JPP Journal of Pharmacy and Pharmacology

JPP 2011, 63: 786–793

Received November 12, 2010
Accepted March 7, 2011
DOI
10.1111/j.2042-7158.2011.01284.x
ISSN 0022-3573

Research Paper

Development of effervescent tablets containing benznidazole complexed with cyclodextrin

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Abstract

Objectives Benznidazole (BNZ), the primary chemotherapy agent used to treat Chagas disease, has poor aqueous solubility, which results in low bioavailability. The purpose of this work was to develop stable effervescent tablets using an inclusion complex of BNZ with cyclodextrin (CD).

Method In the first phase, different CDs were evaluated according to their ability to improve the aqueous solubility of BNZ. Then, inclusion complexes of BNZ in the solid state were produced by the kneading method and the complexes were evaluated using several physical–chemical assays. Finally, effervescent tablets were prepared according to a complete 3^2 factorial design. The effects of the concentration of CD and effervescent mixture on the dissolution rate and physical stability of tablets were evaluated.

Key findings Hydroxypropyl-β-cyclodextrin produced the greatest improvement in the aqueous solubility of BNZ, almost 20-times greater than the water system. Solid systems produced with BNZ and CD showed physical–chemical interactions and increased the drug dissolution rate, suggesting the formation of a true solid inclusion complex. Moreover, the effervescent matrix of the tablets was effective in improving the dissolution behaviour of BNZ complexed with CD.

Conclusions Effervescent tablets produced using an inclusion complex of BNZ with CD suggest a possible improvement in the bioavailability of BNZ, and this could represent a relevant advance in Chagas therapy.

Keywords benznidazole; bioavailability; dissolution rate; effervescent tablets; factorial design

Introduction

Chagas heart disease, which is caused by the protozoan *Trypanosoma cruzi*, is a common cause of cardiomyopathy in the Americas. Currently, 16–18 million people are infected with *T. cruzi*, and 40 million remain at risk of acquiring the disease.[1] The drug benznidazole (*N*-benzyl-2-nitro-1-imidazole-acetamide; BNZ) is the primary chemotherapy agent used to treat Chagas disease. Although this compound can eliminate the symptoms associated with the acute phase and provides a satisfactory cure rate, it is much less effective in the chronic phase of the disease.[2] The poor water solubility of BNZ leads to irregular oral absorption and promotes unfavourable pharmacokinetics.[3] Therefore, research to find strategies to enhance BNZ dissolution is of great interest. There have been a few studies that have focused on the development of new ways to administer BNZ but with no clear improvement in its therapeutic effect.[3,4] Silva *et al*.[5] developed a ruthenium benzidazole complex that was more soluble in water and had greater trypanocidal activity than the free molecule. The synthesis of this derivative is still at the laboratorial scale and it has unknown industrial feasibility.[5] A recent study described the preparation of microparticles of BNZ using chitosan by the coacervation method using organic solvent.[6] This approach provided an increase in drug dissolution rate but required a costly and time-consuming procedure that compromises its scale-up and manufacturability.[6]

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A productive approach to overcome solubility problems is the use of cyclic oligosaccharides or cyclodextrins (CDs). The lipophilic inner cavities and hydrophilic outer surface of CDs are capable of interacting with large drugs, resulting in non-covalent inclusion complexes with improved solubility and dissolution rates.[7] Nevertheless, inclusion complexes in the solid state demand high amounts of CD, which could be a limiting factor for a dosage form administrated by the oral route.[8] This limitation could be avoided by the incorporation of BNZ in the solid inclusion complexes with CD using effervescent tablet matrices. Effervescent tablets can include more than 2000 mg of ingredients in a single dose and they also have other properties that are useful for BNZ administration. For example, these tablets are easy to take, even for patients who have difficulties swallowing. Furthermore, this dosage form is extremely stable, particularly surpassing the stability of liquid forms.[9]

The effect of the effervescence reaction on the drug–CD inclusion complex is an interesting point that is as yet unexplored in the literature. Also, there have been no studies describing the use of CDs in the administration of BNZ. The purpose of this work was to develop stable effervescent tablets using an inclusion complex of BNZ with cyclodextrin. To accomplish this, the effect of the concentration of CD and effervescent mixture (EM) on the dissolution rate and physical stability of tablets were evaluated using a complete 3^2 factorial design.

Materials and Methods

Materials

BNZ was obtained from Roche (lot 13871; 99% purity; Rio de Janeiro, Brazil). Tartaric acid, anhydrous citric acid and sodium bicarbonate were obtained from Natural Pharma, São Paulo, Brazil. Sodium carbonate, mannitol and sodium cyclamate were supplied by Farmos, Rio de Janeiro, Brazil. The natural cyclodextrins, α-cyclodextrin (αCD) and γ-cyclodextrin (γCD), were provided by Wacker Química, Barcelona, Spain. The natural β-cyclodextrin (βCD) as well as the two modifier varieties, hydroxypropyl-β-cyclodextrin (HPβCD, substitution degree of 4.5) and randomly methylated β-cyclodextrin (RMβCD, substitution degree of 12.6) were supplied by Cyclodex, High Springs, FL, USA. All other materials were of analytical grade.

