Unexpected Performance of Physical Mixtures over Solid Dispersions on the Dissolution Behavior of Benznidazole from Tablets

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ABSTRACT: This work investigated the feasibility of developing benznidazole (BZL) tablets, allowing fast, reproducible, and complete drug dissolution, by compressing BZL-Polyethylene Glycol (PEG) 6000 physical mixtures (PMs) and solid dispersions (SDs). SDs were prepared by the solvent evaporation method at different drug:polymer ratios (w/w). BZL-PEG 6000 formulations were characterized by X-ray diffraction (XRD), scanning electron microscopy, and dissolution studies. The preparation of SD-based BZL tablets by the wet granulation method was carried out and the influence of pregelatinized starch (PS) and starch (S) on the disintegration time and drug dissolution rate was analyzed. SDs showed a significant improvement in the release profile of BZL as compared with the pure drug. As demonstrated by XRD, the crystalline character of BZL remained almost unaltered in both PMs and SDs. BZL release from the PEG 6000 tablets increased by the presence of PS instead S. Unexpectedly, the BZL release from tablets containing PMs was almost equal as compared with the BZL release from tablets containing SDs. In conclusion, the results suggest that PEG 6000 and PS are suitable additives for the development of BZL tablets with enhanced dissolution behavior through the preparation of ordinary PMs, instead the laborious SDs. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:1016–1023, 2013

Keywords: solid dispersions; dissolution; excipients; formulation; tablet

INTRODUCTION

Chagas disease is an endemic parasitic disease caused by *Trypanosoma cruzi* and discovered in 1909.[1] In the last years, the transmission of this infection has been successfully controlled through different programs and actions made by the governments. Furthermore, the control of congenital transmission as well as etiologic diagnosis and treatment for the young population has substantially reduced new cases of Chagas disease.[2] Despite it, in Latin America, there are still nearly 10 million people living with this neglected parasitic infection and nearly 100 million people exposed to the risk of infection.[3] Following urban migration from endemic countries, Chagas disease has become a serious health issue in nonendemic regions, such as North America, and countries of the European Community.[4] Even though the disease was discovered more than 100 years ago, there is still a lack of suitable formulations for the treatment of Chagas disease, as mentioned by the World Health Organization (WHO).[5] Benznidazole (BZL) is the primary drug of choice in the treatment of Chagas´ disease. According to the Biopharmaceutics Classification System, BZL belongs to Class III.[6] Recently, it was reclassified as Class I drug according to the Biopharmaceutics Drug Disposition Classification System.[7] On the contrary, the data provided by Maximiano et al.[8] revealed that BZL exhibited an aqueous solubility of 0.237 mg/mL, being classified as very poor soluble in water (Class IV). As a consequence of it, a limited and/or variable absorption might be expected. Although BZL is widely prescribed to treat Chagas´ disease, the problem of its solubility is still an important challenge for the formulation scientists. One of the most widely applied strategies to increase the solubility/dissolution of poorly water-soluble drugs are

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the solid dispersions (SDs).[9,10] In particular, BZL SDs were recently prepared using Polyvinylpirrolidone (PVP) or PEG as carriers. The results showed a significant increase of the drug dissolution profile. However, no attempts were made to develop any final dosage forms from the corresponding SDs.[11] Although SDs have been succesfully applied over the last 40 years, there are still serious concerns related with further development of commercial products containing such SDs, related, particularly, with the production of soft and tacky powders with poor flow properties and compressibility.[12,13] Having on mind, the recommendation of WHO to treat the infected population with BZL, the aim of the present study was, therefore, to evaluate whether PEG 6000-based SDs would be a convenient strategy to formulate BZL tablets with enhanced dissolution rate. SDs were prepared by the solvent evaporation method at different drug:polymer ratios (w/w). For comparison with SDs, physical mixtures (PMs) were also prepared. The solid-state properties of these binary systems were studied by X-ray diffractometry (XRD) and scanning electronic microscopy (SEM). The influence of cornstarch (S) and corn-pregelatinized starch (PS) on disintegration times and drug dissolution rate was further evaluated. To our knowledge, the design and the characterization of BZL-PEG 6000 tablets with improved dissolution rate have not been elucidated to date.

