticles with PVA of ratio 1:4 ($P< 0.05$). This may

be due to the hydrophilic coating of PVA to the drug particles and increased surface area due to formation of spherical smooth surface microparticles [24].

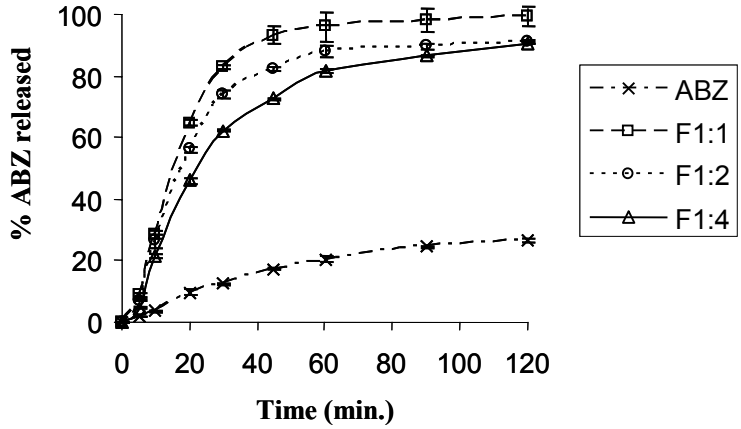

Fig. 6. Dissolution profiles of ABZ–HMPC microparticles in pH 1.2 at 37 ± 0.5 ^{o} C prepared by spray drying. Each point represents the mean ± standard deviation of three experiments (P< 0.05).

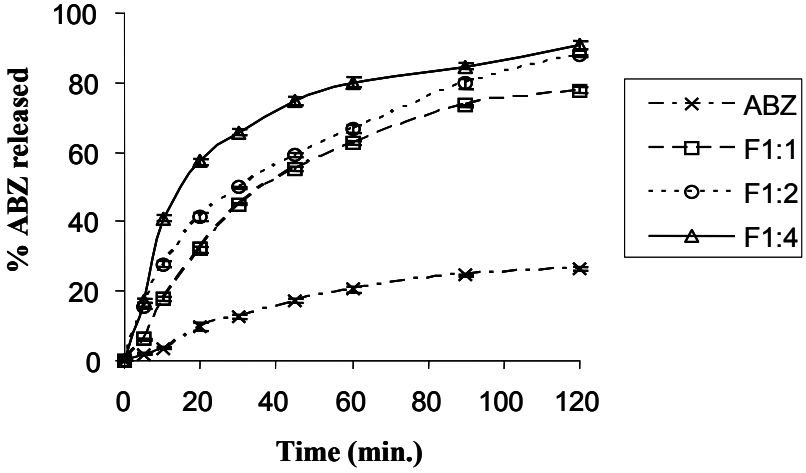

Fig. 7. Dissolution profiles of ABZ–PVA microparticles in pH 1.2 at 37 ± 0.5 ^{o} C prepared by spray drying technique. Each point represents the mean ± standard deviation of three experiments (P< 0.05)

The effect of PVP on ABZ dissolution rate from its spray-dried microparticles is presented in Fig. 8. The amount dissolved of drug from the microparticle of PVP was 95 % after two hour dissolution interval, as compared to 38.4 % from its physical mixture with PVP in 1:4 ratio after the same time. Again, the dissolution rate of ABZ has been enhanced extremely from its microparticles with PVP, which confirm the success of spray drying technique as well as the presence of this polymer for improvement the drug dissolution. It was observed that increasing in PVP content in the system increased the fraction of ABZ released from microparticles prepared by spray drying (Fig. 8). The values of $T_{50\%}$ of the drug from microparticles of 1:1, 1:2 and 1:4 ratios were 34 ± 2.75, 27.06 ± 0.45, and 14.91 ± 0.17 min., respectively. Hence, the highest ABZ dissolution was achieved from the sample of ratio 1:4 ($P< 0.05$). This is due to the same explanation as mentioned previously with PVA, in which hydrophilic coating of PVP to the drug particles and increasing surface area was occurred by spray drying.

