Improved Dissolution of Albendazole from High Drug Loaded Ternary Solid Dispersion: Formulation and Characterization

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ABSTRACT

Bioavailability of a poorly water-soluble drug, e.g., widely used anthelmintic drug Albendazole (ABZ), is very low and thus, to obtain an optimized therapeutic efficacy, the aqueous solubility of such drugs needs to be enhanced. The objective of this study was to develop an effective high drug-loaded solid dispersion (SD) of ABZ with two biocompatible drug carriers, namely Soluplus® and Ludiflash® to improve its physicochemical characteristics. Equilibrium solubility study was performed to choose the optimum polymer ratio among the formulations and it showed up to 50-fold enhanced solubility compared to crystalline ABZ in water. X-Ray Powder Diffraction (XRPD) and Differential Scanning Calorimetry (DSC) studies of SD-ABZ showed reduced crystallinity of ABZ in the SD. The polymeric carriers, notably Soluplus®, are thought to play a key role in the reduction of crystallinity and molecular polydispersity of ABZ. The dissolution studies in water showed improved dissolution of SD-ABZ compared to crystalline ABZ, with a quick onset of drug release followed by gradual dissolution. However, due to high drug-loading and retention of crystalline ABZ in the sample, the dissolution behavior was not as expected, and may require further studies to optimize the SD-ABZ formulation.

Keywords: Albendazole; Solubility; Solid dispersion; Soluplus®; Ludiflash®

INTRODUCTION

Orally formulated drugs are extensively marketed and used because they are convenient and easier to administer as solid dosage forms. However, most of the new drugs marketed as oral dosage forms are classified according to biopharmaceutics classification system (BCS) class II and class IV as having poor aqueous solubility.[1] The aqueous solubility is an essential property for the systemic absorption of drugs after oral administration.[2] Crystallinity plays a crucial role in the aqueous solubility of these drugs.[3] Molecular state of crystalline drugs is packed in regularly ordered and repeating pattern. They have lower energy state and are more stable, hence show low aqueous solubility.[4] Reduction in crystallinity with an amorphous form of the drug can create a meta-stable form with higher free energy state and thus higher solubility.[5,6] Transformation of solid state from crystalline to metastable amorphous form during preparation can be attributed to different drug delivery strategies, among them solid dispersion (SD) is now widely recommended as a promising method of preparation in terms of ease of preparation.[7] Conversely, for the SD, high proportions (50-80% w/w) of polymeric carriers are generally required to achieve targeted

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improvement in dissolution behavior.[8,9] Albendazole (ABZ) is a benzimidazole derivative commonly used as an anthelmintic agent, and classified as a BCS class II drug having poor aqueous solubility and poor oral absorption (less than 5%).[10] Moreover, ABZ stays as in a stable acicular crystalline form which is liable for its poor solubility.[11] Additionally, ABZ has a recommended clinical dose of 200-400 mg.[12] Therefore, preparation of a pharmaceutical solid dosage form of ABZ using low drug loading might be troublesome and might not be commercially feasible for the ease of patient convenience as the final weight and size would be troublesome to swallow.[13] On the other hand, high drug-loading also increases the chance of formation of crystals in the formulation, as in higher drug-loading a loss of polymer from drug in amorphous solid dispersion (ASD) can be observed.[14] Moreover, in ASD with high drug loading, suboptimal disintegration and drug release performance have been reported.[15] Several methods have been developed to improve the solubility and dissolution rate of ABZ, such as chitosan-microsphere preparation[16], oil/water emulsion[17], microcrystals[18], SD[19], liposomal incorporation[20], cyclodextrin complexation[21], co-grinding[22], co-spray drying[23] and, more recently, nanoparticle formulations[24]. Among these strategies, ASD using amphiphilic carriers is a promising strategy for improving the aqueous solubility and dissolution[25] in between 10 to 1600-fold[26,27] Moreover, combined polymeric carriers are also used to decrease the high percentage of carrier concentration successfully in enhancing the dissolution behavior.[28] To achieve a targeted result, high drug-loaded SD with stable amorphous form and adequate drug release can be achieved by optimizing drug and polymer ratio. However, till date very little is known about the feasibility of high-drug loaded SD with mixed polymeric carriers to improve the dissolution behavior of ABZ.

The current study was aimed to overcome the solubility problem of ABZ by the application of SD with high-drug loading using two biocompatible polymers, Soluplus® and Ludiflash®. The SD was prepared with 50% (w/w) ABZ load and 50% (w/w) mixed polymeric carrier. Soluplus® is a novel carrier excipient with excellent amphiphilicity and solubilizing properties which promote *in vivo* absorption.[29] Ludiflash® is a filler, binder, and disintegrant used in orodispersible tablets (ODT).[30] In this study, various polymer ratios of the formulations (0-50% w/w) were selected on a randomized basis, prepared and optimized in terms of solubility enhancement. Equilibrium solubility studies on the different formulations were performed and analyzed. The drug release profile and physicochemical characterization of the optimized SD-ABZ was also assessed with those of crystalline ABZ.

MATERIALS AND METHODS

Materials. ABZ was generously provided by the Beximco Pharmaceuticals Ltd., Dhaka, Bangladesh. Soluplus® and Ludiflash® were a kind gift from the BASF, Bangladesh. The chemicals and solvents used were of analytical grade.