MATERIALS AND METHODS

Materials

Benznidazole was a gift from Produtos Roche Químicos e Farmacêuticos S.A. (Jaguare, Sao Paulo, Brazil), PEG 6000 was purchased from Aldrich Chemical Company (Milwaukee, WI), lactose was purchased from Foremost Whey Products, Div. Wisconsin Dairies (Baraboo, WI). Both S and PS were a gift from Colorcon (West Point, PA). All materials used in this study were of analytical grade.

Methods

Preparation of Physical Mixtures

Physical mixtures of BZL-PEG 6000 at 1:1 and 1:5 (w/w), denoted as $PM_{1:1}$ and $PM_{1:5}$, respectively, were prepared by thoroughly mixing the components in a mortar until a homogeneous mixture was obtained. The resulting residue was dried under vacuum for 2 h and stored overnight in a desiccator. After drying, the residue was ground in a mortar and then passed through a 40-mesh metal screen. The resultant powders were stored in a desiccator until further investigation.

Preparation of Solid Dispersions

Solid dispersions of BZL-PEG 6000 at 1:1 and 1:5 (w/w) were prepared by the solvent method and denoted as $SD_{1:1}$ and $SD_{1:5}$, respectively. BZL was dissolved in ethanol, and PEG 6000 was dissolved in water. The solutions were mixed under magnetic stirring (300 rpm) for 45 min. The solvent was then removed by vacuum rotary evaporator (150 rpm) under reduced pressure (15 mbar) at 40°C. The resulting residue was dried under vacuum (15 mbar) for 2 h and stored overnight in a desiccator. After drying, the residue was ground in a mortar and then passed through a 40-mesh metal screen. The resultant powders were stored in a desiccator until further investigation.

Scanning Electron Microscopy

The images of the samples were analyzed by SEM (AMR 1000 Scanning Microscope, Oberkochen, Baden-Württemberg, Germany). Samples were mounted on a double-faced adhesive tape, sputtered with gold prior to analysis. The pictures were taken at an excitation voltage of 20 Kv.

X-Ray Diffraction

Data collection was carried out in transmission mode on an automated STOE STADIP X-Ray Powder Diffractometer (Darmstadt, Hesse, Germany). Samples were enclosed between two polyacetate films held together by double-sided adhesive tape. Data acquisition and evaluation were performed with the Stoe Visual-Xpow package, Version 2.75 (Germany). The scans were performed between 2° and 6° (2θ) with a scanning speed of 2° θ/min.

Preparation of Tablets

BZL-PEG 6000 SDs equivalent to 100 mg of BZL, lactose, and S, or PS (intragranular) were manually blended in a mortar for 10 min. Thereafter, the powders were granulated with 10% (w/v) PVP ethanolic solution using a mortar and pestle, passed through a 12-mesh metal screen and the granules were dried in a hot air oven at 40°C for 4 h. Finally, magnesium stearate and S or PS (extragranular) were added and the granules were passed through a 14-mesh metal screen. For comparison, a physical mixing of BZL (100 mg), PEG 6000 lactose, and S or PS (intragranular) was manually blended in a mortar for 10 min. Then, the powder mixture was granulated and formulated with magnesium stearate, S or PS (extragranular) in the same conditions than the corresponding SDs. In both cases, tablets of approximately 300 mg weight each were obtained by a single punch-tableting machine Erweka (Heusenstamm, Hesse, Germany) equipped with a 9 mm flat round punches, at a compression force of 14 kN. The composition

Table 1. Composition of BZL 100 mg Tablets

Component (mg)	T1	T2	T3	T4
BZL	100	100	100	100
PEG 6000	100	100	100	100
S	33		33	–
PS		33	–	33
Lactose	62	62	62	62
PVP/EtOH 10%	0.6	0.6	0.6	0.6
Magnesium stearate	5	5	5	5

of PMs (T1 and T2) and SDs-based tablets (T3 and T4) of BZL is presented in Table 1.