Cyclodextrin selection

A solubility assay with different CDs was conducted to select the CD variety for the production of an inclusion complex in a solid state. Excess amounts of drug were added to an aqueous solution containing concentrations near saturation of each CD: 12% (w/v) for αCD, 1.8% (w/v) for βCD, 22% (w/v) for γCD, 45% (w/v) for HPβCD and 25% (w/v) for RMβCD. Suspensions were introduced into an ultrasound bath for 15 min and shaken in an oscillating water bath thermostatically controlled at 25°C for 7 days, which was enough time to guarantee equilibrium according to previous studies. Samples were filtered and diluted appropriately. The concentration of BNZ was determined spectrophotometrically. Experiments were performed in triplicate.

Preparation of inclusion complexes

Physical mixtures of BNZ and HPβCD were obtained by mixing the products in a V mixer (FABBE, São Paulo, Brazil) for 15 min. Inclusion complexes were prepared from the physical mixture by the kneading method. Samples were wetted in a mortar by slowly adding a combination of ethanol/water (1 : 1 v/v) and mixing until the system was homogenised. The wet samples were strained through a 2-mm sieve using an oscillating granulator. The granules were dried in a circulating air oven at 37°C for 2 h.

Preparation of the effervescent mixture

Effervescent granules were prepared from a mixture of organic acids and basic salts through wet granulation. Absolute ethanol was used to wet the material in a mortar. The samples were strained through a 2-mm sieve using an oscillating granulator. The granules were dried in a circulating air oven at 37°C for 2 h. Different formulation compositions were tested to select the formulation with the fastest disintegration time. The EM used in this study included tartaric acid, anhydrous citric acid, sodium carbonate and sodium bicarbonate in equal proportions of 25% (w/w) for each component.

Factorial experimental design

Effervescent tablets of BNZ were made according to a complete 3^2 factorial design. The factors studied were the amount of cyclodextrin and EM in the tablet formulation. The three levels of CD evaluated were as follows: low (8% w/w, corresponding to an equal weight proportion with drug), medium (48% w/w) and high (60% w/w). For the EM, the low, medium and high levels studied were 10, 20 and 30% w/w, respectively. The formulations, according to the experimental design, are given in Table 1. The experiments were conducted in a random sequence.

The responses evaluated were the dissolution efficiency at 15 min and the percentage of water variation in the samples kept in a high relative humidity atmosphere compared with samples kept in the absence of humidity.

The best fitting mathematical model was selected for each response. Model predictor equations were estimated by stepwise multiple regression analysis. The validation of the model was performed through analysis of variance with a significance level of 0.05. The coefficient of determination (R^2) and lack-of-fit were also calculated to confirm the adequacy of the model. All statistical calculations and graphic plots were performed using the software Design-Expert version 8 (Minneapolis, MN, USA).[10]

Preparation of effervescent tablets

Batches of each formulation defined by the experimental design (Table 1) were compressed into tablets on an eccentric press (FABBE, São Paulo, Brazil), using a 16-mm die and circular flat-faced punches. The loading depth of the press was adjusted to obtain tablets with a theoretical weight of 1250 mg containing the BNZ therapeutic dose of 100 mg.

Physical–chemical characterisations

Drug assay

Quantitative BNZ determination was performed using a UV spectrophotometric method in triplicate.[11] The calibration

Table 1 Components used in effervescent tablets based on factorial design

Formulation code	Benznidazole		Saccharin		Mannitol		HPβCD		Effervescent mixture	
	mg[a]	%	mg[a]	%	mg[a]	%	mg[a]	%	mg[a]	%
F1	100.0	8.0	12.5	1.0	12.5	1.0	750.0	60.0	375.0	30.0
F2	100.0	8.0	12.5	1.0	162.5	13.0	600.0	48.0	375.0	30.0
F3	100.0	8.0	12.5	1.0	662.5	53.0	100.0	8.0	375.0	30.0
F4	100.0	8.0	12.5	1.0	137.5	11.0	750.0	60.0	250.0	20.0
F5	100.0	8.0	12.5	1.0	287.5	23.0	600.0	48.0	250.0	20.0
F6	100.0	8.0	12.5	1.0	787.5	63.0	100.0	8.0	250.0	20.0
F7	100.0	8.0	12.5	1.0	262.5	21.0	750.0	60.0	125.0	10.0
F8	100.0	8.0	12.5	1.0	412.5	33.0	600.0	48.0	125.0	10.0
F9	100.0	8.0	12.5	1.0	912.5	73.0	100.0	8.0	125.0	10.0

[a]One tablet with theoretical weight of 1250 mg.

curve in water/methanol (1 : 1 v/v) was made with standard solutions of BNZ over the range of 8 to 28 μg/ml using an UV-vis spectrophotometer (Helios Alpha; Thermo Electron Corporation, Waltham, MA, USA) with the detector set at 324 nm. No effect of excipient addition on the UV spectrum of BNZ solution was found.