Preparation of SD-ABZ. To prepare the SD-ABZ, drug and polymers (Soluplus® and Ludiflash®) were physically mixed using kneading method.[31,32] In brief, 50% (w/w) of ABZ was weighed and taken in a mortar, and drop wise addition of pure distilled water was used as the solvent. Slurry was prepared where all the drug particles are wetted by trituration. In this slurry, the polymers, Soluplus® and Ludiflash®, (50% w/w) were added in different ratios (% w/w) (Table 1). The sample was then triturated until a uniform mixture was formed. To obtain a dried sample, solvent evaporation technique was used.[33] The solvent of the sample was evaporated using a rotary vacuum evaporator (Rotary Solvent Evaporator, Heidolph, GmbH, Germany) at 50°C under vacuum to yield a solid and dried sample.

Table 1. Selection of suitable ratio of the polymers.

Sample	Ratio (%) Soluplus®: Ludiflash®:ABZ	Equilibrium solubility (µg/ml)
Crystalline ABZ		0.67 ± 0.15
F1	25 : 25 : 50	24.9 ± 1.82
F2	37.5 : 12.5 : 50	33.5 ± 5.62
F3	12.5 : 37.5 : 50	9.5 ± 1.15
F4	33.3 : 16.7 : 50	25.9 ± 1.27
F5	16.7 : 33.3: 50	16.5 ± 1.06

Data represent the mean ± SD of 3 experiments.

ABZ determination. ABZ in the samples was determined by a UV-spectrophotometric method.[34] In this regard, 10 mg of ABZ was taken in a closed test tube and 100 mL of methanol was used to dissolve the drug sample to prepare a solution of 0.1 mg/ml. The mixture was then filtered and diluted with the dissolution media to prepare standard concentrations of 0.5 µg/ml, 1 µg/ml, 2 µg/ml, 3 µg/ml, 5 µg/ml, 7.5 µg/ml, 10 µg/ml and 15 µg/ml, respectively. The diluted samples were then analyzed by a UV Spectrophotometer (Shimadzu, Japan) at the wavelength of 281 nm.

Equilibrium solubility studies. The solubility of ABZ in formulations containing different ratios of Soluplus® and Ludiflash® were measured. Approximately 50 mg of formulation was added to a closed test tube containing 10 ml of distilled water to prepare an excess concentration of ABZ compared to reported solubility.[35] The samples were then incubated using a digital shaking incubator (Model: I10-OE+OL30-ME), for 6 hours at 50 RPM and at 37±0.5°C temperature. After incubation, aliquots of test solutions were collected, filtered, and then centrifuged at 10,000×*g* for 5 min to separate the undissolved drug particles. The supernatant of the centrifuged sample was obtained and diluted using 50% methanol. The ABZ content was analyzed by a UV Spectrophotometer described in the aforementioned section.

Surface Morphology

Scanning electron microscopy (SEM). The surface morphology of crystalline ABZ and SD-ABZ was observed by scanning electron microscopy (SEM) technique using Miniscope® TM3030 (Hitachi, Tokyo, Japan). The crystalline ABZ and SD-ABZ samples were placed on an aluminum sample holder and fixed using double sided carbon tape. A magnetron sputtering device, MSP-1S (Vacuum Device, Ibaraki, Japan) was used to coat over the samples with platinum.[36]

Polarized light microscopy (PLM). The crystallinity of the crystalline ABZ and SD-ABZ was evaluated using Polarized Light Microscopy (PLM) technique.[37] The ABZ samples were suspended in silicone oil. The observation was done using a CX41 microscope (Olympus Co. Ltd., Tokyo, Japan) under various conditions which included differential interface contrast, slightly uncrossed polar and using a red wave compensator.

Crystallinity Study

X-ray powder diffraction (XRPD). The x-ray powder diffraction (XRPD) was performed using a Mini Flex II (Rigaku, Tokyo, Japan) with Cu Kα radiation generated at 40 mA and 35 kV. The instrument was operated at a scanning speed of 4°/min and the ABZ samples were scanned over a range of 2θ angles from 10° to 35° with a step size of 0.2°.

Differential scanning calorimetry (DSC). Thermal analysis of ABZ samples were done using a DSC Q1000 (TA Instruments, New Castle, DE, USA) at a heating rate of 5°C/min under purging nitrogen gas (50 mL/min). The ABZ samples were placed and sealed in aluminum sample pans. Accurately weighed (ca. 3 mg) samples were subjected to the DSC thermal analysis. Indium was used to calibrate the system as a reference standard (8-10 mg, 99.999% pure, onset at 156.6°C).

Dynamic light scattering (DLS). For the analysis of mean hydrodynamic particle size and zeta potential of the aqueous suspended SD-ABZ, the dynamic light scattering (DLS) technique, using a Zetasizer Ultra (MALVERN, Worcestershire, UK), was performed. Prior to the measurement, the concentration of ABZ was kept 10 µg/mL, sample was suspended in Milli-Q. The measurement was performed at 25°C and at a measurement angle of 90°. The analysis was done in triplicate.

Dissolution studies. The *in vitro* dissolution test was performed on crystalline ABZ and SD-ABZ in distilled water using a USP type II dissolution test apparatus (Logan Model UDT 804, USA). Temperature and paddle rotation speed were set to 37.0 ± 0.5°C and 75 RPM, respectively.[38] Sample collection time intervals were selected at 15, 30, 60, 120, 180, 240, 300 and 360 min, respectively. 10 mL of sample was withdrawn from the dissolution vessels. The sample was then filtered using Whatman

filter papers placed in a conical flask into a test tube. Dilutions with dissolution media were performed for each sample solution in order to compare with standard drug concentration. Absorbance of the diluted sample from different time points were analyzed using the Shimadzu UV Spectrophotometer mentioned earlier at 281 nm. The dissolution test was performed thrice and their mean value was calculated to obtain the dissolution profile.

