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Improvement of Albendazole Solubility and Dissolution Rate by Ternary Solid Dispersion Technique

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ABSTRACT

A ternary solid dispersion (SD) system was developed for the enhancement of the solubility and dissolution rate of albendazole (ABZ), a BCS class II drug. The effect of different ratios of one of two poloxamer grades (P 188 and P 407) in combination with PVP K30 was investigated. The ABZ SDs were prepared by conventional solvent evaporation method and evaluated for solubility, dissolution rate, powder X-ray diffraction (XRD), differential scanning calorimetry (DSC) and fourier transform infrared spectroscopy (FTIR).Results showed an improvement in solubility and dissolution rate of ABZ for all prepared $\mathrm{SD_S}$. SD containing (ABZ: PVP K30: P 407) (50%: 48%: 2%) w/w achieved the highest dissolution rate. It released 83.8 % at 5 min in comparison with only 18% at75min of pure ABZ. Powder XRD demonstrated a decrease in ABZ crystallinity. This led to a decrease in melting point of ABZ as seen in the DSC study. The formulated SDs were stable for 6 months with no change in crystallinity at room temperature. There was no chemical interaction between ABZ and polymers in SD as demonstrated by FTIR analysis.The results showed improvement of solubility and dissolution rate of ABZ from the developed ternary SD system.

Keywords: Albendazole; Dissolution rate, Ternary solid dispersion, PVP K30; Poloxamer.

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INTRODUCTION

In drug discovery, the number of drug candidates having low solubility has increased, and nearly 70% of the new drug candidates have shown poor aqueous solubility in recent years(1) and (2). Many problems arise from their poor solubility in formulation technology. Poor aqueous solubility of drug limits its dissolution rate, which results in low bioavailability of orally administered drugs. Albendazole (ABZ) is a benzemidazole derivative with broad spectrum anthelmintic activity against human and animal helminthes infection (3). ABZ was used as a model BCS class II drug(4). Poor aqueous solubility of ABZ limits its oral absorption (3). To increase the solubility of a poorly water-soluble drug and thus improve its bioavailability, several strategies can be employed. Some of the methods to improve ABZ aqueous solubility and bioavailability included solubilization by micelle formation (5),complexation with cyclodextrin(6),(7) and formation of nanosuspension(8). SDs may be described as a dispersion of one or more poorly water soluble drugs in hydrophilic carriers prepared either by melting or solvent evaporation method(9). Three different mechanisms were suggested for the improvement of the dissolution of drugs from SD_S, namely the drug wettability due to direct contact with the hydrophilic matrix, the reduction in particle size and consequently increase in surface area as well as the conversion of the crystalline to the more soluble amorphous state (10). Torrado et al. prepared (ABZ: PVP K25) SD in different ratios with low drug content, and it was found that the (1:40) ratio improved dissolution efficiency of ABZ by 20 fold after 60 min (11).Furthermore, Castro et al. prepared (ABZ: Poloxamer 188) binary solid dispersion, and the combination (25: 75% w/w) achieved the highest dissolution rate of ABZ (12). PVP K30 is a hydrophilic polymer(13). Using it as a carrier for SD improves solubility and dissolution rate of different drugs such as lansoprazole(14), carbamazepine (13) and temazepam(15). Its high glass transition temperature enables it to retard and inhibit drug recrystallization(13). Poloxamers are nonionic surfactant available in different grads(16). Two poloxamer grades poloxamer 188(P 188) and poloxamer 407 (P 407) were used as a carrier in SD for improvement of solubility and dissolution rate of different drugs such as desloratadine(17), co enzyme Q10 (18) and Ibuprofen (19). Third generation SD improves the bioavailability of poorly water soluble drugs. It is basically composed of a carrier mixture of polymer and surfactant, where the drug is entrapped in it. It has the highest dissolution rate and improves stability of drug in SD formulation (9). Therefore, the aim of this study was to investigate the effect of a combination of PVP K 30 and one of two poloxamer grades, P 188 or P 407, on the improvement of ABZ solubility and dissolution rate in a ternary solid dispersion system with high drug loading.

MATERIALS AND METHODS

ABZ was kindly supplied as a gift by EIPICO Company for pharmaceutical industry, EGYPT. PVP K30, PoloxamerP188 and P407 were purchased from Sigma Aldrich, USA. All other solvents were of analytical grade.

Preparation of physical mixture and solid dispersion

Physical mixtures (PM_s) were prepared by manually mixing ABZ powder with other ingredients according to the ratios in (Table1). The powders were sieved with a 450-µm sieve and were stored in a screw-cap vial at room temperature until further analysis. SD of ABZ in PVP K30 alone or in combination with either P 188 or P 407 was prepared in different ratios (Table1) by conventional solvent evaporation method. Drug and carrier were dissolved in minimum volume of 95% ethanol. The solvent was then evaporated under stirring at 80°C using hot plate stirrer. The result residue was then cooled in a refrigerator for 48 h. Dispersion was then pulverized using mortar and pestle and passed through a 450-µm sieve.

Table 1: Solid dispersions and physical mixtures Composition (% w/w)

Formula	ABZ	PVP K30	P 188	P 407
PM_1	50%	50%	—	—
PM_2	50%	48%	2%	—
PM_3	50%	48%	—	2%
SD_1	50%	50%	—	—
SD_2	50%	49%	1%	—
SD_3	50%	48%	2%	—
SD_4	50%	47%	3%	—
SD_5	50%	45%	5%	—
SD_6	50%	49%	—	1%
SD_7	50%	48%	—	2%
SD_8	50%	47%	—	3%
SD_9	50%	45%	—	5%

Phase solubility diagram for ABZ with PVP k30

The solubility studies for ABZ were performed according to the method described by Higuchi and Connors (20). An excess amount of ABZ added to vials containing 5 ml of 0.1 N HCL solution of different concentration of PVP K30 from 0%, 1%, 2%, 3%, 5%, 10%, 15% and 20% . These vials were allowed to be mechanically shaken in water bath shaker at 25°C for 4 days to reach equilibrium solubility. The suspension were filtered through 0.45 µm membrane filter, the clear filterates were diluted and analyzed for ABZ concentration using a UV—VIS spectrophotometer (JASCO V- 630, Japan)at 291 nm.