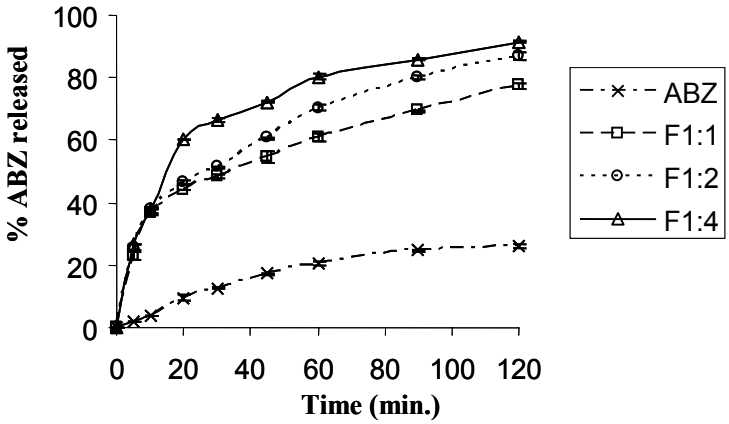

Fig. 8. Dissolution profiles of ABZ-PVP microparticles in pH 1.2 at 37 ± 0.5 ^{o} C prepared by spray drying technique. Each point represents the mean ± standard deviation of three experiments ($P< 0.05$)

Moreover, the dissolution rate of ABZ from its spray dried microparticles using the three different types of hydrophilic polymers (HPMC, PVA, and PVP) can be compared according to the values of $T_{50\%}$ and $T_{80\%}$. The values of $T_{50\%}$ of drug microparticles prepared from HPMC (1:1), PVA (1:4), and PVP (1:4) were 15.55 ±

0.13, 14.68 ± 0.53 ,and 14.91 ± 0.17 min., respectively. The values of $T_{80\%}$ (the time required to dissolve 80% drug) of microparticles prepared from HPMC, PVA, and PVP were 27.65 ± 0.58, 60.1 ± 5.76 ,and 59.27 ± 2.76 min., respectively. The highest dissolution rate of ABZ was achieved with HPMC microparticles ($P< 0.05$) as confirmed from the shortest value of its $T_{80\%}$ than that with polyvinyl polymers by more than two folds. Overall, the results indicate that HPMC is considered the best carrier used which enhanced the dissolution rate of ABZ remarkably in comparison to PVA and PVP.

In conclusion, spherical smooth surface microparticles of ABZ with the studied polymers were produced by spray drying technique. ABZ was transformed from crystalline state to amorphous state in these microparticles as confirmed by DSC and PXRD results. The dissolution rate of ABZ was improved from co-spray dried microparticles as compared to its physical mixtures. Dissolution rate of ABZ was influenced by the type of the polymer and drug: polymer ratio. In case of HPMC the release rate of ABZ is reduced with increasing polymer content whereas in case of PVA and PVP the release rate increased concurrent with the polymer content. The highest ABZ dissolution rate was achieved from microparticles of HPMC at ratio 1:1. Therefore, the expected bioavailability of ABZ in co-spray dried microparticles will be improved due to the significant enhancement of the dissolution of drug.

Experimental

Materials

Albendazole (ABZ) was kindly donated from Saudi Pharmaceutical Industries (Riyadh, SA). Hydroxypropyl methylcellulose (HPMC, Methocel K100) is a water soluble polymer and was kindly donated from DOW (Midland, MI, USA). Polyvinyl alcohol (PVA, MW 115000) was purchased from BDH laborator supplies poole, England, and Polyvinyl pyrrolidone k15 (PVP, MW 10,000) was purchased from Fluka, Chemika AG, Switzerland. Both PVA and PVP are soluble in water. All other chemicals and solvents used were of pharmaceutical grade.

Methods

Preparation of albendazole microparticles by spray drying technique:

Polymeric solution of HPMC was prepared by dissolving the polymer in boiled water (0.5%, 1% or 2% w/v according to the ratio desired) followed by immediate cooling to form clear solution [17]. PVA and PVP polymeric solutions were prepared directly by dissolving the polymers in water (0.5%, 1% or 2% w/v according to the ratio desired) to form a clear solution. Albendazole was dissolved in ethanol(0.5% w/v) and this ethanolic solution was added slowly to the polymeric solutions to form ABZ suspensions in 10 % v/v ethanol in water solution. Albendazole: polymers ratios were adjusted in the preparations to give 1:1, 1:2 and 1:4 (Table 1).

