

Benznidazole drug delivery by binary and multicomponent inclusion complexes using cyclodextrins and polymers

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ABSTRACT

Benznidazole (BNZ) is the drug of choice for Chagas disease treatment, which affects about 9.8 million people worldwide. It has low solubility and high toxicity. The present study aimed to develop and characterize inclusion complexes (IC) in binary systems (BS) with BNZ and randomly methylated- β -cyclodextrin (RM β CD) and in ternary systems (TS) with BNZ, RM β CD and hydrophilic polymers. The results showed that the solid BS had a large increase in dissolution rate ($Q > 80\%$). For the solid IC obtained, the kneading method, in ratio of 1:0.17 (77.8% in 60 min), appeared to be the most suitable for the development of a solid oral pharmaceutical product, with possible industrial scale-up and low concentration of CD. The solid TS containing 0.1% of hydroxypropylmethylcellulose (HPMC) showed no significant advantages compared to the binary IC in solid state. The use of cyclodextrins proved to be a viable tool for effective, standardized and safe drug delivery.

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1. Introduction

Chagas disease is endemic in Latin America and is transmitted by the parasite *Trypanosoma cruzi*. It is considered by the World Health Organization (WHO) to be a serious public health problem, affecting about 9.8 million people, with a further 4–5% of the Latin American population at risk of infection (Lima et al., 2011). Benznidazole (BNZ) is the drug of choice for treating this disease, but, owing to its poor aqueous solubility, its absorption in gastrointestinal fluids is severely limited (Soares-Sobrinho, Lyra, Alves, & Rolim-Neto, 2010).

Cyclodextrins (CDs) are cyclic carbohydrates of natural origin with a hydrophobic cavity and hydrophilic exterior. This characteristic enables the formation of water-soluble inclusion complexes (ICs) with a large variety of molecules of low solubility, such as BNZ. Pharmaceutical applications have encouraged the development of derived CDs and randomly methylated- β -cyclodextrin (RM β CD), derived from naturally occurring β -cyclodextrin (Andreaus, Dalmolin, Oliveira-Junior, & Barcellos, 2010).

One of the main features of CDs is the possibility of forming ICs in solution and in solid state. The characterization of the CI obtained is extremely relevant for understanding the interaction between the

molecules. In this study the characterization of the complexes in a liquid state was performed using phase solubility diagrams and, for the complexes in a solid state, X-ray diffraction spectroscopy, Fourier transform infrared (FT-IR), scanning electron microscopy (SEM) and a dissolution test (Lyra, Alves, Fontes, Soares-Sobrinho, & Rolim-Neto, 2010).

Generally, the ratio of CD:drug is 1:1 (mol:mol), but combinations such as 2:1, 1:2, 2:2 or more complex patterns may be observed. Depending on the presence of different molecules and the size of the guest molecules, ternary complexes may also be formed, with association constants apparently different from those of binary complexes (Andreaus et al., 2010).

The ternary complexes of drug, CD and a third component can be obtained using a water soluble polymer. This class of polymer is widely used as a pharmaceutical excipient (Ribeiro, Figueiras, Santos, & Veiga, 2008). Polymers interact with ICs, leading to the formation of ternary complex polymers, also called systems or multicomponent complexes. This combination has been of great interest to the scientific and technical community, because of the physical, chemical and biological properties of drugs that can thereby be optimized, although the use of polymers in ternary systems can both increase and reduce the complexation of these systems (Ribeiro, Carvalho, Ferreira, & Veiga, 2005).

In view of this, the present study aimed to obtain and characterize these ICs using RM β CD with BNZ, and ternary solid systems in combination with hydrophilic polymers, in order to evaluate the

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increase in drug solubility and dissolution rate of these systems. It also aimed to evaluate the influence of hydrophilic polymers on the behavior of the ICs formed, in an effort to identify the most appropriate system for obtaining future formulations for oral administration.

2. Materials and methods

2.1. Materials

The BNZ was donated by the Laboratório Farmacêutico de Pernambuco (LAFEPE) with 99.9% purity, measured using differential scanning calorimetry (DSC) and high performance liquid chromatography (HPLC). The RM β CD (molar substitution 0.57) was donated by Roquette® (Spain), the polyvinylpyrrolidone (PVP) K-30 by BASF®, Germany; and the hydroxypropylmethylcellulose (HPMC) K100 by Methocel K 100, Colorcon®, Brazil. The solutions were prepared using ultrapure water (MILLI Q) and filtered through a 0.22 μ m Millipore® (Millipore Corp, Billerica, MA). Other reagents and chemicals were of analytical reagent grade.