Solubility studies

Excess of ABZ or prepared SDs were suspended in 5 ml 0.1 N HCL and stored in sealed glass vials in water bath shaker with 100 rpm for 4 days to reach the equilibrium solubility at 25 °C and 37 °C. Before measurements were taken, the suspensions were filtered using 0.45µm filter. The filterates were diluted and analyzed for ABZ concentration using UV spectroscopy at 291 nm .

Dissolution studies

Dissolution rate of ABZ and its release from different PM_S and SD_S were investigated in a USP paddle apparatus (Tablet Dissolution tester, Dis 6000, 6 cup, U.K), 900 ml 0.1 N HCL (100 rpm, 37±0.5 °C, n=3). 25 mg of ABZ was used (cover the sink condition) and an amount of each PM and SD equivalent to 25 mg ABZ was used according to their drug content. Three ml samples were withdrawn at 5, 10,15,20,25,30,40,50 and 60 min and replaced with fresh medium to keep the volume constant. Then samples were filtered and analyzed for ABZ concentration at 291 nm usingUV spectroscopy

Dissolution efficiency

To compare the release profile of different formulations the dissolution efficiency parameter was calculated at 30 min. This is defined as the area under a dissolution curve between defined time point that have been compared for the complete dissolution profiles (100 % dissolution) between the same two point (21).

$$Dissolution.Efficiency.(D.E.) = \left(\frac{\int_{t2}^{t1} Y.dt}{Y100(t_2 - t_1)} \right) x100$$

Where, y is the percentage of dissolved product, D.E. is the area under the dissolution curve between time point t_1 and t_2 expressed as a percentage of the curve at maximum dissolution, Y_{100}, over the same time period.

Characterization of solid dispersion

Powder x-ray diffraction (XRD)

The powder XRD pattern was traced at room temperature employing an automated X´- pert PRO- PAnalytical differactometer (PAnalytical, Netherlands) for the samples. Monochromatic Cu & K radiation was obtained and a system of diverging and scattering slits of 1^0. The data were collected with a step size of 0.02^0 and a scan time of 0.5 s. About 200 mg of each sample powder was carefully side- loaded in a sample holder to minimize possible preferential orientation.

Differential scanning calorimetry (DSC)

Thermal analysis of various solid dispersions was performed in a Shimadzu DSC- 50 (Shimadzu Scientific instrument, USA) differential scanning calorimeter. Approximately 5 mg of sample were placed into a perforated aluminum pan, subsequently heated from 25 to 230°C at a rate of 10 °C/min, using nitrogen as a pure gas at a flow rate of 25 ml/ min. An empty aluminum pan was used as reference and the experiment was performed in triplicate.

Fourier transforms infrared spectroscopy (FTIR)

Infrared (IR) spectra for the ABZ and prepared SD systems were obtained at room temperature using a Shimadzu Infrared Spectrophotometer (FTIR Shimadzu 8400S, Lab Wrench, Japan). Sample was prepared in KBr disks (ratio 1:9) by means of a hydrostatic press. The scanning range was 400 - 4000 cm^{-1}. The spectra were collected, with a resolution of 4 cm^{-1}, using a mercury cadmium telluride (MCT) detector. Infrared analysis was carried out on the pure drug and solid dispersions in equimolar ratio.

RESULTS AND DISCUSSION

Phase solubility diagram

The phase solubility diagram (Figure1) followed an A_L- type system. Where solubility of ABZ was increased more than threefold (from 0.4 to 1.4 mg/ml) as the concentration of PVP K30 in solution increased from 0 % to 20 % (w/v). This improvement in solubility of ABZ may bedue to the formation of a soluble complex between the hydrophilic polymer (PVP K30) and ABZ.

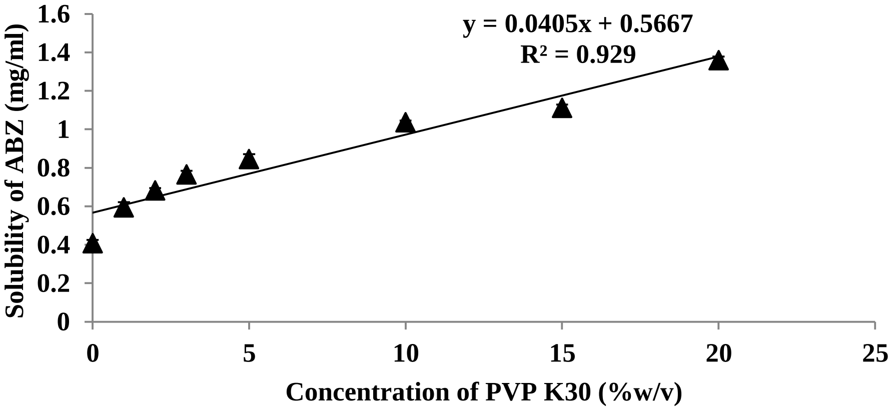

Figure 1: Phase solubility diagram of ABZ in 0.1 N HCL with different concentration of PVP K30 at 25°C

Solubility studies

It was found that the solubility of pure ABZ was 408.06 ± 0.2µg/ml at 25 °C and 820.05 ± 0.2µg/ml at 37 °C(Table2). An increase in solubility was observed for all prepared SDs. SD with 2% P 407gave the highest solubility of 818.33 ± 6.1µg/ml at 25 °C and 1514.67 ± 2.4µg/ml at 37 °C(Table2). Higher and lower concentrations of P 407showed lower solubility.The same pattern was observed for P 188, at less solubility improvement. This increased solubility was due to the combination effect of hydrophilic polymer and surfactant on the drug solubility and the micellarsolubilization effect of the surfactant (22).