Statistical Analysis

All experiments in solubility and drug dissolution studies were repeated at least three times. All data are represented as mean ± standard deviation (SD). The graphs were plotted using Graphpad, Prism 6.0 (GraphPad Software, LaJolla, CA).

RESULTS AND DISCUSSION

SDs are primarily binary mixtures of drug and polymer.[39] Solvent evaporation and hot-melt extrusion are two widely used methods to prepare SDs of drugs with low solubility. For high drug-loaded SD, the hot-melt extrusion method can cause degradation of the drug.[40] On the other hand, solvent evaporation method does not require exposure to high temperature and reduces risk of drug degradation. Based on the above mentioned analyses the results are discussed below.

Optimization of polymer ratio. In this study, to select the optimum polymer ratio, five different polymer ratios with 50% (w/w) ABZ were assessed through equilibrium solubility studies to optimize the best drug-polymer ratio for the formulation by comparing them with the crystalline ABZ sample. Table 1 shows the equilibrium solubility data of the selected drug-polymer ratios. From the equilibrium solubility study results, we could see that the F2 with Soluplus®: Ludiflash®: ABZ ratio (37.5: 12.5: 50 %) had the highest solubility among the test samples. The study showed about 50-fold enhancement in solubility of the F2 compared to that of the crystalline ABZ in water (Table 1). The result demonstrated the higher solubility compared to crystalline ABZ in the formulation containing higher ratio (%) of Soluplus® compared to Ludiflash®. The considerable reason for this to occur is that the hydrophobic crystalline molecules of ABZ preferably interacted with Soluplus® more and drug molecular dispersion was higher.[39] This result is supported by a finding that suggests a higher molecular dispersion is in accordance with the better drug release from the polyethylene glycol (PEG)-drug system**.**[41] The comparison indicates a promising enhancement of the solubility in water under the specific conditions of the equilibrium solubility study. Several investigations suggested that in ternary system, the synergistic effect of polymers is a result of both head-head and electrostatic interactions[42]. In addition, the hydrophobic blocks of the copolymer form the core of the micelle that serves as a microenvironment for incorporation and accommodation of the lipophilic molecules.[43] thus, the solubility of the hydrophobic drug is enhanced by the nature of the interior of the micelles through hydrophobic-hydrophobic interactions.

Therefore, on the basis of improved solubility, F2 was chosen as the optimal one for further physicochemical characterization and dissolution studies.

Physicochemical Characterization

SEM study. The SEM images of crystalline ABZ and SD-ABZ are shown in Figure 1A. The microscopic image of crystalline ABZ shows the presence of crystalline solids. For amorphous materials, it might exist as irregular shape which can be distinguish as transparent glass like nature.[44] The SD-ABZ presented a SEM image with discrete surface morphology where most of the materials cannot be observed. However, the SEM image also presents distinguishable portions of the material which are regularly arranged. Thus, it can be noted that there was a retention of crystalline ABZ in the SD-ABZ formulation.

PLM study. The PLM study clearly shows the presence of ABZ crystals (Figure 1B). ABZ crystals have long range orders and different arrangement of particles in different directions, hence are anisotropic. On the other hand, SD-ABZ clearly shows a

reduction in particles that are anisotropic. However, presence of crystalline ABZ can be detected in the images from PLM (Figure 1B). Comparing the images, it can be observed that in crystalline ABZ the fine crystals were agglomerated in larger scale, whereas the crystals though present in the SD-ABZ were not agglomerated that much (Figure 1B).