Scanning electron microscopy

Scanning electron micrographs were taken using a JEOL JSM-5510 microscope (Tokyo, Japan). Samples were fixed on a brass stub using double-sided tape and coated with graphite in a vacuum.

X-ray powder diffractometry

X-ray powder diffractograms were obtained using a Shimadzu XRD 6000 diffractometer (Kyoto, Japan) equipped with an iron tube and a graphite monochromator. The scans were done between 5–70° (2θ) with a scanning speed of $2°\theta$/min.

Differential scanning calorimetry

Samples (2–3 mg) were placed in crucible aluminium pans and heated from 25°C to 250°C at a rate of 10°C/min using a DSC 2010 (TA Instruments, New Castle, DE, USA). Nitrogen was used as purge gas at a flux rate of 50 ml/min. The differential scanning calorimetry instrument was calibrated using indium and zinc as standards.

Dissolution studies

Dissolution studies were conducted in sink conditions using Nova Ética 299 dissolution equipment (Vargem Grande Paulista, Brazil), following FDA recommendations for immediate release solid oral dosage forms.[12] The rate of stirring was 75 ± 1 rev/min and the temperature of the dissolution media was set at 37°C. The dissolution medium (900 ml) simulated gastric fluid with a pH of 1.2.[13] BNZ samples of 100 mg or equivalent amounts of each system were used.

Inclusion complex samples prepared with different concentrations (low, medium and high) as described above were placed in hard gelatine capsules and tested using the USP basket method (apparatus 1). Tablets prepared as described in Table 1 were tested using the USP paddle method (apparatus 2). This experiment was performed in triplicate.

At regular time intervals until 180 min, a suitable amount of sample medium was withdrawn and replaced with the same amount of fresh medium. Samples were properly diluted and filtered through a syringe filter (0.45 μm). After dilution, the concentration of dissolved drug in the medium was determined spectrophotometrically at 324 nm. The dissolution profiles were evaluated and compared using the dissolution efficiency at 15 min parameter.[14]

Weight

The weight of twenty randomly selected effervescent tablets was determined individually, and the mean weight and coefficient of weight variation were calculated.

Disintegration time

Tablets from each batch were placed in 250 ml of water at 25°C. The tablets were considered disintegrated when completely dispersed fragments were obtained and the liberation of gas stopped. Six replicates of this experiment were performed.

Water sorption assay

To evaluate the physical stability of BNZ effervescent tablets against adverse atmospheric conditions of relative humidity, sorption water assays proposed by Callahan *et al*.[15] were used.

The tablets were stored at 25°C under 0 or 80% relative humidity achieved using silica or a saturated solution of ammonium sulfate in hermetic systems for 7 days.[16] The water sorption behaviour in each condition was evaluated by gravimetric measurements. Experiments were performed in triplicate.

Statistical analysis

The effects of formulation composition on the quality control assays weight, disintegration time and dissolution efficiency at 15 min was performed by the Kruskal-Wallis test. Post-hoc comparisons of the means of individual groups were performed using Fisher's least significant difference test (Statgraphic plus version 5, Warrenton, VA, USA). A level of $P < 0.05$ denoted significance in all cases.

Results and Discussion

According to the Biopharmaceutics Classification System, benznidazol is a class IV drug with poor aqueous solubility