Flow Properties of Granulates

Flow properties were measured by the angle of repose ϕ, pouring the granules through a glass funnel onto a flat surface. Each granulate was placed in a 100-mL funnel with an orifice of 6 mm and the powder was allowed to flow under the force of gravity. The amount of powder used was 50 g and the height of the funnel was 10 cm.

Characterization of Tablets

The weight variation, hardness, friability, disintegration, average weight, and content uniformity tests were carried according to USP30.[14]

Drug Content

Quantification of the BNZ was measured using UV spectrophotometry in accordance with the methodology developed and validated by Soares Sobrino et al.[15] The equipment used was an UV/vis spectrophotometer (Ultrospec II, LKB-UV, Cambridge, England) at a wavelength of 324 nm. Ten randomly selected tablets were crushed, and an amount equivalent to 100 mg of drug was weighed, extracted with methanol, and filtered through a 0.45-μm membrane. This test was carried out in triplicate.

Weight Variation

The weights of twenty randomly selected tablets were determined individually. The mean weight variation was calculated.

Hardness

The hardness of ten randomly selected tablets was determined using an ERWEKA TBT 28 apparatus (Heusenstamm, Hesse, Germany). The mean hardness variation was calculated.

Friability

Friability of the tablet samples was measured using the Roche friabilator, which complies with USP testing standards. Forty tablets of each sample were weighed, placed into the friabilator, and rotated for 4 min at a speed of 25 rpm. The tablets were removed from the equipment, brushed gently to remove any loose dust from their surface, and again collectively weighed. Friability of the tablets was calculated as a percentage according to the following equation:

$$\text{Friability}(\%) = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Thickness and Diameter

Thickness and diameter were determined using a Vernier Calipter (Mitutoyo, Hiroshima, Japan). Ten tablets of each formulation, randomly selected, were analyzed.

Disintegration Time

Disintegration time of six randomly selected tablets was determined with an apparatus (UC-21 Disintegration Test System, Hanson Research, Chatsworth, CA) according to USP testing standards employing degassed distilled water at 37°C as disintegration media.

Dissolution Studies

Dissolution studies of BZL from PMs, SDs, and corresponding tablets were performed in 900 mL HCl 0.1 N at 37°C, using a USP XXIV apparatus (SR8 8-Flask Bath, Hanson Research, Chatsworth, CA) with paddle rotating at 50 rpm. Samples of pure BZL, PMs, and SDs equivalent to 100 mg of the drug were dispersed on the surface of the dissolution medium while tablets containing 100 mg of BZL were introduced in the flask and the time 0 was recorded. At different time intervals, 5 mL samples were withdrawn through a filter. The amount of released BZL was determined by UV analysis, as described in "*Drug Content*." The results presented are mean values of three determinations. Preliminary tests demonstrated that there was no change in the λ_{max} of BZL due to the presence of PEG 6000 dissolved in the dissolution medium.

Batch Reproducibility

Three batches of each formulation were prepared and their release characteristics were evaluated under the same conditions as prescribed in "*Drug Content*." In vitro release data pertaining to reproducibility studies were compared by f_2 metric (similarity factor) values.[16] The statistical analysis of the drug release profiles was carried out by one-way analysis of variance (ANOVA) at three levels (Statgraphics Plus 5.1 software, Statpoint Technologies, Warrenton, VA).[17]

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RESULTS AND DISCUSSION

Solid-State Characterization of BZL–PEG 6000 Systems

Scanning Electronic Microscopy

Figure 1 shows SEM micrographs of BZL, PEG 6000, $PM_{1:1}$, $PM_{1:5}$, $SD_{1:1}$, and $SD_{1:5}$. BZL (a) appeared as a mixture of irregular and acicular crystals, while PEG 6000 (b) existed in a crystalline mixture of smooth-surfaced particles (100–300 μm) with few smaller particles (20–40 μm). Both $PM_{1:1}$ (c) and $PM_{1:5}$ (e) exhibited particles of irregular shape, which were similar to PEG 6000 particles. By contrast, $SD_{1:1}$ (d) and $SD_{1:5}$ (f) consisted of more spherical particles of rather irregular surface. From these micrographs, it was appreciated the homogeneity of SDs, being impossible to distinguish the presence of BZL crystals among PEG particles.[11] These novel arrangements between them might be responsible for the enhanced drug dissolution rate found, later on, for BZL-PEG 6000 SDs, in comparison with pure drug.