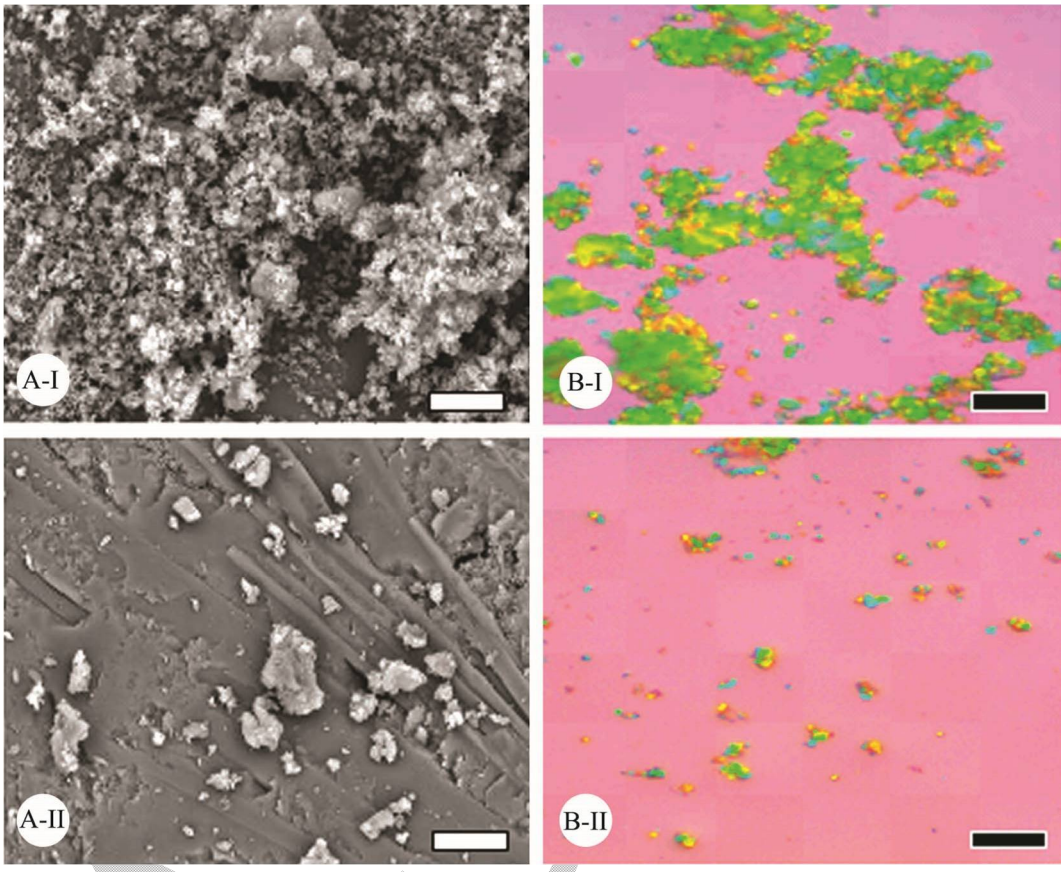

Figure 1. Microscopic images observed by scanning electron microscope (A) and polarized light microscope (B). (I) Crystalline ABZ and (II) SD-ABZ. Each black and white bar represents 50 μm and 100 μm, respectively.

XRPD pattern study. In the XRPD analysis, crystalline ABZ showed a series of sharp peaks with high intensity. It is due to the long periodicity and regular distribution of molecules across dimension, which caused the characteristic high intensity narrow peaks at 2θ angles from 10° to 35° (Figure 2A). Amorphous materials do not have the long range in order, they rather have molecules randomly distributed across dimension, which results in x-rays being scattered in many directions leading to a large peaks or "halo" distributed in wide angle.[45] The XRPD patterns of SD-ABZ demonstrated diffraction peaks as ABZ with significantly reduced intensity. This is indicative of reduction of crystallinity in SD-ABZ formulation. However, it is notable that the intensity of crystalline peaks of SD-ABZ was significantly less than that of crystalline ABZ. This observation suggests that the SD had lower crystallinity compared to crystalline ABZ. This can be explained by the high drug-loading of ABZ in the SD system. Since the formulation has a high drug-loading, even though a portion of the drug was distributed in amorphous state, some portions of ABZ retained its crystallinity with reduced intensity.

DSC study. In the DSC thermal analysis of crystalline ABZ, two sharp endothermic peaks

around 220°C and 230°C corresponds to the melting point of ABZ (Figure 2B). From the thermograms of SD-ABZ, the characteristic melting endothermic peak for ABZ is absent. The near absence of the peak is indicative that ABZ was dissolved in the polymers.[46] An endothermic peak at 158°C can be observed, which can correspond to the melting point of Ludiflash®. Ludiflash® is a co-processed polymer with 90-95% of mannitol, and mannitol has a melting point around 164-169°C.[47] The other polymeric carrier Soluplus® is amorphous and does not have a melting endothermic peak.[48] However, in between the temperature of 175-190°C, we can observe a broad endothermic peak (Figure 2B). In this temperature region, ABZ could have undergone melting with Soluplus® and Ludiflash® during the DSC scans of the SD-ABZ that suggests the amorphization during preparation could result in improved dissolution.[49]

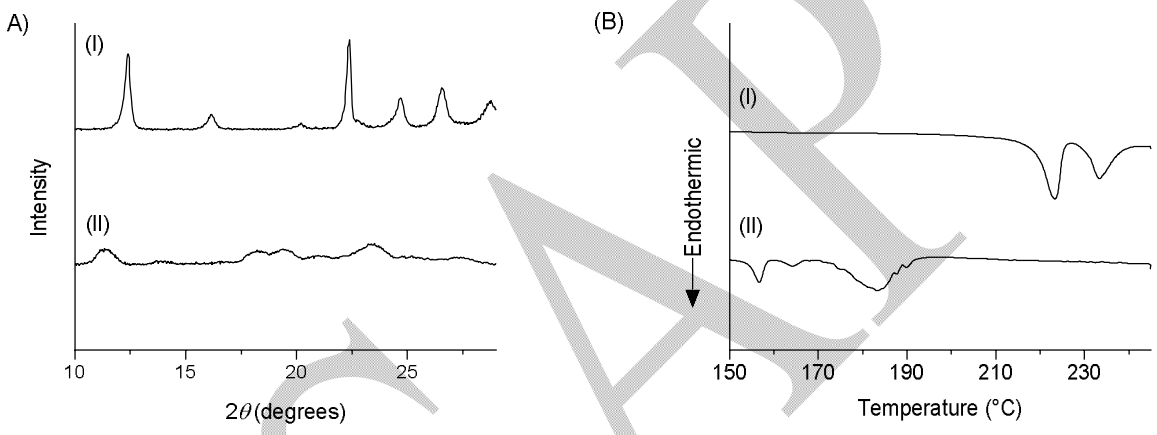

Figure 2. Crystallinity analysis of ABZ samples using (A) XRPD and (B) DSC. (I) Crystalline ABZ and (II) SD-ABZ.

DLS study. In the SD systems, particle size has a strong impact on drug dissolution and on drug absorption. DLS study for the SD-ABZ revealed that the prepared high drug-loaded SD has a particle size in the range of 40-1000 nm (Figure 3). However, a maximum number of particles are in the size range between 100-1000 nm with a mean diameter of 389 nm. The particle sizes are relatively smaller with higher disjoining pressure and increased surface area, which increases the interfacial solubility of the formulation compared to crystalline ABZ according to Noyes Whitney equation.[50] The polydispersity index was 0.51. Polydispersity value larger than 0.7 corresponds to broad size distribution of particles.[51] Considering the formulation had high drug-loading, 0.51 polydispersity index value shows promising reduction in particle size. The DLS study also revealed the zeta potential value of -24.6 mV. Zeta potential can reveal the charge on the particle surface and the physical stability of the solid dispersion.[52] Since dissolution and absorption are closely related, the impact in this regard is that the solubility increases with decreasing particle size. Therefore, we believe that this SD-ABZ might be beneficial in improving the dissolution behavior of ABZ due to generation of small particle in dispersed phase when introduced in aqueous media.