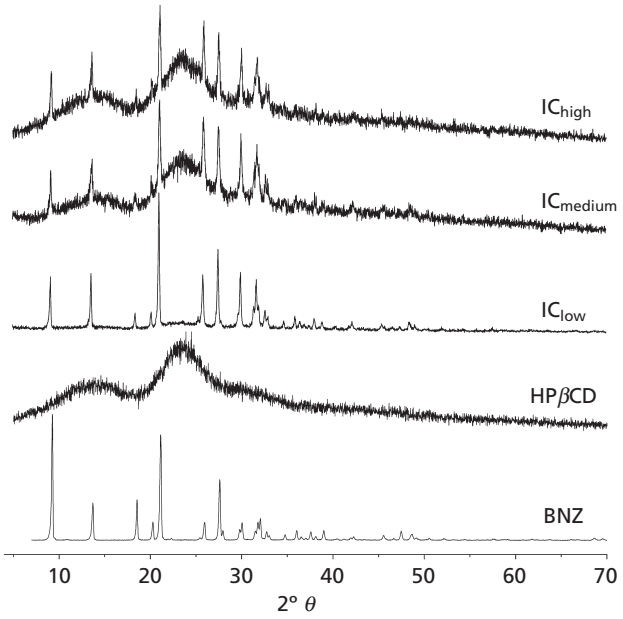

Figure 1 X-ray powder diffractograms of benznidazole, hydroxypropyl-β-cyclodextrin and inclusion complexes. BNZ, benznidazole; HPβCD, hydroxypropyl-β-cyclodextrin; IC_{low}, IC_{medium} and IC_{high}, cyclodextrin content in the inclusion complexes corresponding to concentrations of 8, 48 and 60% (w/w), respectively.

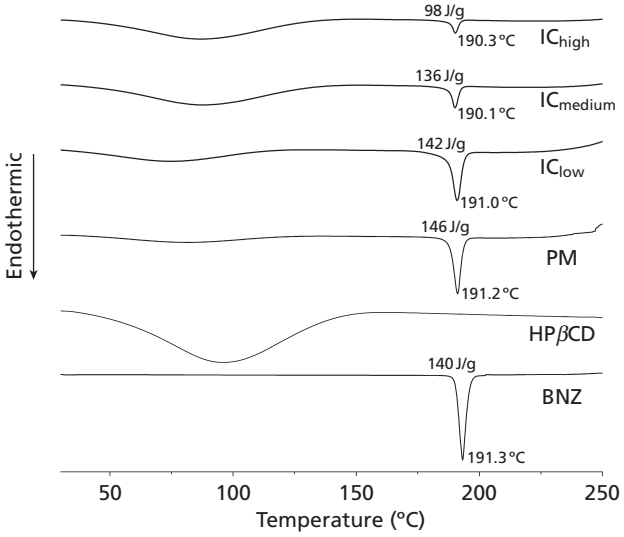

Figure 2 Differential scanning calorimetry curves of benznidazole, hydroxypropyl-β-cyclodextrin, physical mixture of benznidazole and hydroxypropyl-β-cyclodextrin, and inclusion complexes showing the melting peak temperature and the enthalpy associated per gram of drug. BNZ, benznidazole; HPβCD, hydroxypropyl-β-cyclodextrin; IC_{low}, IC_{medium} and IC_{high}, cyclodextrin content in the inclusion complexes corresponding to concentrations of 8, 48 and 60% (w/w), respectively; PM, physical mixture of BNZ–HPβCD.

(~0.2 mg/ml), which compromises its therapeutic efficiency.[17] To select the most promising CD by considering its ability to increase BNZ water solubility, different natural and modified CDs were tested in a solubility assay.

All cyclodextrin systems were able to increase the aqueous solubility of BNZ, however, the variety and its saturation concentration played an important role. While natural CDs achieved solubility of around 0.5 mg/ml (0.59 ± 0.02 mg/ml for αCD, 0.40 ± 0.01 mg/ml for βCD and 0.47 ± 0.02 mg/ml for γCD), the modified cyclodextrins, HPβCD and RMβCD, reached 4.57 ± 0.16 and 4.22 ± 0.22 mg/ml, respectively. HPβCD produced the greatest improvement in the aqueous solubility of BNZ, almost 20-times greater than the water system. HPβCD is one of the most common cyclodextrins, with several studies reporting its safety for human use and the economic cost of this product compared with other modified CDs.[7,18,19] The impressive improvement of drug solubility obtained with HPβCD as well as its industrial advantages made this CD the best choice for use in the later stages of the study.

According to the experimental design used in this study, three inclusion complexes of BNZ–HPβCD were made using different proportions of drug and CD (low, medium and high levels). A physical–chemical characterisation was performed with the aim of establishing the degree of interaction between the compounds and the effect on the dissolution rate of the drug.

The X-ray powder diffractometry patterns of BNZ and HPβCD singly and processed together in the inclusion complex systems are shown in Figure 1. BNZ as supplied presented a typical polycrystalline diffraction pattern, exhibiting main sharp peaks at 9.3, 13.7, 18.6, 21.1 and 27.6°2θ. HPβCD showed a diffuse pattern typical of an amorphous product. As can be seen in Figure 1, the presence of amorphous CD was noted in the baseline of inclusion complex samples and was present in a more intense form for inclusion complexes with medium and high levels, thus reflecting the greater proportion of HPβCD. All the main peaks of the drug were indentified in their original positions in the inclusion complex systems. This suggests that no change in the crystalline phase of the drug took place. However, some marked changes in the relative intensity of some peaks were observed for inclusion complex samples (Figure 1). These crystallographic modifications occurring during the kneading formulation process could indicate an interaction between the components.