X-Ray Diffraction

The polymorphic transformation and/or amorphization of BZL, which may occur during preparation of the SDs, were evaluated. The powder X-ray diffraction (XRD) patterns of BZL, PEG 6000, $PM_{1:1}$, $PM_{1:5}$, $SD_{1:1}$, and $SD_{1:5}$ are shown in Figure 2. PEG 6000 revealed two distinct peaks at 19 and 23° 2θ, characteristic of its crystallinity.[18] BZL was characterized by several prominent diffraction peaks in the range of 10–35° 2θ. The diffraction patterns of BZL in all PMs and SDs were similar to those of the pure drug, indicating that the crystalline character of BZL did not essentially change, in agreement with previous data.[11] By increasing PEG 6000 content, some characteristic peaks of the drug gradually decreased, suggesting a dilution effect by the polymer at higher ratio. Also the major peaks observed for PEG 6000 in all the evaluated samples were almost superimposable. This suggested the absence of any significant interactions between BZL and this polymer.[19] In agreement with the XRD analysis, the enhanced drug dissolution, shown later on in Figure 3, would be a consequence of the increased wettability and/or solubilization of BZL by the polymer at the diffusion layer, in combination with the modification of surface and size of the resulting particles, as shown in Figure 1.

Dissolution Rate Studies of BZL–PEG 6000 Solid Dispersions

Figure 3 shows the *in vitro* dissolution profiles of BZL alone and from the corresponding $PM_{1:1}$, $PM_{1:5}$, $SD_{1:1}$, and $SD_{1:5}$. During dissolution experiments, it was noticed that the PMs and SDs powders sank immediately to the bottom of the dissolution vessel, whereas

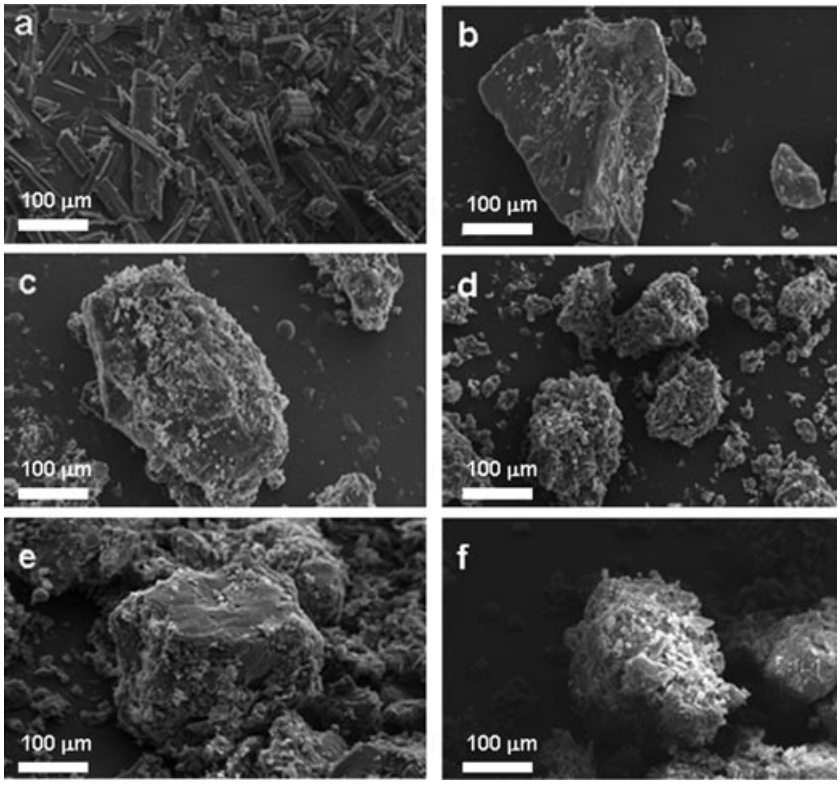

Figure 1. SEM micrographs of the pure components, PM, and SD systems, a) BZL; b) PEG 6000; c) $PM_{1:1}$; d) $SD_{1:1}$; d) $PM_{1:5}$; f) $SD_{1:5}$.