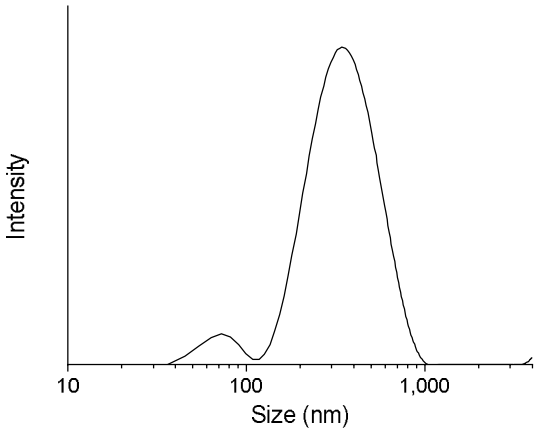

Figure 3. Particle size distribution of SD-ABZ sample.

Dissolution behavior. The optimized SD-ABZ was further studied for dissolution profile. The dissolution rate of F2 was examined by plotting the percentage of drug released versus time in comparison with that of the crystalline ABZ (Figure 4). At initial, up to the 15 min mark, the SD-ABZ showed an average of 4.69% of drug release and the average value of the drug release reached to 5.01% at 30 minutes. This is indicative of an initial quick release compared with that of the crystalline ABZ.

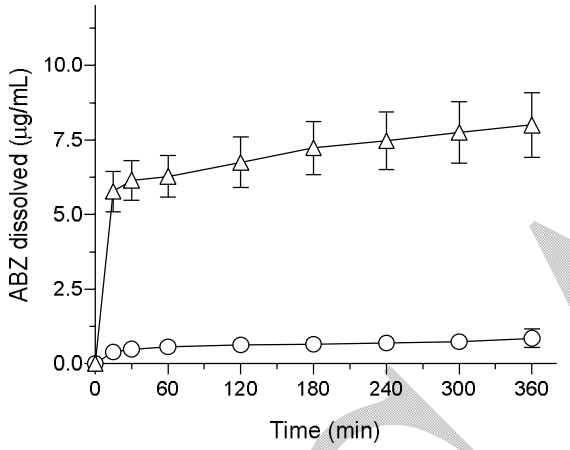

Figure 4. Dissolution tests of ABZ samples in phosphate buffer media (0.05 M, pH 6.8). ○, crystalline ABZ; and △, SD-ABZ. Data represent the mean ± SD of 6 experiments.

The average value of the drug release reached to 6.07% at the last time point of 360 min. The results showed a quick onset of release followed by a prolonged release of drug over time, which can be attributed to characteristics of high drug-loaded SD.[53] Dissolution profile of crystalline ABZ was also performed to compare the results of the sample. The initial release of crystalline ABZ was 0.32% at 15 min, which enhanced to only 0.39% at the 30 min mark. At the final time point of 360 min, the average value of the drug release was 0.57%. Comparing the initial release profiles, it was found that the SD-ABZ showed about 15-fold and 13-fold higher initial dissolution rate at 15 min and 30 min, respectively, compared to crystalline ABZ. However, at 360 min, the sample showed 10.6-fold enhanced dissolution rate compared to the crystalline ABZ. The crystalline nature of ABZ is the reason behind its poor solubility in the aqueous media and shows very poor dissolution rate. On the other hand, the high drug-loaded SD-ABZ showed comparatively higher dissolution rate than that of the crystalline ABZ. This was supposedly due to the effect of molecular dispersion of ABZ in the two polymers, Soluplus® and Ludiflash®, and due to the reduction of crystallinity of ABZ in the SD-ABZ during preparation. These results are supported by the previously performed physicochemical characterization of the SD-ABZ. Additionally, in another study Ludiflash® has been used to increase the dissolution rate of a similar drug, mebendazole in simulated gastric fluid[54], and Soluplus® has been used to prepare a hot-melt extrudate solid dispersion of artemether with improved solubility and dissolution rate in aqueous media.[55] These data represent the increase in dissolution behavior of SD-ABZ compared to crystalline ABZ. However, while comparing the dissolution profile of the high drug-loaded SD-ABZ with the existing findings, it can be seen that the results were notable but not up to the expected marks. A fusion method preparation of ABZ solid dispersion with Poloxamer 407 showed 3 to 20 times increase in dissolution rate in 0.1N HCl media compared to physical mixtures, ABZ, and commercial formulation.[56] Another study revealed that a co-spray dried ABZ formulation with sugars, polyols, ionic and non-ionic surfactants showed 3 to 25 times increase in ABZ dissolution rate in 0.1N HCl compared to ABZ.[57] A novel hot melt extrusion of ABZ and PVP K12 showed high dissolution improvement up to 70% drug release, however the method only applied 1/99 and 1/9 (w/w) drug to polymer ratio for the preparation.[58]

The surface morphology and crystallinity study showed that there was reduction in crystallinity of ABZ in the formulation, however presence of ABZ crystals were still observed. Possibly this phenomenon might took place due to presence of ABZ crystals in high drug loaded SD-ABZ.[59] An optimum polymer ratio corresponding to a significant enhancement of the solubility of the SD-ABZ was established in this study. Most importantly, the novelty of this study is that the high drug loaded ternary solid dispersion of ABZ shows improved

solubility and dissolution behavior which has been clearly shown in the above discussed equilibrium solubility as well as dissolution studies of the proposed formulation, though not highly significant.