Table 2:Solubility of ABZ and different solid dispersions at 25 °C and 37 °C in 0.1N HCL

Formula	Solubility (µg/ml) At 25 °C Mean ± SD	Solubility (µg/ml) At 37 °C Mean ± SD
Pure ABZ	408.1 ± 0.2	820.1 ± 0.2
SD_1	610.1 ± 3.8	964.1 ± 4.1
SD_2	693.3 ± 3.7	1290.7± 5.1
SD_3	753.7 ± 4.3	1391.1 ± 4.2
SD_4	719.9 ± 5.3	1341.3± 2.6
SD_5	710.2 ± 2.8	1273.2± 4.1
SD_6	686.2 ± 4.1	1407.3 ± 5.7
SD_7	818.3 ± 6.1	1514.7± 2.4
SD_8	782.3 ± 5.2	1437.3 ± 4.5
SD_9	737.7 ± 3.5	1372.5 ± 4.3

Dissolution studies

The physical mixtures, PM_1, PM_2 and PM_3 showed higher dissolution rate of ABZ compared to the pure drug alone (Figure2). This increase however, was not as high as their corresponding SD, due to non-homogeneity of ABZ distribution and randomization. Consequently some ABZ particles were not surrounded by polymer and surfactant, which lead to lower wettability and lower dissolution rate of isolated particles (12). Dissolution profile of the binary solid dispersion (SD_1) showed that PVP K30 improved dissolution rate and increased percent of drug released up to 47.25 % at 75 min in comparison with only 18% of pure ABZ at the same time point (Figure2). This improvement in dissolution rate was due to dispersion of ABZ in water soluble polymeric carrier (PVP K30), which caused a linear increase in the solubility of ABZ by increasing its concentration. Formula SD_3, containing 2% (w/w) P 188 gave the highest dissolution rate in comparison with lower and higher concentrations of P 188. It released 59.3 % at 5 min and achieved its maximum release of 94% at 30 min (Figure3). Ternary SD containing P 407 showed similar dissolution pattern. However,SD_7 containing 2% (w/w) P407 showed faster release profile compared to SD_3. It released already 83.8 % at 5 min only and reached maximum release of 89.7% at 25 min (Figure3). The increase in dissolution rate of binary SD by addition of small percent of surfactant until 2% (w/w) might be explained by the combination effect of hydrophilic polymer and surfactant on the drug release, the micellarsolubilization effect of surfactant as well as the reduction of the interfacial tension between the drug and the dissolution media, thus improving dispersibility and dissolution rate of solid dispersion(22). The further decrease in dissolution rate at higher than 2% (w/w) concentration of the surfactant might be explained by the micelle formation theories. Poloxamers above their critical micelle concentration (CMC) will aggregate to form micelles(23). CMC of P 188 is 0.000125 M(12), while the CMC of P 407 is 0.000603×10^{-3}M(24), which are both lower than the amount used for the formulated SD_S. Lower concentration of poloxamers forms monomolecular micelles, which enhance the dissolution rate of drug. But their higher concentration forms aggregates of micelles with different size which increase solubility of drug and increase its stability with the result of lower dissolution rate of drug(25)as observed in 3% (w/w) and 5% (w/w) of two grades of poloxamers. In addition, poloxamers have a hydro gel property at higher concentration and under the physiological condition (26). This results in relative delay in dissolution rate of ABZ at higher concentrations.

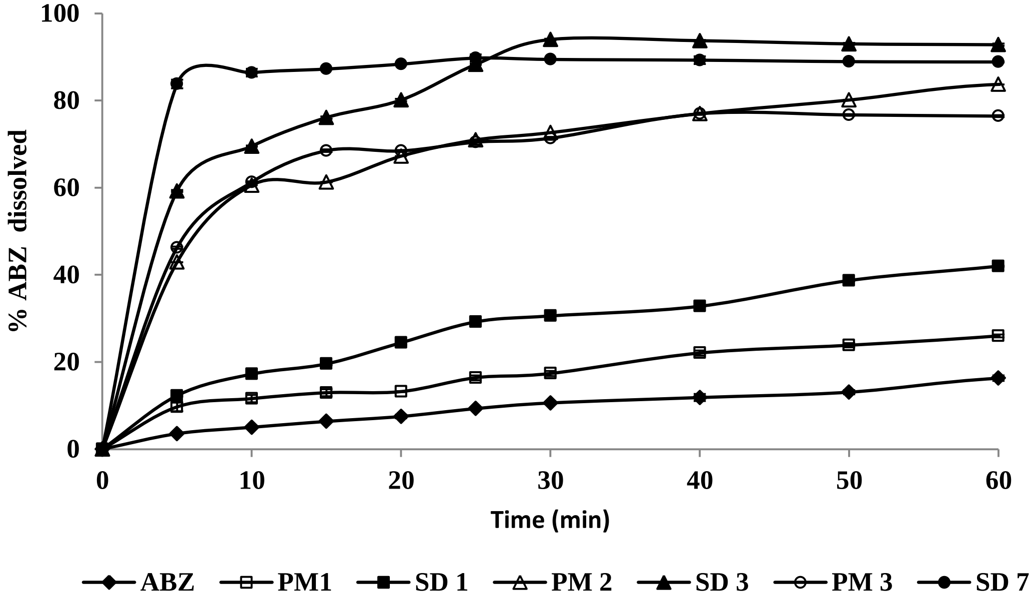

Figure 2:Dissolution profile of ABZ, PM_1(ABZ: PVPK30) (50%: 50%), SD_1(ABZ: PVP) (50%: 50%), PM_2 (ABZ: PVPK30: P188) (50%: 48%: 2%),SD_3(ABZ: PVPK30: P188) (50%: 48%: 2%), PM_3 (ABZ: PVPK30: P407) (50%: 48%: 2%) and SD_7 (ABZ: PVPK30: P407) (50%: 48%: 2%).