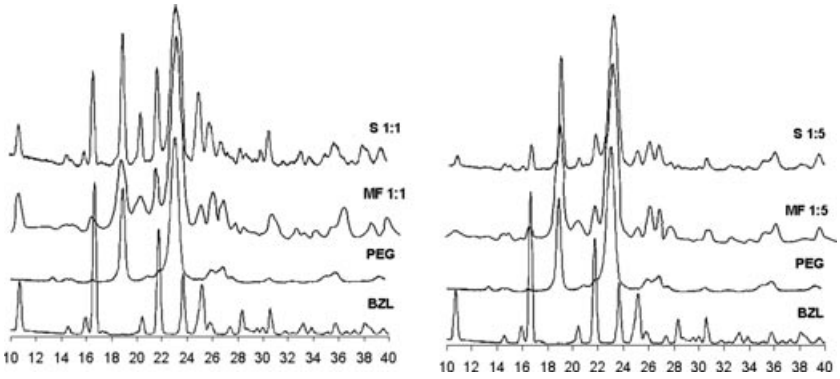

Figure 2. X-ray diffraction patterns of BZL, PEG 6000, and $PM_{1:1}$; $SD_{1:1}$; $PM_{1:5}$; and $SD_{1:5}$.

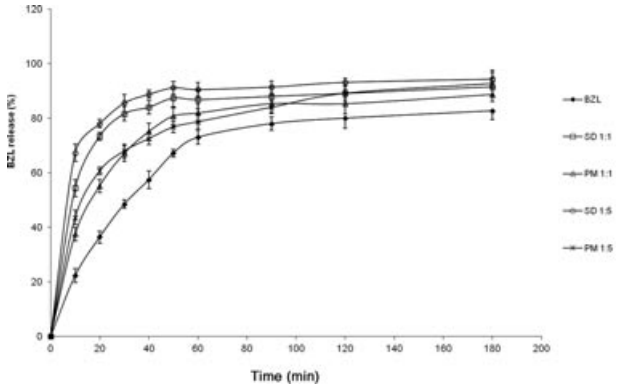

Figure 3. Dissolution profiles of BZL alone and from BZL–PEG 6000 PMs and SDs at 1:1 and 1:5 drug polymer ratio (w/w).

the pure drug floated for a long period on the surface of the dissolution medium. In all cases, PMs and SDs exhibited faster dissolution rates than the intact drug, as described by Lima et al.[11] The dissolution rate of pure drug was about 21% and 73% in 10 and 60 min, respectively. In comparison, the dissolution rate of BZL from $PM_{1:1}$ and $PM_{1:5}$ was 37% and 43% in 10 min, respectively. After 60 min, both $PM_{1:1}$ and $PM_{1:5}$ released nearly 85% of drug. Regarding the SDs samples, the dissolution rate of BZL from these SDs was higher than the corresponding PMs. Both the $SD_{1:1}$ and $SD_{1:5}$ exhibited about 80% drug dissolution within 10 min, whereas after 60 min $SD_{1:1}$ and $SD_{1:5}$ released nearly 95% of BZL. As the proportion of PEG increased, BZL dissolution rates increased. Probably, the hydrophilic properties of PEG 6000 resulted in greater wetting and increases surface available for dissolution by reducing interfacial tension between hydrophobic drug and dissolution media.[20] Because the diffraction patterns of BZL were not modified (Fig. 2), the enhanced drug dissolution rate would be caused by the modification of both the particle surface and shape (Fig. 1), and/or the wetting and solubilizing properties of PEG 6000.