CONCLUSION

Major obstacles to therapeutic efficacy of ABZ are its poor biopharmaceutical properties and poor patient compliance due to its large single dose. To overcome such problems, a high drug-loaded solid dispersion of ABZ was formulated, optimized and assessed in this study. Although, crystallinity in the formulation persisted; overall results showed improvement in dissolution rate and solubility compared to crystalline ABZ. For each repetition of experiments, Formulation 2 with 37.5: 12.5: 50 Soluplus®: Ludiflash®: ABZ ratio (%) showed the best results. Considering the drug-polymer ratio optimization it should be noted that, higher portion of Soluplus® in the polymer ratio showed higher solubility in repeated experiments. Thus, high drug-loaded SD-ABZ still promises to be viable strategy to improve dissolution behavior of ABZ, possibly with further optimization of the polymer ratios and the formulation.

ABBREVIATIONS

ABZ, albendazole; BA, bioavailability; BCS, biopharmaceutics classification system; DLS, dynamic light scattering; DSC, differential scanning calorimetry; ODT, orodispersible Tablet; PLM, polarized light microscopy; SD, solid dispersion; SEM, scanning electron microscopy; UV, ultraviolet; WHO, World Health Organization; XRPD, X-ray powder diffraction

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Delmoral-sanchez, J. M., Gonzalez-alvarez, I., Gonzalez-alvarez, M., Navarro, A., and Bermejo, M. 2019. Classification of WHO essential oral medicines for children applying a provisional pediatric biopharmaceutics classification system. *Pharmaceutics* **11**, 1-16.
2. Simonazzi, A., Cid, A. G., Paredes, A. J., et al. 2018. Development and in vitro evaluation of solid dispersions as strategy to improve albendazole biopharmaceutical behavior. *Ther. Deliv.* **9**, 623-38.
3. Perrut, M., Jung, J., and Leboeuf, F. 2005. Enhancement of dissolution rate of poorly-soluble active ingredients by supercritical fluid processes: Part I: Micronization of neat particles. *Int. J. Pharm.* **288**, 3-10.
4. Chu, K., and Yalkowsky, S. 2010. Predicting aqueous solubility: the role of crystallinity. *Curr. Drug Metab.* **10**, 1184-91.
5. Murdande, S. B., Pikal, M. J., Shanker, R. M., and Bogner, R. H. 2011. Aqueous solubility of crystalline and amorphous drugs: Challenges in measurement. *Pharm. Dev. Technol.* **16**, 187-200.
6. Zhang, G. G. Z., Law, D., Schmitt, E. A., and Qiu, Y. 2004. Phase transformation considerations during process development and manufacture of solid oral dosage forms. *Adv. Drug Deliv. Rev.* **56**, 371-390.
7. Bikiaris, D. N. 2011. Solid dispersions, Part I: recent evolutions and future opportunities in manufacturing methods for dissolution rate enhancement of poorly water-soluble drugs. *Expert Opin. Drug Deliv.* **8**, 1501-1519.
8. Sethia, S., and Squillante, E. 2004. Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. *Int. J. Pharm.* **272**, 1-10.
9. Owusu-Ababio, G., Ebube, N. K., Reams, R., and Habib, M. 1998. Comparative dissolution studies for mefenamic acid-Polyethylene glycol solid dispersion systems and tablets. *Pharm. Dev. Technol.* **3**, 405-412.
10. Sawatdee, S., Atipairin, A., Sae Yoon, A., Srichana, T., Changsan, N., and Suwandecha, T. 2019. Formulation Development of Albendazole-Loaded Self-Microemulsifying Chewable Tablets to Enhance Dissolution and Bioavailability. *Pharmaceutics* **11**, 134.
11. Prashant, R., Rakesh, M., Tanaji, N., and Sushilkumar, P. 2016. Solubility and dissolution enhancement of albendazole by spherical crystallization. *Asian J. Biomed. Pharm. Sci.* **6**, 09-014.
12. Palanichamy, S., Anusha, V., Solairaj, P., Parasakthi, N., Rajadhas, G., and ThangaThirupathi, A. 2011. Formulation and evaluation of albendazole fast dissolving tablets. *Res. J. Pharm. Technol.* **4**, 1717-1720.
13. Mudie, D. M., Buchanan, S., Stewart, A. M., et al. 2020. A novel architecture for achieving high drug loading in amorphous spray dried dispersion tablets. *Int. J. Pharm. X.* **2**, 100042.