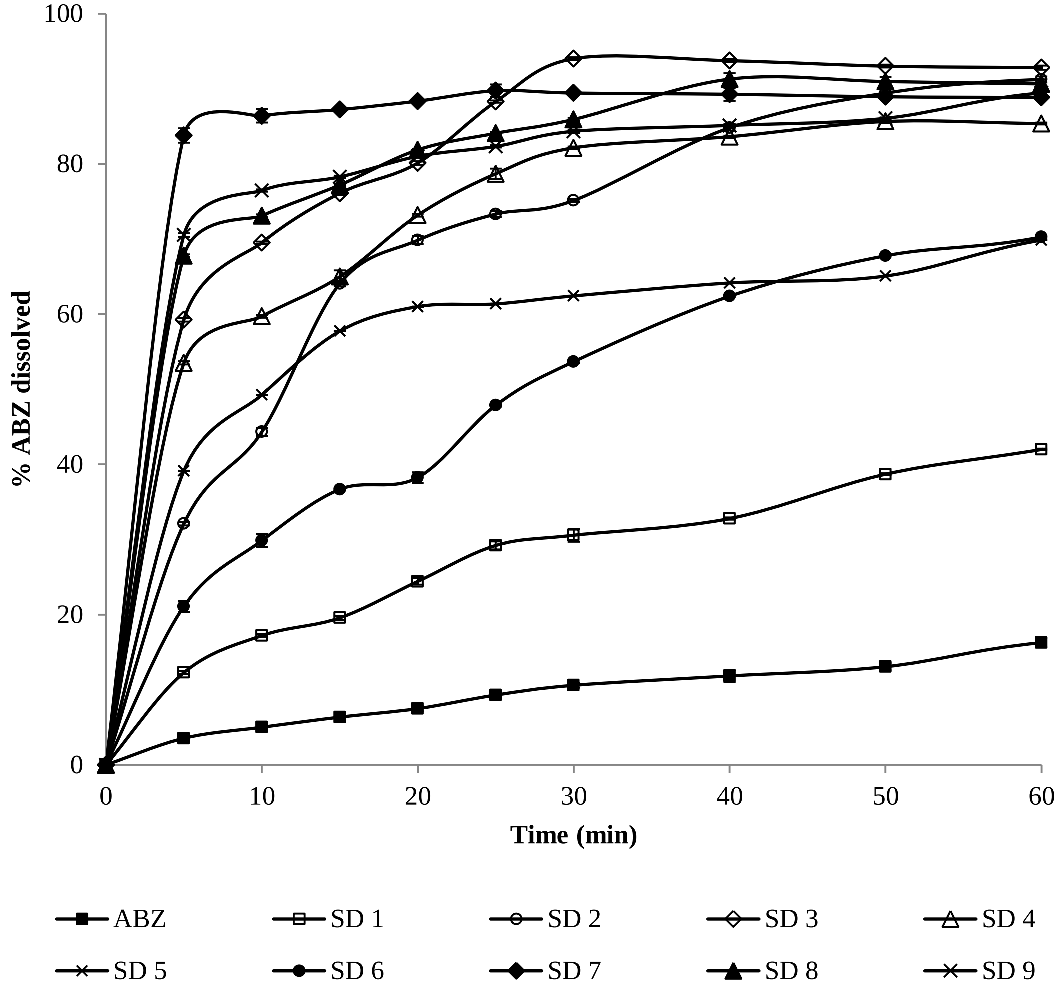

Figure 3:Dissolution profile of ABZ, SD$_1$(ABZ: PVPK30) (50%: 50%), SD$_2$ (ABZ: PVPK30: P188) (50%: 49%: 1%), SD$_3$ (ABZ: PVPK30: P188) (50%: 48%: 2%), SD$_4$ (ABZ: PVPK30: P188) (50%: 47%: 3%), SD$_5$(ABZ: PVPK30: P188) (50%: 45%: 5%), SD$_6$ (ABZ: PVPK30: P407) (50%: 49%: 1%), SD$_7$ (ABZ: PVPK30: P407) (50%: 48%: 2%), SD$_8$ (ABZ: PVPK30: P407) (50%: 47%: 3%) and SD$_9$ (ABZ: PVPK30: P407) (50%: 45%: 5%).

Dissolution efficiency

The calculated dissolution efficiency of pure ABZ was 6.2% at 30 min. (Table 3).By calculating the dissolution efficiency of the different PMs and SDs at 30 min, it was found that formula SD$_7$ containing 2% (w/w) P407 gave the highest value of 79.9% (Table3).

Table 3: % Dissolution efficiency of different physical mixtures and solid dispersions after 30 min.