Studies of BZL–PEG 6000 Tablets

Flow Properties

Although SDs represents a very attractive strategy to improve the solubility and dissolution rate of poorly water-soluble drugs, some disadvantages limit their formulation into tablets and capsules.[21] Difficulty in pulverization, poor compressibility, and poor flow of SDs are some of the challenging factors during the development of solid dosage forms. The flow of granulates containing PEG 6000 were determined by the angle of repose φ. As seen in Figure 1, BZL-PEG 6000 micrographs showed some crystals of variable shape that could lead to poor flow characteristics because of friction and cohesiveness between particles.[22] However, the blends prepared from PMs and SDs exhibited "fair" or "passable" flow because its angles of repose were between 37° and 41°, suggesting the suitability of those blends for compression. Particularly, the powders prepared with PS exhibited a minor angle of repose in comparison with those prepared with S. Similar findings were already observed in the use of other types of PS for improving flow properties during process compression.[23]

Characterization of PEG 6000 Tablets

Tablets diameter, thickness, friability, weight, and content of formulated tablets are described in Table 2. The technical characterization indicated that the tablets were acceptable in terms of uniformity of mass. Friability obtained (<0.80%) confirmed the suitability of wet granulation technology.

Disintegration Time

Tablets formulations (Table 2) fulfiled the USP pharmacopoeia requirements regarding disintegration time (<15 min). Radanil®, the commercial tablet (CT) formulated without PEG 6000 was rapidly disintegrated (1 min). On the contrary, the formulations T1 and T3, prepared with S (10%) and PEG 6000 (33%), exhibited a disintegration time of 4 and 4.5 min,

Table 2. Technological Characterization of BZL 100 mg Tablets

	T1	T2	T3	T4
Content uniformity (%)	98.9 ± 2.8	99.4 ± 1.4	100.3 ± 1.1	99.3 ± 2.3
Weight variation (%)	3.3 ± 0.2	2.9 ± 0.7	3.0 ± 0.3	3.1 ± 0.4
Friability (%)	0.71 ± 0.09	0.60 ± 0.03	0.57 ± 0.08	0.64 ± 0.07
Hardness (k_p)	4.7 ± 0.8	5.1 ± 0.2	4.9 ± 1.1	5.2 ± 0.2
Thickness (mm)	4.8 ± 1.2	4.8 ± 0.2	4.7 ± 0.9	4.8 ± 0.7
Diameter (mm)	9.0 ± 0.2	9.1 ± 0.5	9.2 ± 0.8	9.4 ± 0.5
Disintegration time (min)	4.0 ± 0.3	3.5 ± 0.9	4.5 ± 0.8	3.0 ± 0.7

respectively. This fact can be explained by the binding properties of PEG, when applied in high amounts, which is stronger than the disintegrating excipients. This finding is in agreement with previous works, which described the influence of PEG 4000 on the disintegration time of tablets.[24,25] By contrast, the formulations T2 and T4, prepared with PS (10%) and PEG 6000 (33%), were disintegrated in 3.5 and 3 min, respectively. It is postulated that the break-up of the tablets would be governed by the disintegration, but it depends on the rate at which the binder is dissolved, because the latter is distributed across the particle surface.[26] Thus, the addition of the disintegrant (S or PS) partially reduced the binding action of PEG 6000, and disintegration time of the different formulation was governed mainly by the disintegrant excipient. In particular, the tablets prepared with PS exhibited minor disintegration time as compared with those formulated with S, probably because PS present higher swelling volumes and hydration capacities than S.

Dissolution Studies of Tablets

Usually, the works dealing with SDs describe that the wettability, attributed to the water-soluble carriers, is one of the main reasons for improving the drug dissolution.[27] However, few studies are reported regarding the concomitant effect of the hydrophilic carriers and excipients, with high water absorption capacity, on the drug dissolution behavior from tablets. Therefore, $PM_{1:1}$ and $SD_{1:1}$ powders were subjected to the compression process to evaluate whether the replacement of S by PS might yield PEG 6000-based tablets with increased dissolution rates. As observed in Figure 4, the released amount of BZL from CT, formulated with lactose and S, was around 37% during the first 30 min, and almost 70% was released after 90 min. Both the $PM_{1:1}$ and $SD_{1:1}$ tablets containing S (T1 and T2) exhibited a drug dissolution rate slightly higher than the commercial tablets (CT). After 30 min, nearly 49% of the drug was released from T1 and T2, whereas nearly 75% of the drug was released in both cases after 90 min. On the contrary, a remarkable increase of dissolution rates was obtained for the tablets (T3 and T4) prepared with PS. When compared with the formulations T1 and T2, prepared with S, T3 and T4 clearly performed better