The differential scanning calorimetry curves in Figure 2 show that the inclusion complexes produced their individual components and the physical mixture of each in equal proportion to mass. The thermal profile of BNZ displays a sharp endothermic peak at 191.3°C due to melting. The thermal behaviour of HPβCD revealed a broad peak associated with water loss from inside the cavity. The physical mixture presented a slight shift of the drug melting peak to lower temperatures. In inclusion complex samples, these changes were more intense and appear together with a broadening in the drug melting peak. These modifications are indicative of interactions between compounds, suggesting the formation of inclusion complexes. A robust change in the enthalpy of the drug melting peak was noted for the inclusion complex with a high level of CD, which presented a reduction of around 30% in the enthalpy value (Figure 2). This alteration is indicative of a reduction in crystallinity of the sample, which is a common effect of complexation.[20]

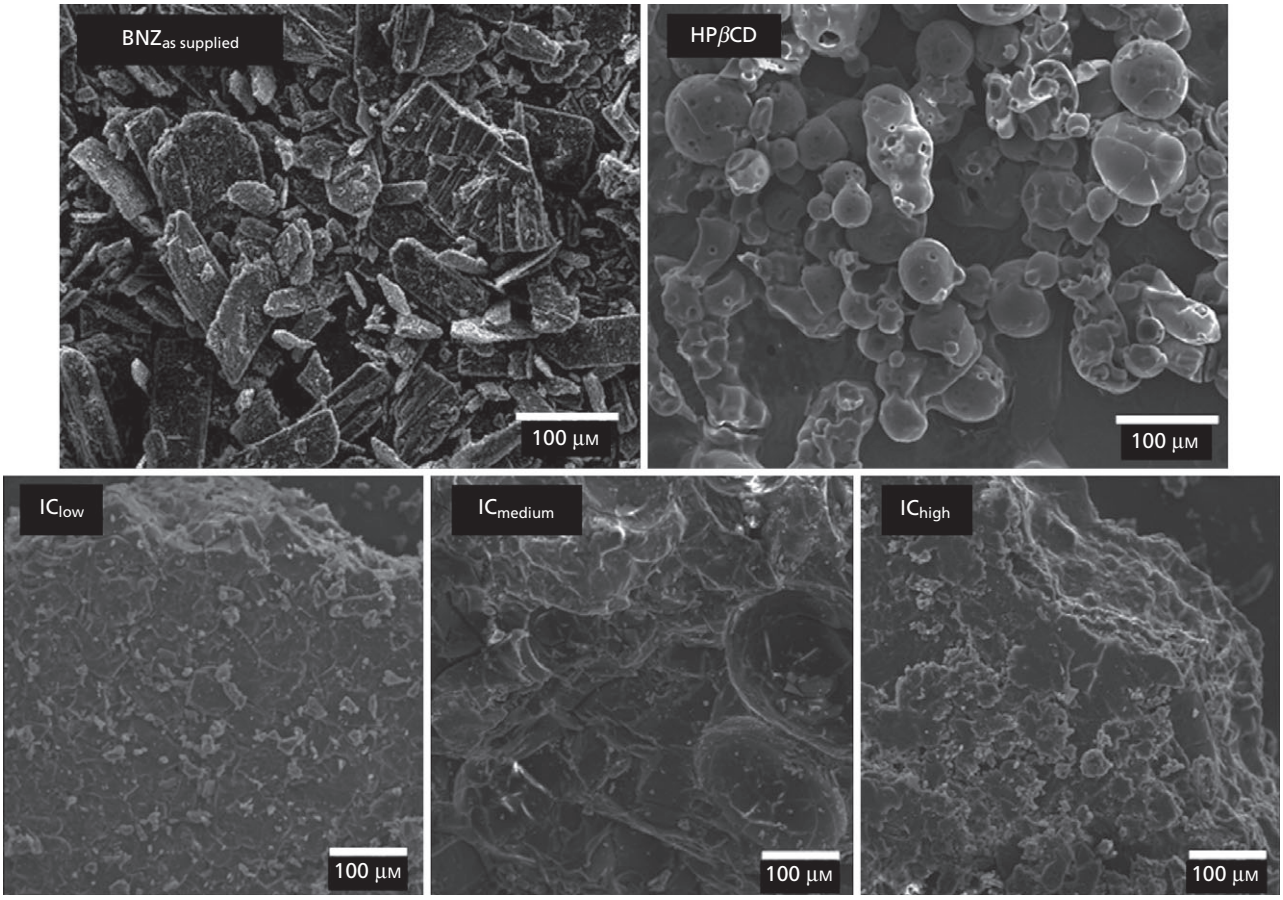

Figure 3 Scanning electron micrographs of benznidazole, hydroxypropyl-β-cyclodextrin and inclusion complexes. BNZ, benznidazole; HPβCD, hydroxypropyl-β-cyclodextrin; IC_{low}, IC_{medium} and IC_{high}, cyclodextrin content in the inclusion complexes corresponding to concentrations of 8, 48 and 60% (w/w), respectively.