Formula	AUC (µg.min/ml)	% DE_{30}
Pure ABZ	184.9	6.2
PM_1	362.5	12.1
PM_2	1642.2	54.7
PM_3	1752.8	58.4
SD_1	589.9	19.6
SD_2	1486.2	49.5
SD_3	2068.1	68.9
SD_4	1855.5	61.8
SD_5	1498.5	49.9
SD_6	1002.9	33.4
SD_7	2396.6	79.9
SD_8	2134.8	71.2
SD_9	2153.8	71.8

Characterization of solid dispersion

Powder x-ray diffraction (XRD)

ABZ, a crystalline drug, can be identified by its specific signals at (theta/2theta= ABZ: 7, 11.4, 13.97, 17.89, 24.71, 27.7, 29.9, and 30.5) (Figure 4). In addition, P 407, also crystalline in nature, has its characteristic peaks at (theta/2theta= PP 407: 19.04, 23.18, 26.16, 36). On the other hand, PVP K30 is amorphous in nature as shown in (Figure4). XRD diffractogram for the binary SD_1 (Figure5) clearly showed that the signals assigned to each component were not changed, i.e. ABZ remained in its crystalline form and no interaction occurred between ABZ and PVP K 30. However, signals were present with lower intensity, which suggests a decrease in crystallinity. That may be due to the higher drug loading of ABZ in the formulated SD_1, which might have prevented amorphous formation of ABZ (27). By comparing XRD diffractograms of SD_1 with that of SD_7 it was found that the crystallinity decreased more in the latter, which may explain the higher dissolution rate of SD_7 than that of SD_1. ABZ remained in its crystal form in the formulated SD, avoiding the drawback of amorphous drug formation, i.e. recrystallization process and hence change in its solubility and drug release properties over time (28). That will support its long-term physical stability. The XRD diffractogram of SD_7 has not been changed after 6 months of storage at room temperature as seen in (Figure6).Using PVP K30 in SD retards and inhibits recrystallization of ABZ due to its high glass transition temperature (13). In addition using a mixture of polymer and surfactant as a carrier for SD improved long term stability of technique(9).

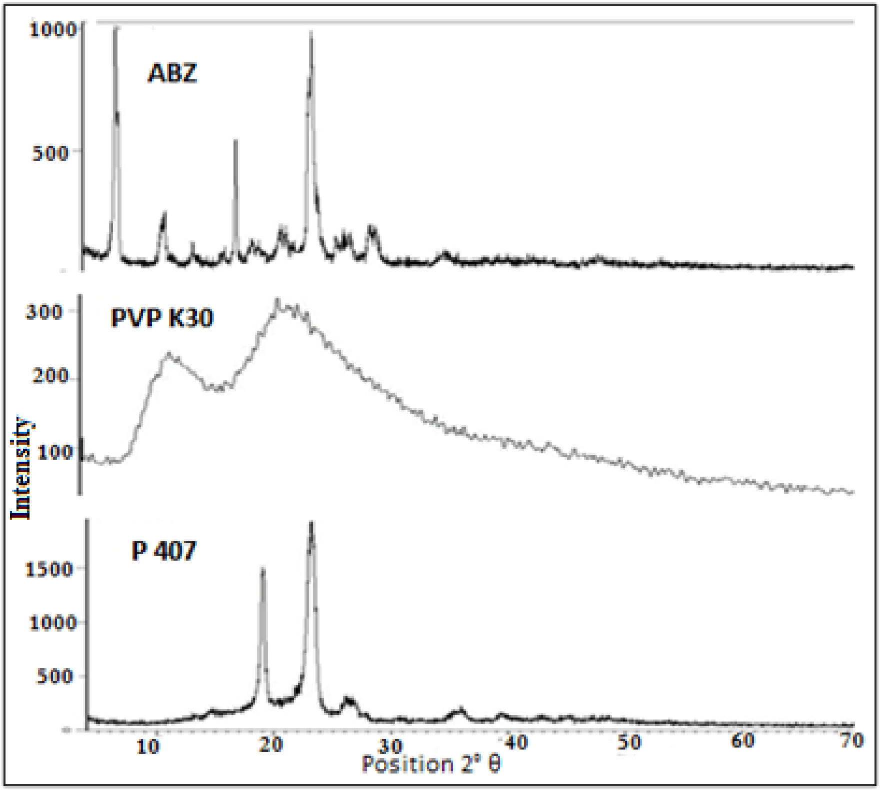

Figure 4:XRD diffractogram of ABZ, PVPK30 and P407.

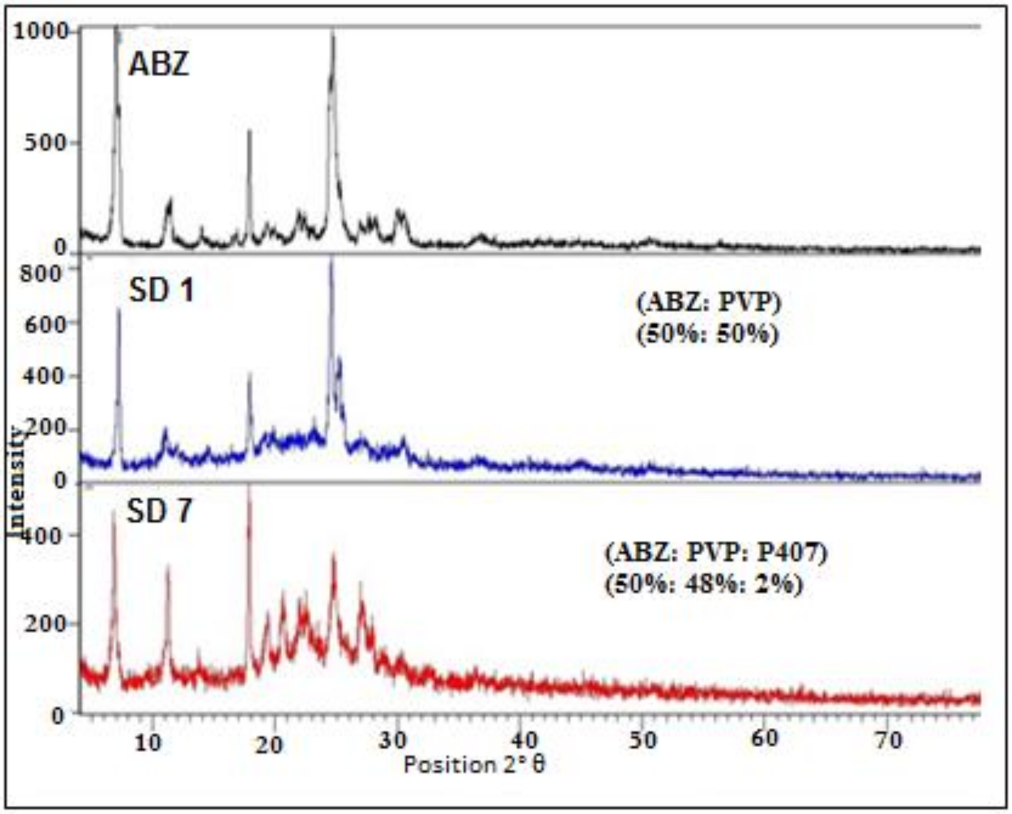

Figure 5: XRD diffractogram of ABZ, SD_1 (ABZ: PVPK30) (50%: 50%)and SD_7 (ABZ: PVPK30: P407) (50%: 48%: 2%).