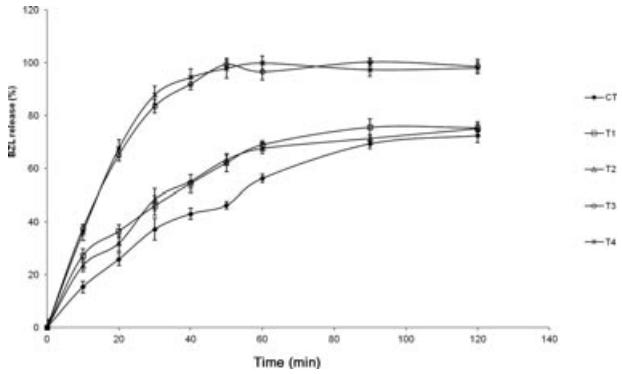

Figure 4. Dissolution profiles of BZL from BZL–PEG 6000 (1:1 ratio) PMs and SDs tablets with 10% of corn starch (S) (T1 and T2) or 10% of pregelatinized starch (PS) (T3 and T4).

and a significant enhancement in dissolution characteristics was observed. The drug dissolution rate was faster for T3 and T4 with 85% released within 30 min as compared with 49% determined for T1 and T2 formulations, whereas 100% of BZL was released after 90 min as compared to 75% determined for T1 and T2 formulations. It would be postulated that the synergy of hydrophilic characteristics of PEG 6000 and swelling and disintegrant properties of PS display a significant role in dissolution enhancement from both PMs and SDs tablets. Probably, the swelling effect of PS increased the "wetted" surface of PEG 6000 that further assist to enhance drug dissolution. As a consequence, the properties of PS would be a key factor for the dissolution behavior of BZL, from both PMs and SDs tablets, as shown in Figure 4. Furthermore, since most common carriers, such as PEGs, used on SDs are soft and sticky and, as a result, the pulverized resulting powder mixtures may not be suitable for compression, the preparation of PMs would be preferred over, the corresponding SDs, as a convenient strategy for increasing BZL dissolution behavior.

Lot Reproducibility

Three batches of each formulation (T1, T2, T3, and T4) were prepared and the dissolution rate of BZL was evaluated by UV spectrophotometry (see *Drug Content*). No significant difference was observed in the release profiles of the formulations between

Table 3. *f*2 (Similarity Factor) Values of Three Batches of BZL 100 mg Tablets

	T1	T2	T3	T4
*f*2 value Batch 1–Batch 2	97.9	97.2	97.7	96.4
*f*2 value Batch 2–Batch 3	95.4	97.6	96.2	97.1
*f*2 value Batch 1–Batch 3	97.8	95.9	95.6	97.6

different batches, as indicated by *f*2 metric (similarity factor), shown in Table 3, and by the statistical analysis (ANOVA) [T1 ($P = 0.2643$); T2 ($P = 0.2119$); T3 ($P = 0.1526$) and T4 ($P = 0.1841$)]. The batch reproducibility study indicated that the formulation methodology employed was found to be suitable for manufacturing BZL tablets.

CONCLUSIONS

SDs of BZL-PEG 6000 prepared by the solvent evaporation method resulted in greater increases in drug dissolution, in comparison with the pure drug. As demonstrated by XRD, the crystalline character of BZL remained almost unaltered in both PMs and SDs. Then, the modification of the surface morphology and shape of the particles offered an explanation of better dissolution rate from the BZL-PEG 6000 systems. Flow properties of the granules as well as disintegration analysis and technological parameters of the tablets indicated that PEG 6000 and PS are suitable excipients for the development of BZL tablets with improved dissolution rate. Unexpectedly, it was found that tablets containing PMs exhibited the same release patterns of BZL as compared with the corresponding SDs systems. As a consequence, it is concluded that BZL tablets with enhanced dissolution behavior was successfully formulated through the preparation of ordinary PMs, avoiding the disadvantages associated with the laborious SDs.

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