Morphological changes can be used as evidence of interactions between molecules and complex formation.[8,21] Selected photomicrographs by scanning electron microscopy of the studied systems are presented in Figure 3. BNZ showed heterogeneous acicular crystals, while HPβCD particles presented a typical amorphous aspect. Significant modifications in shape and size were observed after the kneading process of binary systems. It was not possible to distinguish between the two components. The inclusion complex samples showed compact bulky particles that correspond to a crystalline material. The new morphological structures corroborate the interaction of compounds and confirm the X-ray powder diffractometry and differential scanning calorimetry data.

The dissolution profiles of BNZ as supplied and the inclusion complex, BNZ-HPβCD, as well as the dissolution efficiency at 15 min are presented in Figure 4a. Relevant improvements in the drug dissolution rate were observed for all inclusion complex samples as compared with BNZ as supplied. The Kruskal-Wallis test of the dissolution efficiency at 15 min (DE_{15}) showed significant differences among the inclusion complexes studied ($P < 0.05$). IC_{low} showed a slightly slower dissolution than IC_{medium} and IC_{high}, which presented similar profiles (Fisher's least significant difference test).

All formulations presented results according the pharmacopoeia quality specifications.[13] The results of weight analysis showed no difference between the formulations (Kruskal–Wallis test, $P < 0.05$). However, a significant difference was found among formulations for disintegration time using the Kruskal-Wallis test ($P > 0.05$). The Fisher's least significant difference test presented four subsets as follows: F1 = F4 > F2 = F9 > F8 = F7 = F5 > F3 = F6. Formulations with high concentrations of CD presented clear difficulties with disintegration (F1, F4), while the samples F3 and F6 (with only 8% of HPβCD) needed less than 1 min to disintegrate completely. Thus, the presence of CD seems to produce a negative effect on this parameter.

The dissolution profiles of BNZ effervescent tablets and the commercial BNZ tablet (Rochagan) are presented in Figure 4b. BNZ effervescent formulations showed a noticeably faster dissolution rate as compared with the Rochagan tablet: for BNZ effervescent formulations more than 80% of the drug dissolved in just 15 min, while for the Rochagan tablet, the value was only about 30%.

It is interesting to note that the compaction process to produce tablets did not compromise the dissolution profile of BNZ inclusion complexes. On the contrary, the incorporation of the inclusion complex in the effervescent matrix caused a