14. Schittny, A., Huwyler, J., and Puchkov, M. 2020. Mechanisms of increased bioavailability through amorphous solid dispersions: a review. *Drug Deliv*.**27**, 110-127.
15. Chin, S., Petkovic, M., Zuniga, R., Santarra, B., Conklin, B., Hou, H.H., Nagapudi, K., Gruenhagen, J.A., Yehl, P., and Chen, T. 2021. Impact of polymer type, ASD loading and polymer-drug ratio on ASD tablet disintegration and drug release. *Int. J. Pharm*. **592**, 120087.
16. Abulaihaiti, M., Wu, X.W., Qiao, L., Lv, H.L., Zhang, H.W., Aduwayi, N., Wang, Y.J., Wang, X.C., and Peng, X.Y. 2015. Efficacy of albendazole-chitosan microsphere-based treatment for alveolar echinococcosis in mice. *PLoS Negl. Trop. Dis*. **9**, 1-16.
17. Mingjie, W., Shuhua, X., Junjie, C., et al. 2002. Albendazole-soybean oil emulsion for the treatment of human cystic echinococcosis: evaluation of bioavailability and bioequivalence. *Acta Trop*. **83**, 177-181.
18. Priotti, J., Codina, A. V., Leonardi, D., Vasconi, M. D., Hinrichsen, L. I., and Lamas, M. C. 2017. Albendazole microcrystal formulations based on chitosan and cellulose derivatives: physicochemical characterization and in vitro parasiticidal activity in trichinella spiralis adult worms. *AAPS PharmSciTech* **18**, 947-956.
19. Castro, S. G., Sanchez Bruni, S. F., Urbizu, L. P., et al. 2013. Enhanced dissolution and systemic availability of albendazole formulated as solid dispersions. *Pharm. Dev. Technol*. **18**, 434-442.
20. Wen, H., New, R. R. C., Muhmut, M., et al. 1996. Pharmacology and efficacy of liposome-entrapped albendazole in experimental secondary alveolar echinococcosis and effect of co- administration with cimetidine. *Parasitology* **113**, 111-121.
21. Palomares-Alonso, F., González, C.R., Bernad-Bernad, M.J., Montiel, M.D.C., Hernández, G.P., González-Hernández, I., Castro-Torres, N., Estrada, E.P., and Jung-Cook, H. 2010. Two novel ternary albendazole-cyclodextrin-polymer systems: dissolution, bioavailability and efficacy against Taenia crassiceps cysts. *Acta Trop*. **113**, 56-60.
22. Vogt, M., Kunath, K., and Dressman, J. B. 2008. Dissolution improvement of four poorly water soluble drugs by cogrinding with commonly used excipients. *Eur. J. Pharm. Biopharm*. **68**, 330-337.
23. Alanazi, F. K., El-Badry, M., Ahmed, M. O., and Alsarra, I. A. 2007. Improvement of albendazole dissolution by preparing microparticles using spray-drying technique. *Sci. Pharm*. **75**, 63-79.
24. Paredes, A. J., Bruni, S. S., Allemandi, D., Lanusse, C., and Palma, S. D. 2018. Albendazole nanocrystals with improved pharmacokinetic performance in mice. *Ther. Deliv*. **9**, 89-97.
25. Craig, D. Q. M. 2002. The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int. J. Pharm*. **231**, 131-144.
26. Karagianni, A., Kachrimanis, K., and Nikolakakis, I. 2018. Co-amorphous solid dispersions for solubility and absorption improvement of drugs: Composition, preparation, characterization and formulations for oral delivery. *Pharmaceutics* **10**, 1–26.
27. Hancock, B. C., and Parks, M. 2000. What is the true solubility advantage for amorphous pharmaceuticals? *Pharm. Res*. **17**, 397-404.
28. Mura, P., Faucci, M. T., Manderioli, A., Bramanti, G., and Parrini, P. 1999. Thermal behavior and dissolution properties of naproxen from binary and ternary solid dispersions. *Drug Dev. Ind. Pharm*. **25**, 257-264.
29. Zhang, X., Xing, H., Zhao, Y., and Ma, Z. 2018. Pharmaceutical dispersion techniques for dissolution and bioavailability enhancement of poorly water-soluble drugs. *Pharmaceutics* **10**, 1-33.
30. Jacob, B., Bisht, L.K., and Chandy, V. 2018. Ludiflash- A novel excipient for patient friendly dosage form Ludiflash. *Res. Rev. J. Phar*. **7**, 3–6.
31. Modi, A., and Tayade, P. 2006. Enhancement of dissolution profile by solid dispersion (kneading) technique. *AAPS PharmSciTech* **7**, 1-6.
32. Azad, A.K., Jahan, K., Sathi, T., Sultana, R., Abbas, S., and Uddin, A. 2018. Improvement of dissolution properties of albendazole from different methods of solid dispersion. *J. Drug Deliv. Ther*. **8**, 475-480.
33. Sarfraz, R.M., Bashir, S., Mahmood, A., Ahsan, H., Riaz, H., Raza, H., Rashid, Z., Raza, S. A., Abrar, M.A., Abbas, K., and Yasmeen, T. 2017. Application of various polymers and polymers based techniques used to improve solubility of poorly water soluble drugs: a review. *Acta Pol. Pharm.Drug Res*. **74**, 347-356.
34. Ahmed, D. A., Abdel-Aziz, O., Abdel-Ghany, M., and Weshahy, S. A. 2018. Stability indicating determination of Albendazole in bulk drug and pharmaceutical dosage form by chromatographic and spectrophotometric methods. *Futur. J. Pharm. Sci*. **4**, 161-166.
35. Fülöp, V., Jakab, G., Tóth, B., Balogh, E., and Antal, I. 2020. Study on optimization of wet milling process for the development of albendazole containing nanosuspension with improved dissolution. *Period. Polytech. Chem. Eng*. **64**, 401-420.
36. Wang, S., Gu, Z., Wang, Z., Chen, X., Cao, L., Cai, L., Li, Q., Wei, J., Shin, J.W., and Su, J. 2018. Influences of mesoporous magnesium calcium silicate on mineralization, degradability, cell responses, curcumin release from macro-mesoporous scaffolds of gliadin based biocomposites. *Sci. Rep*. **8**, 1-12.
37. Li, C., and Zhu, Y. 2015. Quantitative polarized light microscopy using spectral multiplexing interferometry. *Opt. Lett*. **40**, 2622-2625.
38. Hu, C., Liu, Z., Liu, C., Zhang, Y., Fan, H., and Qian, F. 2020. Improvement of antialveolar echinococcosis efficacy of albendazole by a novel nanocrystalline formulation with enhanced oral bioavailability. *ACS Infect. Dis*. **6**, 802-810.