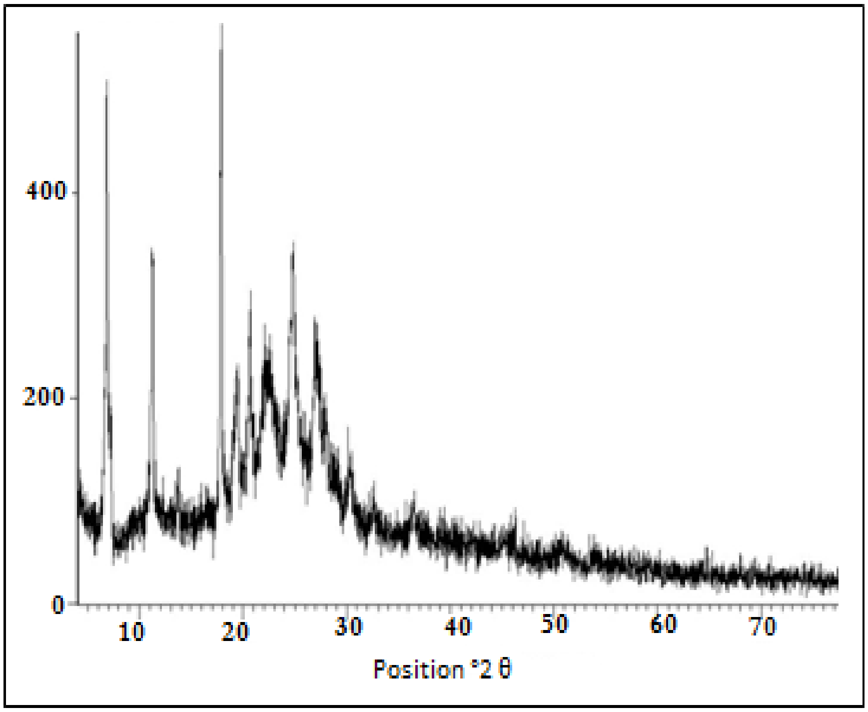

Figure 6: XRD diffractogram of SD_7(ABZ: PVPK30: P407) (50%: 48%: 2%) after storage for 6 months at room temperature.

Differential scanning calorimetry (DSC)

Pure ABZ showed an endothermic peak at199.5 °C with a shoulder at 212.8 °C, PVP K30 DSC thermogram showed an endothermic peak at 82.2 °C, and DSC thermogram of P407 showed endothermic peak at 58.8 °C (Figure 7). The binary physical mixture (PM_1) showed two characteristic peaks for both ABZ and PVP K30 at 194 °C and 68.37 °C, respectively (Figure8). Its corresponding solid dispersion SD_1 showed further reduction in the melting point of ABZ reaching 186.9 °C, where PVP K30 melting point decreased to 65.5 °C (Figure 8). The ternary physical mixture PM_3 showed characteristic peaks at 192.26 °C, 71.67 °C and 55.4 °C for ABZ, PVPK30 and P 407, respectively (Figure 8). There was further decrease in melting point in the ternary solid dispersionSD_7 with peaks showing at176.5 °C, 68.4 °C and 55 °C for ABZ, PVP K30 and P 407, respectively (Figure8). This decrease in melting point of drug was due to reduction in crystallinity of ABZ in the SDs, as shown in the XRD (Figure 5). In addition, the decrease in melting point of PVP K30 by incorporation of surfactant P 407 might be due to an increase in the chain mobility of the polymer molecules (22). There was no chemical interaction between ABZ and polymers in all preparations as the endothermic peak of ABZ was identified in all PM_S and SD_S.