2.2. Experimental

The study was conducted in two steps: liquid and solid state, the liquid state was verified the influence of CD, the isolated polymer and ternary system the solubility of the drug (BNZ), through the phase diagram. After choosing the type and concentration of polymer, was obtained in solid state systems. The concentrations ranged from CD (1:1–1:0.17 mol:mol), and the presence or absence of polymer (0.1% HPMC). These systems were properly characterized by X-ray diffraction (XRD), scanning electron microscope (SEM), infrared spectroscopy (IR-TF), dissolutions studies.

2.2.1. Analytical method for assay

Quantification of the BNZ was measured using UV spectrophotometry in accordance with the methodology developed and validated by Soares-Sobrinho, Silva, Granjeiro-Júnior, Medeiros, and Rolim-Neto (2006). The equipment used was an UV/vis spectrophotometer (Agilent 8453, Agilent Corp, Santa Clara, CA) at a wavelength of 324 nm. The calibration curve was prepared in water within a concentration range of 4–40 μ g/mL of BNZ. To confirm the non-interference of the addition of the CDs on the samples measured, a sweep was first carried out of the range between 200 and 700 nm, with no observed change in the spectra of BNZ in the solutions evaluated.

2.2.2. Phase-solubility diagram

The phase-solubility diagram was produced using the previously described method (Gema, Francisco, González-Álvarez, & Mendicuti, 2008). This study examines the effects of the addition of a complexing agent on the compound to be dissolved, enabling the complexation constant (K_c) and the stoichiometry of complex formation of the intrinsic solubility of the substrate (S_0) and the slope of the resulting solubility diagram (Eq. (1)) (Lyra, Alves, Fontes, Soares-Sobrinho, & Rolim-Neto, 2010).

$$K_c = \frac{\text{slope}}{S_0(1 - \text{slope})} \quad (1)$$

Other parameters such as thermodynamics can be obtained as a function of the temperature and stability constant of the ICs (Gema et al., 2008). The change in Gibbs' free energy (ΔG) in the complexation process was determined using Eq. (2), where R is the universal gas constant (8.314472 J K⁻¹ mol⁻¹) and T is temperature in Kelvin (Grillo et al., 2008) (Eq. (2)).

$$\Delta G = -RT \ln K \quad (2)$$

2.2.3. Evaluating the effect of varying the concentration of polymers (PVP and HPMC), with fixed concentration of binary RM β CD

Excess quantities of BNZ were added to a solution of RM β CD at a fixed concentration of 2%, to which increasing concentrations of PVP K-30 (0.01–0.50%, w/v) and HPMC (0.01–0.25%, w/v) were added, in a manner similar to that used in the studies conducted by Loftsson, Frikdriksdóttir, Sigurkdardóttir, and Haruhisa (1994). Owing to the differing viscosities presented by the polymers, solutions of PVP and HPMC were prepared at different concentrations.

The samples were subjected to mechanical agitation in a water bath at a temperature of 25 °C for 72 h for the equilibrium of the system. Subsequently, the samples were filtered through filter membranes with 0.45 μ m pores. Quantification of the BNZ was carried out using UV spectrophotometry, with water as a blank, thereby ascertaining the specificity of the method used. The samples submitted to heating were placed in an autoclave at 120 °C for 20 min in order to enhance the solubilization capacity of the systems. The experiments were performed in triplicate.

2.2.4. Effect of polymer concentration at fixed concentrations associated with variables in RM β CD binary systems

Excess quantities of BNZ were added to the solution at increasing concentrations of RM β CD (0.1, 0.5, 1.0, 2.0, 3.0 and 4.0%, w/v) and a fixed concentration of polymers, whose solubility increased more in this study. Quantification of the BNZ was also carried out using UV spectrophotometry, as described in Section 2.2.3.

2.2.5. Preparation of complexes in solid state

The BNZ:RM β CD complexes with and without the polymer (HPMC 0.1%) were prepared with the following ratios: 1:1.00, 1:0.66, 1:0.33, 1:0.17 (mol:mol), using the kneading and evaporation techniques. Physical mixtures (PM) were also prepared for the purposes of comparison.

2.2.5.1. Preparation of physical mixtures (PMs). The PMs of BNZ, RM β CD and HPMC were obtained by homogenizing them for 20 min in a WAB T2C mixer (Willy A. Bachofen Corp., Basel, Switzerland) with the following ratios: 1:1.00, 1:0.66, 1:0.33; 1:0.17 (mol:mol).