39. Huang, Y., and Dai, W.-G. 2014. Fundamental aspects of solid dispersion technology for poorly soluble drugs. *Acta Pharm. Sin. B* **4**, 18-25.
40. Hengsawas Surasarang, S., Keen, J. M., Huang, S., Zhang, F., McGinity, J. W., and Williams, R. O. 2017. Hot melt extrusion versus spray drying: hot melt extrusion degrades albendazole. *Drug Dev. Ind. Pharm.* **43**, 797-811.
41. Okonogi, S., and Puttipipatkhachorn, S. 2006. Dissolution improvement of high drug-loaded solid dispersion. *AAPS PharmSciTech* **7**, 148-153.
42. Fujimori, M., Kadota, K., and Tozuka, Y. 2017. Mixed micelle system produced by interaction between transglycosylated stevia and an ionic surfactant improves dissolution profile of mefenamic acid. *J. Pharm. Sci.* **106**, 1117-1723.
43. Bernabeu, E., Gonzalez, L., Cagel, M., Gergic, E. P., Moretton, M. A., and Chiappetta, D. A. 2016. Novel Soluplus®-TPGS mixed micelles for encapsulation of paclitaxel with enhanced in vitro cytotoxicity on breast and ovarian cancer cell lines. *Colloids Surfaces B Biointerfaces* **140**, 403-411.
44. Ul-Hamid, A. 2018. *A Beginners' Guide to Scanning Electron Microscopy*. *A Beginners' Guid. to Scanning Electron Microsc.* Springer, Newyork, p. 334.
45. Murthy, N.S., and Minor, H. 1990. General procedure for evaluating amorphous scattering and crystallinity from X-ray diffraction scans of semicrystalline polymers. *Polymer* **31**, 996-1002.
46. Kalaiselvan, R., Mohanta, G. P., Manna, P. K., and Manavalan, R. 2006. Studies on mechanism of enhanced dissolution of albendazole solid dispersions with crystalline carriers. *Indian J. Pharm. Sci.* **68**, 599-607.
47. Rowe, R.C., Sheskey, P.J., Cook, W.G., and Quinn, M. E. 2012. *Handbook of Pharmaceutical Excipients- 7th Edition*. The Pharmaceutical Press, London (UK), pp. 479-482.
48. Zhang, Y., Liu, Y., Luo, Y., Yao, Q., Zhong, Y., Tian, B., and Tang, X. 2016. Extruded Soluplus/SIM as an oral delivery system: characterization, interactions, in vitro and in vivo evaluations. *Drug Deliv.* **23**, 1902-1911.
49. Paredes, Alejandro Javier, Litterio, N., Dib, A., Allemandi, D.A., Lanusse, C., Bruni, S.S., and Palma, S.D. 2018, A nanocrystal-based formulation improves the pharmacokinetic performance and therapeutic response of albendazole in dogs. *J. Pharm. Pharmacol.* **70**, 51-58.
50. Sun, J., Wang, F., Sui, Y., She, Z., Zhai, W., Wang, C., and Deng, Y. 2012, Effect of particle size on solubility, dissolution rate, and oral bioavailability: Evaluation using coenzyme Q10 as naked nanocrystals. *Int. J. Nanomedicine* **7**, 5733-5744.
51. Mourdikoudis, S., Pallares, R.M., and Thanh, N.T.K. 2018. Characterization techniques for nanoparticles: comparison and complementarity upon studying nanoparticle properties. *Nanoscale* **10**, 12871-12934.
52. Jambhekar, S. S., and Breen, P. J. 2013. Drug dissolution: Significance of physicochemical properties and physiological conditions. *Drug Discov. Today* **18**, 1173-1184.
53. Tres, F., Posada, M. M., Hall, S. D., Mohutsky, M. A., and Taylor, L. S. 2018. Mechanistic understanding of the phase behavior of supersaturated solutions of poorly water-soluble drugs. *Int. J. Pharm.* **543**, 29-37.
54. Sandulovici, R., Mircioiu, C., Voicu, V., Ghafil, F., Mati, E., Anuta, V., Sarbu, I., and Mircioiu, I. 2020. Modelling of release kinetics of mebendazole from solid dispersion based formulations in simulted gastric fluid. *Rom. Biotechnol. Lett.* **25**, 1473-1481.
55. Fule, R.A., Meer, T.S., Sav, A.R., and Amin, P.D. 2013. Artemether-soluplus hot-melt extrudate solid dispersion systems for solubility and dissolution rate enhancement with amorphous state characteristics. *J. Pharm.* **2013**, 1-15.
56. Campos, S. N., Cid, A. G., Romero, A. I., Villegas, M., Briones, N., Cintia, A., Gonzo, E.E., and Bermudez, J.M. 2021. Solid dispersions as a technological strategy to improve the bio-performance of antiparasitic drugs with limited solubility. *Proceedings* **78**, 1-8.
57. Ghanbarzadeh, S., Khalili, A., Jouyban, A., Emami, S., Javadzadeh, Y., Solhi, M., and Hamishehkar, H. 2016. Dramatic improvement in dissolution rate of albendazole by a simple, one-step, industrially scalable technique. *Res. Pharm. Sci.* **11**, 435-444.
58. Martinez-Marcos, L., Lamprou, D.A., McBurney, R.T., and Halbert, G.W. 2016. A novel hot-melt extrusion formulation of albendazole for increasing dissolution properties. *Int. J. Pharm.* **499**, 175-185.
59. Leuner, C., and Dressman, J. 2000. Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Biopharm.* **50**, 47-60.