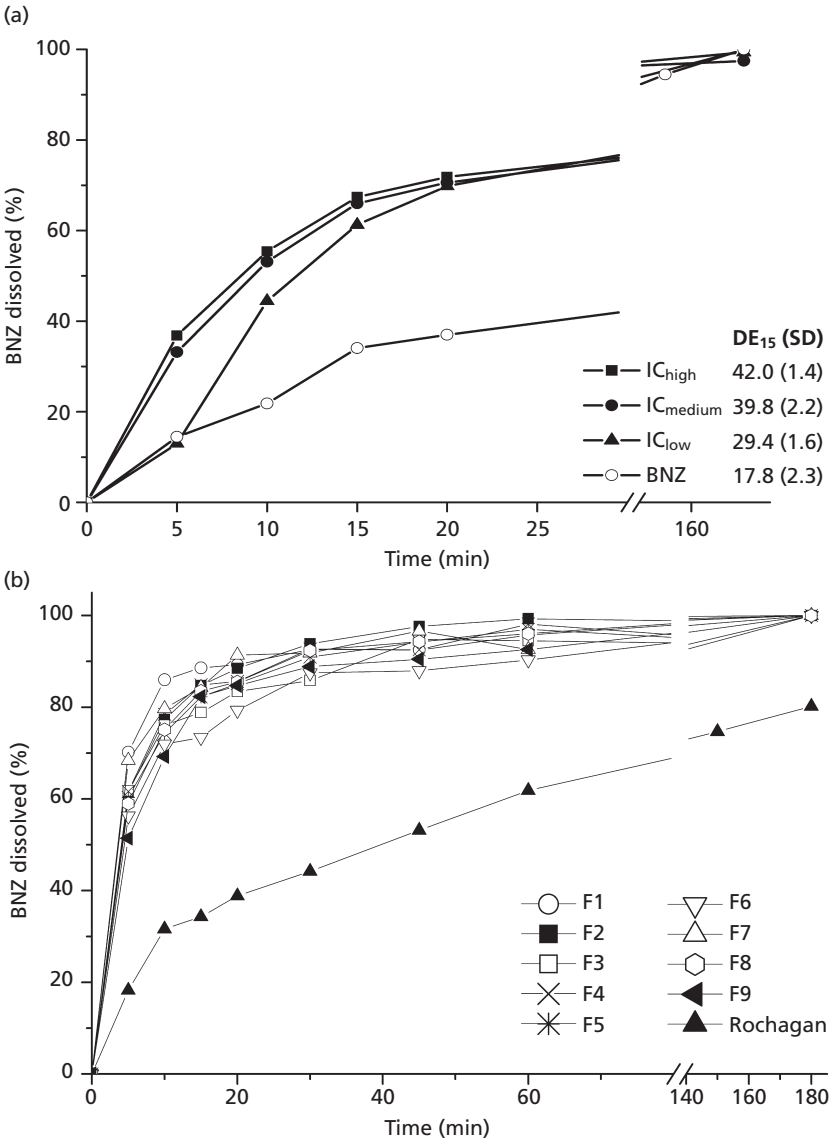

Figure 4 Dissolution profiles in sink conditions. (a) Benznidazole (BNZ) and inclusion complexes together with the dissolution efficiency at 15 min (DE_{15}) and the corresponding standard deviations (SD). IC_{low}, IC_{medium} and IC_{high}, cyclodextrin content in the inclusion complexes corresponding to concentrations of 8, 48 and 60% (w/w), respectively. (b) Commercial Rochagan and effervescent tablets developed according to factorial design.

notably increase the drug dissolution rate. Although the CD inclusion complex has often been used to improve the biopharmaceutical characteristics of drugs, this is the first time that the effervescent reaction has been used to improve the properties of a drug in an inclusion complex with CD. The gas liberated during tablet disintegration disturbs the system, which leads to an improvement in the wettability of the drug and a possible formation of an in-situ inclusion complex. This finding could explain the fast dissolution behaviour of drugs in the effervescent tablets as compared with the complexes alone. The DE_{15} of inclusion complex samples achieved values of up to 42, while BNZ effervescent tablets presented DE_{15} values between 53 and 66 (Table 2). The Kruskal-Wallis test showed that there were significant differences among the formulations ($P < 0.05$), which in order of increasing DE_{15} were ranked by the Fisher's least significant difference test as follows: F9 = F6 < F8 = F5 = F4 = F3 = F2 < F7 = F1.

Routine experimental studies involve the use of one factor at time, while keeping other factors constant. Therefore, the results obtained from such studies do not provide any information about the potential interactions between factors. Factorial design is a way to study the individual contribution of each factor and the possible interactions among them.[22]

The experimental design of BNZ effervescent tablets provided a predictive equation for each response examined, according to a refined model. A summary of the regression analysis is shown in Table 2. The fitted models gave an adequate approximation of the true values. The lack-of-fit for the responses evaluated was not significant, and the experimental variations could be attributed only to randomised error.

Table 2 Dissolution efficiency and the changes in water amount of benznidazole effervescent tablets according to factorial design

Formulation	DE_{15}	Water absorption (%) in high relative humidity	Water lost (%) in low relative humidity
F1	66.3 ± 4.1	5.38 ± 0.00	−1.64 ± 0.00
F2	60.4 ± 1.5	6.10 ± 0.04	−1.16 ± 0.00
F3	59.1 ± 0.5	2.40 ± 0.11	−0.76 ± 0.00
F4	60.9 ± 0.6	6.11 ± 1.91	−1.37 ± 0.00
F5	58.6 ± 2.3	5.31 ± 1.41	−1.11 ± 0.00
F6	55.0 ± 2.6	2.15 ± 0.63	−0.66 ± 0.00
F7	63.1 ± 1.2	6.57 ± 0.10	−0.45 ± 0.20
F8	58.1 ± 0.1	4.94 ± 0.36	−0.59 ± 0.68
F9	53.9 ± 1.2	2.27 ± 0.03	−1.06 ± 0.01
Fitted model	Linear	Linear	2-factor interaction
Predictive equation	= 52.42 + 0.10·HPβCD + 0.16· effervescent mixture	= 1.69 + 0.076·HPβCD	= −1.36 + 0.021·HPβCD + 0.029· effervescent mixture − 0.0013·HPβCD· effervescent mixture
R^2	0.43	0.84	0.45
F	8.26	83.4	3.70
Lack-of-fit	1.81	0.47	0.17

DE_{15}, dissolution efficiency at 15 min. Data are mean ± SD. The fitted model and predictive equations for each response are presented, together with the validation parameters of the model.