2.2.5.2. Preparation of the kneading (KN) complexes. The compounds obtained by kneading were obtained by physically mixing them in small measures by the gradual addition of a 50% hydroalcoholic solution (ethanol:water), corresponding to 20% (w/w) of the weight of the sample, and mixed until completely homogeneous (Hedges, 1998). The samples were dried at 40 °C in an oven for 24 h and subsequently sieved through a 250 μ m mesh.

2.2.5.3. Preparation of the evaporation (EV) complexes. A 50% water–alcohol solution was added to the PM until it became homogeneous. The solution was evaporated in a vacuum at 50 °C in a rotaevaporator. It was subsequently sieved through a 250 μ m mesh to homogenize the particles.

2.2.6. Characterization of the solid state complex

2.2.6.1. X-ray diffraction (XRD). The powder resulting from X-ray diffraction was collected using copper radiation equipment (40 kV, 30 mA) in a Philips Diffractometer PW 1729 (Philips Corp., Netherlands) with Bragg–Brentano geometry, in the range of $2 < 2\theta < 60$ with a slit size of 0.02° and a time of 2 s per socket.

2.2.6.2. Scanning electron microscope (SEM). The morphology of the sample surfaces was examined using an LEO-435VP Scanning

Electron Microscope (Leica Microsystems, Cambridge, UK). The particles were fixed on a support coated with gold in a vacuum.

2.2.6.3. Infrared spectroscopy (IR-TF). The infrared spectrum was obtained using a Bruker IFS-66V Spectrometer (Bruker Daltonics Inc., Bremen, Germany). The samples were collected and mixed with potassium bromide pellets.

2.2.6.4. Dissolution studies. The dissolution studies were conducted using a Turu Grau DT-6 paddle apparatus (Barcelona, Spain) at 75 rpm and 37 °C (± 0.5 °C). The volume was 900 mL of medium and the pH 1.2 hydrochloric acid sodium chloride. The samples of the complexes were placed in capsules containing the equivalent of 50 mg of BNZ with particle size of 50–200 μm . The collection times were 5, 10, 15, 20, 30, 45 and 60 min, and the concentration of the samples was determined after collection by spectrophotometry at 324 nm. For each system obtained, three models were tested. The dissolution profiles were evaluated using the dissolution efficiency at intervals of 15 and 20 min (ED15 and ED20) (Khan & Rhodes, 1972).

3. Results

3.1. Phase solubility diagrams

3.1.1. Evaluation of the effect of variation of the concentration of the polymers (PVP and HPMC), at a fixed concentration of RM β CD in the binary systems

This study confirmed an increase in the solubility of BNZ through complexation with the CD and the interactions of the drug with the PVP and HPMC polymers, when heated at room temperature. The results also enabled the type and concentration of polymer to be used to obtain the BNZ–RM β CD–polymer ternary system, as shown in Fig. 1(a) and (b).

The results show that the dissolution rate of BNZ in a 2% RM β CD solution, in the presence of growing concentrations of hydrophilic polymers, PVP and HPMC, with or without heating, rises until it reaches an optimum concentration, after which solubility declines for both polymers. For the PVP, the best concentration obtained was 0.25% (w/w) under heating, while, without heating, the maximum concentration achieved was 0.2%. In this case, the heating provided a higher increase in solubility at a higher concentration of PVP, while, without heating, the solubility was somewhat lower, despite requiring a lower concentration of PVP.

HPMC produced greater solubility in the presence of heat, despite the fact that in both situations the best concentration tested was 0.1% (w/w). In this case, the heating had a positive influence, which can be explained by the high viscosity of this polymer in solution, which, when heated, produces greater dispersion of the polymer and dissolution of the drug. These results corroborate the figures obtained in previous studies (Ribeiro et al., 2005; Thorsteinn & Sigurðardóttir, 1994).

Comparison of the systems obtained using each of the polymers concluded that HPMC achieved better results than PVP, even in the absence of heating. The results of this study thus suggest that HPMC would be the best option for systems in a liquid state. An evaluation was subsequently carried out of the effect on the solubility of BNZ in HPMC in the presence of RM β CD.