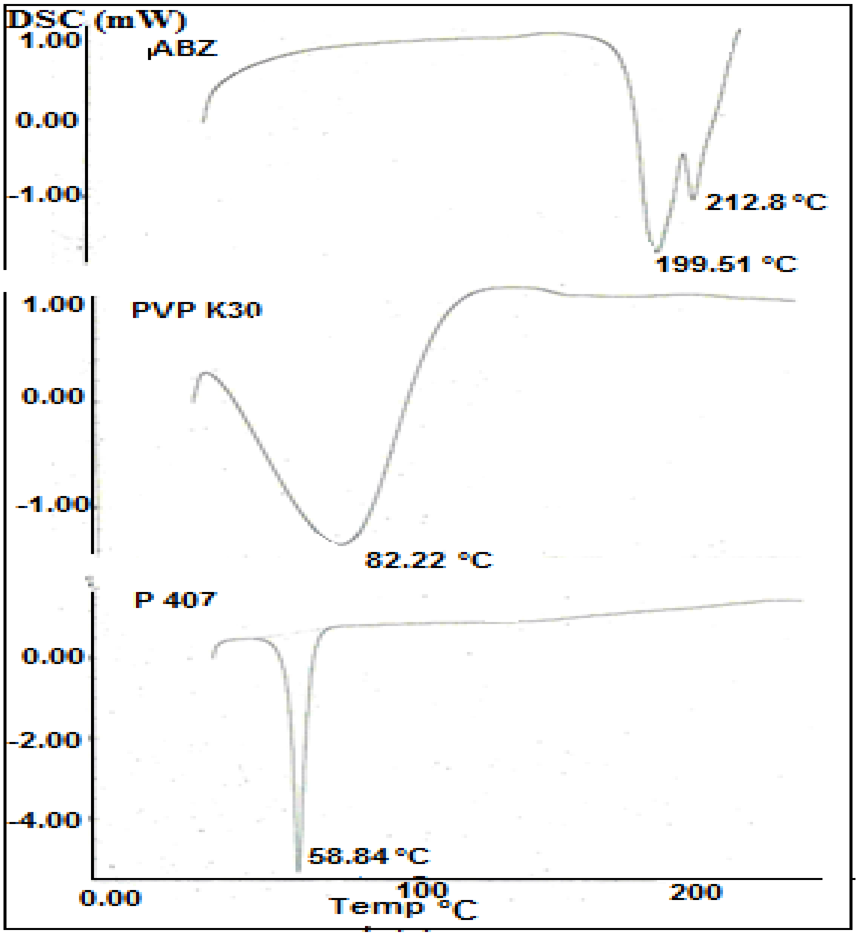

Figure 7:DSC thermogram of ABZ, PVP K30 and P 407.

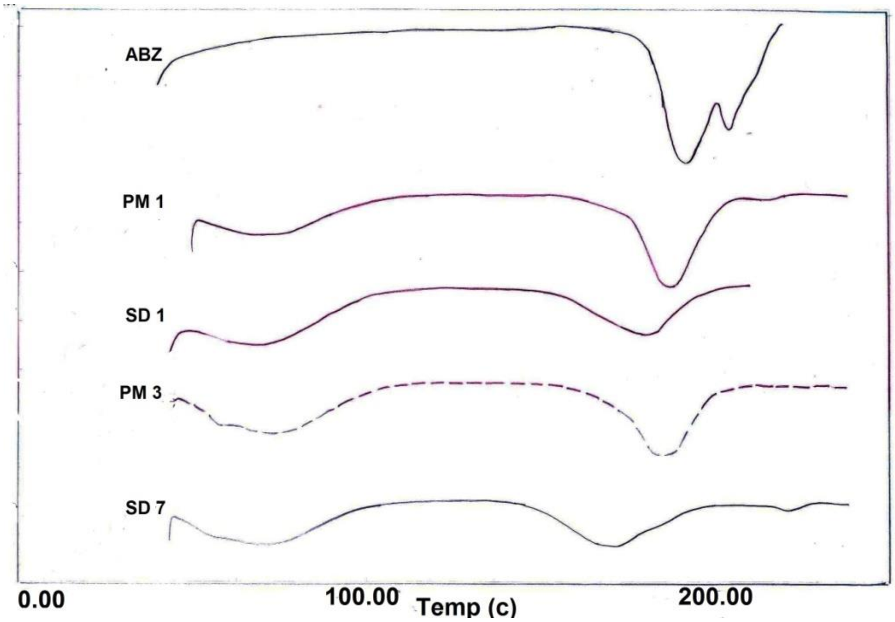

Figure 8: DSC thermogram of ABZ, PM$_1$ (ABZ: PVPK30) (50%: 50%), SD$_1$(ABZ: PVPK30) (50%: 50%), PM$_3$(ABZ: PVPK30: P407) (50%: 48%: 2%) and SD$_7$ (ABZ: PVPK30: P407) (50%: 48%: 2%).

Fourier transforms infrared spectroscopy (FTIR)

The FTIR spectrum of ABZ (Figure 9) showed a peak at 3332 cm^{-1}, which represents the N-H stretching vibration. Two peaks were seen at 2953 cm^{-1} and2856 cm^{-}1, representing the aromatic and aliphatic C-H of Benzene ring, respectively as well as a highly intense narrow peak at 1630 cm^{-1}was observed, due to C=O stretching. Peaks found at 1527 cm^{-1} and 1449 cm^{-1} represent the benzene ring in the compound. A group of peaks at 1269 cm^{-1}, 1189 cm^{-1}, 1094 cm^{-1} and 1007 cm^{-1} are due to the C-O group of ABZ. The region from1323-512 cm^{-1},represents the characteristic fingerprint region of ABZ. In the FTIR spectrum of PVP K30 (Figure 9), the peaks were found at 2955 cm^{-1}, due to C-H aliphatic and 1658 cm^{-1}, due to C=O group. In addition, a large broad band was visible at 3435 cm^{-1}, which was attributed to the presence of water (15).The region from 1432-573cm^{-1}represents the characteristic fingerprint region of PVP K30. In the spectrum of P 407 (Figure 9) there was a characteristic peak at3456 cm^{-1},due to OH group. Another peak was seen at 2884 cm^{-1} due to C-H aliphatic and a peak at 1108 cm^{-1} due to C-O stretching. The region from 1476-525 cm^{-1}represents the characteristic fingerprint region of P 407. Both PMs and SDs, showed an additive spectra of the individual compounds and ABZ peaks remained unaltered and nearly at the same wave numbers, which confirms no possible interaction between ABZ and polymers (Figure 10).