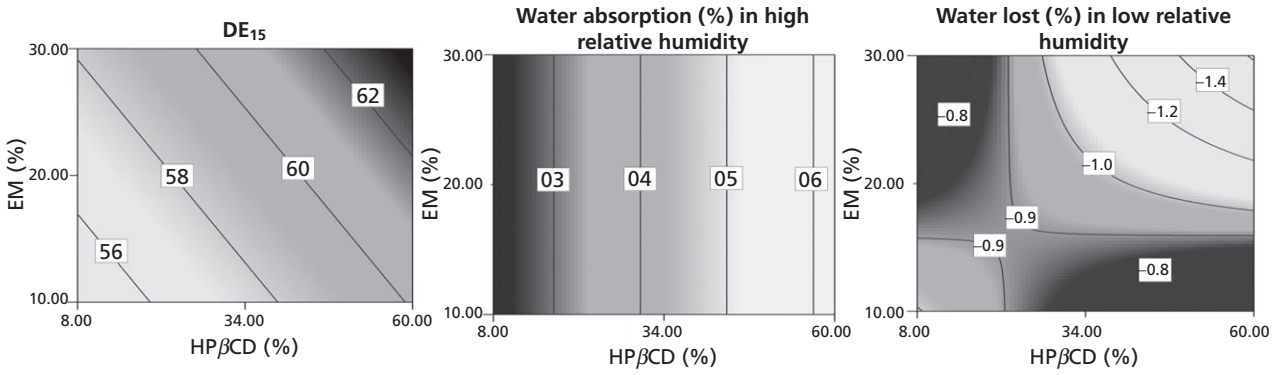

Figure 5 Contour diagrams of effervescent tablets developed according to factorial design. DE_{15}, dissolution efficiency at 15 min; EM, effervescent mixture; HPβCD, hydroxypropyl-β-cyclodextrin. Each contour represents a constant response factor. Grey areas show regions where conditions promote the best response.

The fitted model for dissolution efficiency at 15 min was linear and showed that both variables studied (concentrations of EM and HPβCD) presented statistically significant effects. The interaction term of these two factors was not significant. The refined model was used to draw contour plots as shown in Figure 5. The grey areas represent the amounts of CD and EM that produced the best results. According to the predictive equations (Table 2), the positive sign of the terms refer to an increasing effect, and the magnitude of coefficients indicate a similar contribution of the factors to the response. It was noted from the contour diagram that higher amounts of EM and HPβCD led to a clear increase in the BNZ dissolution rate.

The physical stability of effervescent tablets in the adverse conditions of atmospheric relative humidity was also evaluated in the experimental design. A linear model was also fitted for the water absorption in relative humidity conditions of around 80% (Table 2). As seen in the contour diagram in Figure 5, only the amount of CD produced statistical effects for this response. The literature reports the high hygroscopicity of CDs.[23] Surprisingly, the amount of EM in the formulation did not affect this parameter significantly. Despite the known hygroscopicity of the effervescent compounds, the excipients in this study were selected to prevent moisture incorporation. Therefore, non-hygroscopic components, such as tartaric acid and sodium carbonate, were used in the EM to equilibrate the hygroscopicity of citric acid and sodium bicarbonate.[24] On the other hand, effervescent tablets stored in a low relative humidity atmosphere (near 0%) presented water loss dependent on both factors studied. Analysis of variance indicated that the 2-factor interaction model is appropriate for use for this response (Table 2). The interaction term HPβCD EM presented a coefficient with a negative sign, indicating that both factors combined promote the drying of tablets and render them more friable and fragile. According to the contour diagram, the regions that exist with only one factor in

high concentration show the best result, preventing water loss in samples (Figure 5).

Conclusions

BNZ–HPβCD inclusion complexes produced by kneading methods showed physical–chemical interactions and increased the drug dissolution rate, suggesting the formation of true solid inclusion complexes. Moreover, the incorporation of inclusion complexes in the effervescent matrix of tablets was effective in improving the dissolution behaviour of BNZ.

The application of the factorial design led to a good knowledge of the studied phenomenon with the least expenditure of time and materials. The study revealed that higher amounts of EM and HPβCD lead to an increase in the BNZ dissolution rate. However, a high concentration of cyclodextrin seems to hamper the effervescency, raising the disintegration time of tablets and also making the formulations more vulnerable to variations in atmospheric relative humidity. Therefore, the optimal formula for achieving outstanding enhancement of the dissolution rate of BNZ as well as suitable results for quality control and physical stability was found to contain HPβCD and EM in medium levels, around 48 and 20% w/w, respectively.

This technique offers a simple way to produce effervescent tablets of BNZ for oral administration, which is important from an industrial point of view. The effervescent tablets developed suggest a possible improvement in the bioavailability of the drug and this could represent a relevant advance in Chagas therapy.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

This work was supported by the CNPq, Brazil (project no. 472134/2008–6).

Acknowledgements

The authors are thankful to LAFEPE (Brazil) and Professor José Lamartine Soares Sobrinho (Universidade Federal do Piaui, Brazil) for their donation of the benznidazole used in our studies.

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