3.1.2. Evaluation of the effect of the polymer at a fixed concentration associated with varying concentrations of RM β CD in binary systems

Fig. 1(c) shows the solubility diagram of the phases of BNZ in the presence of varying concentrations of CD and a fixed concentration of 0.1% of HPMC. The results demonstrate that the solubility of BNZ increased in a linear fashion both in the binary (BNZ–RM β CD) and

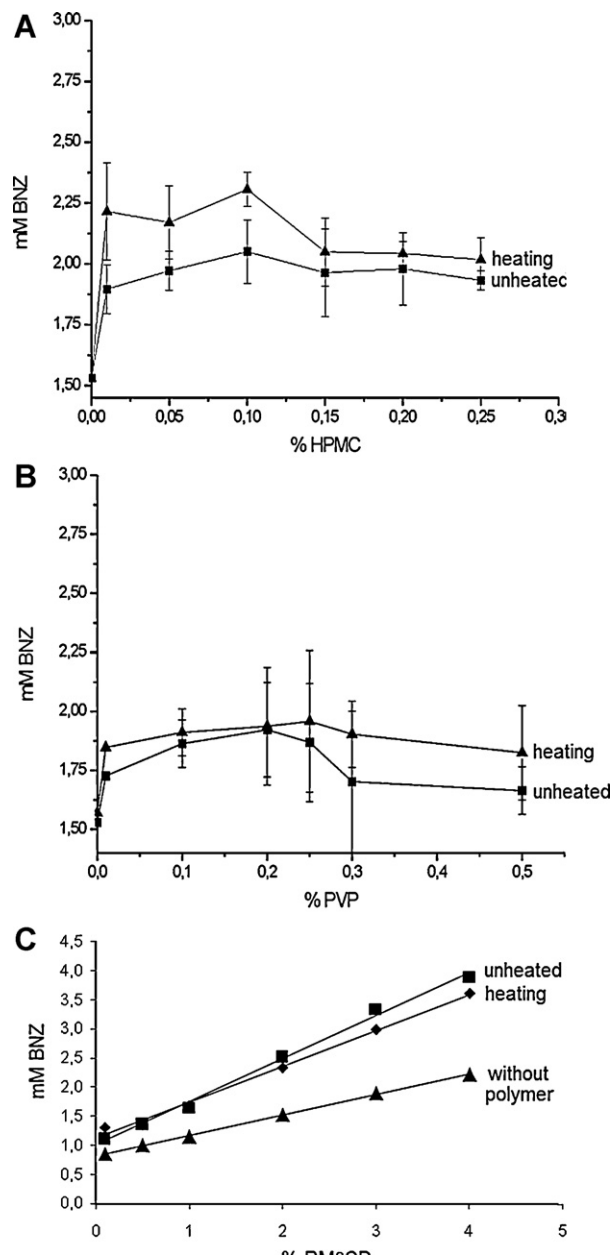


Fig. 1. BNZ solubility diagram in a fixed concentration of RM β CD (2%), with different concentrations of PVP (a) and HPMC (b), with and without heating; and Solubility diagram for BNZ in a fixed concentration of HPMC (0.1%) associated with RM β CD in different concentrations with (♦) and without (■) heating, compared to the diagram for the complex in the absence of the polymer (▲) (c).

the ternary (BNZ–RM β CD–HPMC) systems, in the latter case both with and without heating, and thus correspond to the type A_L profile established by Higuchi and Connors (1965), which is related to the formation of a soluble inclusion complex. It can also be seen that the presence of RM β CD brings about a slightly higher increase in dissolution with HPMC in the absence of heating, at concentrations of 2% of RM β CD and higher, which is different from the result obtained using HPMC in isolation.

The slope value in each of these diagrams is lower than 1, suggesting the formation of a complex with 1:1 stoichiometry. According to Jullian et al. (2008), the CD:drug complex with 1:1 stoichiometry is the most common type of association, since this involves a single molecule of the drug being inserted in the cavity of a molecule of CD, with a complexation constant ($K_{1:1}$) providing equilibrium between free and associated species.

Table 1Apparent complexation constants ($K_{1:1}$) and thermodynamic complexation parameters for BNZ with CD and polymer determined by phase solubility diagram.

Binary and ternary systems	Slope	Intercept	$K_{1:1}$ (M^{-1})	ΔG (kJ/mol)
BNZ:RM- β -CD	0.356	0.810	699.82	–21.40
BNZ:RM- β -CD:HPMC ^a	0.379	0.836	772.68	–21.72
BNZ:RM- β -CD:HPMC ^b	0.566	0.963	1654.00	–24.21

^a Without heating.^b With heating.

The complexation constants ($K_{1:1}$) and the change in Gibb's free energy (ΔG) are given in Table 1. The $K_{1:1}$ calculated on the basis of the phase solubility diagram shows that the formation of inclusion complexes is stable with BNZ, since, according to Jun et al. (2007), the association constants for drugs with CDs appear in the 50–2000 M^{-1} band.