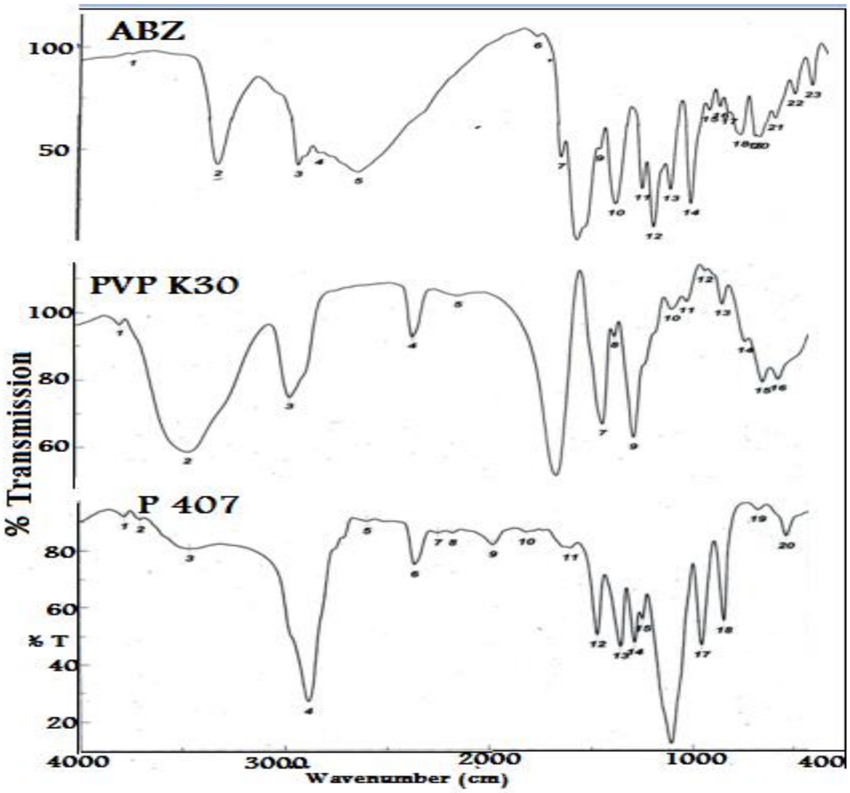

Figure 9: FTIR spectrum of ABZ, PVP K30 and P 407.

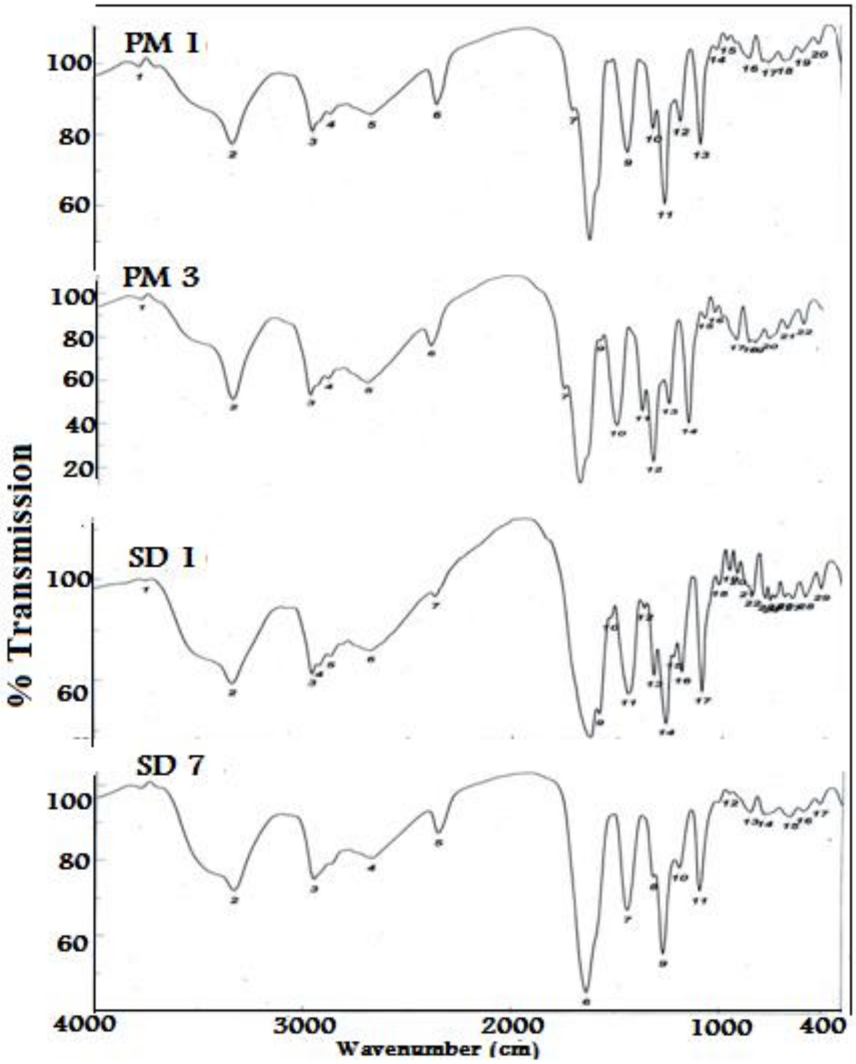

Figure 10: FTIR spectrum ofPM$_1$ (ABZ: PVPK30) (50%: 50%), PM$_3$ (ABZ: PVPK30: P407) (50%: 48%: 2%), SD$_1$(ABZ: PVPK30) (50%: 50%) and SD$_7$ (ABZ: PVPK30: P407) (50%: 48%: 2%).

CONCLUSION

In the present study, a ternary SD of ABZ was designed with the use of hydrophilic polymer PVP K30 and one of two poloxamer grades (P 188 or P 407). P 407 in combination with PVP K30 showed higher solubility and dissolution rates than P 188. Formula SD$_7$ containing (ABZ: PVP k30: P 407) (50%: 48%: 2%) (w/w) gave the fastest dissolution rate at the shortest time. This formula was chemically stable as shown in DSC and FTIR results with no chemical interaction between ABZ and the polymers. No amorphous formation of ABZ with only a decrease in the drug crystallinity was observed, which remained stable for 6 months. Therefore, this ternary system is a potentially useful carrier for improvement of solubility and dissolution rate of BCS class II drugs.

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