All batches of microparticles were prepared by spray-drying using Buchi 190 mini spray drier (Büchi Labortechnik AG, Germany) with 0.5mm nozzle. The ABZ: polymer suspensions were fed to the nozzle via peristaltic pump (spray flow rate of 16 ml/min.). The volume of suspension was 200 ml. The suspensions were sprayed as atomized droplets by the force of the compressed air (air flow rate of 4 pound per square inch). The solvents in the droplets were evaporated in drying chamber by the blown hot air (inlet air temperature of 160 ^{o}C and outlet air temperature of 90 ^{o}C). The dried products were collected in collection vessel and weighed. The microparticles which passed through 250 μm sieve (Endocott Sieve Ltd, London, UK) was used in this study.

Morphology of the prepared ABZ microparticles:

The morphology of the prepared microparticles was studied and photographed using biological microscope model DN-200M (Novel, China) which equipped with digital camera connected to PC set with imaging software. The microparticles were dispersed with liquid paraffin in a microscope slide and samples were observed microscopically. The ABZ in microparticles is insoluble in liquid paraffin as it coated with the hydrophilic polymer.

Also, samples morphology was examined under scanning electron microscope (Jeol, JSM-6360LV scanning microscope, Tokyo, Japan). Before microscopy, the dried microparticles were mounted at carbon tape and were sputter-coated using

gold (Jeol, JFC-1100 fine coat ion sputter, Tokyo, Japan). The photomicrographies were taken at an acceleration voltage of 20 kV.

Differential scanning calorimetry:

Differential scanning calorimetery studies were done for the drug and the prepared microparticles using Universal V4.1D TA Instrument (Q100, TA Instruments, Delaware, USA) and they were carried out under the following conditions: sample weight 3-5 mg, scanning speed 10 ^{o} C/ min, in the 25-300 ^{o} C temperature range. Indium was used as standard.

Powder X-Ray Diffractometry:

Powder X-ray diffraction patterns of the prepared spray dried microparticles were carried out using a wide-angle X-ray diffractometer (Siemens D-500, Bruker AXS, Coventry, UK). The instrument was operated in 2- Theta scale. The angular range was 5^{o} to 40^{o} (2θ), and counts were accumulated for 1 second at each step.***Drug content:***

The drug content of the microparticles was determined spectrophotmetrically (λ =291 nm). The HPMC, PVA and PVP microparticles loaded with ABZ (equivalent to 20 mg of ABZ) were dissolved in 15 ml of ethanol under sonication. Before determination of the drug content the samples were filtered by Millipore filter of pore size 0.45 µm. Then, the amount of ABZ in filtrate was measured.Preliminary studies showed that the investigated polymer dilution range used didn't interfere with ABZ absorbance at 291 nm.

Dissolution study:

Dissolution measurements were carried out in a USP dissolution test apparatus (Caleva Ltd., Model 85T, Philips, UK). The dissolution profiles of ABZ from microparticles were studied in 0.1 N HCl (pH =1.2). The drug-loaded microparticles containing 20 mg of ABZ were placed in a rotating basket (100 rpm) filled with 500 ml of the dissolution medium, thermostated at 37 ± 0.5 ^{o}C. At schedule time intervals, the samples (5 ml) were withdrawn and replaced immediately with fresh dissolution medium. The samples were assayed spectrophotmetrically at 291 nm for dissolved drug, where samples were automatically filtered before measuring the

absorbance. The dissolution experiments were conducted in triplicate and the means of the absorbance were calculated. The times required for 50% of the drug to be dissoluted(T_{50} %) and for 80% of the drug to be dissoluted(T_{80} %) were calculated graphically and used as comparison parameter in dissolution studies.

Statistical analysis:

One-way analysis of variance (ANOVA) and t-test were performed using Statgraphics plus 2 software to compare the mean values of T_{50} % for all formulations. Multiple Range Test (Fisher's least significant difference procedure, LSD) was used to determine which means are significantly different from other. The level of confidence was 95%.

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