The alterations in the thermodynamic parameters during complexation are phenomena that result from changes in van der Waals interaction energy, hydrogen bridges and hydrophobic interactions between drugs and CDs. Gibb's free energy for all systems was $\Delta G < 0$, indicating that the complexations with CDs were spontaneous and that the complexation constants are inversely proportionate, *i.e.* the less variation in energy (more negative), the greater the efficiency of the complexation (K_c).

3.2. Characterization of solid state complexes

3.2.1. X-ray diffraction (XRD)

Powder X-ray diffractograms were obtained from isolated samples of BNZ, RM β CD and HPMC, PM and processed using evaporation (EV) and kneading (KN), in order to investigate the behavior of the systems formed. The diffractograms are shown in Fig. 2. The diffraction profile of BNZ demonstrates its crystalline nature, showing numerous high-intensity diffraction peaks, with the three of highest intensity at 7.5; 16.5° and 22° 2θ , in addition to several secondary peaks, indicating crystalline behavior. HPMC and RM β CD, however, are predominantly amorphous in nature.

Comparison of the diffraction profiles of the pure components with those obtained from the systems confirms the lack of significant variation between the diffractograms for the PMs, which correspond to the simple juxtaposition of the diffractograms of the components in isolation.

The diffraction profiles for KN and EV, with and without the polymer, still show the crystalline character typical of the drug, being most evident in those samples that had the greater proportion of the drug (1:0.17). The same can be said of the diffractograms of the MFs. However, there is evidence of a slight decrease in the diffractogram peaks, especially in the case of KN. Likewise, comparison of BNZ–RM β CD–HPMC and BNZ–RM β CD, in all proportions, showed a similar crystalline structure and it was not possible to differentiate the two systems with any clarity.

3.2.2. Scanning electron microscopy (SEM)

The micrographs obtained for the binary and ternary systems, for the various proportions, are shown in Fig. 3. These micrographs are frequently used to observe the microscopic morphological aspects of single components: drugs, cyclodextrines, polymers, and the processed systems (Naidu et al., 2004).

BNZ characteristically takes the form of regular crystals (Soares-Sobrinho, Cunha-Filho, Rolim-Neto, Torres-La Bandeira, & Dacunha-Marinho, 2008), confirming the results found for DRX. RM β CD however takes the form of spherical particles and HPMC is a clearly amorphous material. The photomicrographs of the MFs show the form of all the components and it can be seen that RM β CD and HPMC are adsorbed on the surface of the drug.

The samples processed showed changes in the morphology of the particles, both in the binary and the ternary systems, without any significant difference between the two. As for the techniques used, the systems using KN formed aggregates of amorphous particles, while the EV systems formed needle-shaped crystals, which is the distinct shape of the original particle of BNZ. A reduction was also found in the size of the particles.

The characterization of the systems using MEV enabled morphological changes to be observed in the particles, indicating the formation of new solid phases in the products obtained (KN and EV). These alterations may indicate modifications related to solubility and dissolution of the drug by way of these systems.

3.2.3. Infrared spectroscopy (IR-TF)

The IR spectrogram for BNZ (Fig. 4) present the characteristic peaks, especially in relation to the bands typical of the amides, N–H stretching vibration (N–H), carbonyl stretching (amide band I) and N–H deformation (amide band II), in addition to vibrations resulting from the benzylic and imidazole group, and, in particular from the nitro group. The band produced by N–H stretching vibrations occurs at 3330 cm^{-1} . The carbonyl stretching band occurs at 1685 cm^{-1} and the N–H deformation (amide II) at 1565 cm^{-1} , as is characteristic of the secondary amide. In addition to these, the band at 1318 cm^{-1} is attributed to C–N stretching. The cluster of bands at 3180, 3160, 3120, 3090 and 3000 cm^{-1} suggests symmetrical and asymmetrical stretching vibrations for the methylene in the benzyl group and stretching of the aromatic C–H, albeit with a higher than expected wave number.

No significant absorption bands characteristic of BNZ were found in the FT-IR spectra corresponding to the PMs with BNZ–RM β CD the bands of the components in isolation being superimposed on one another, demonstrating the absence of interactions.

The IR results obtained for the processed products of BNZ–RM β CD–HPMC (Fig. 4) show slight alterations in the region corresponding to the stretching vibrations of the BNZ's benzene group (3100–2900 cm^{-1}), for the EV and KN samples.

Changes were also observed in the bands corresponding to the drug in the 1300–1000 cm^{-1} region, which are related to the C–N bonds of the amide grouping. These results point to a concentrated interaction on the central-aromatic part of the drug, which indicates possible inclusion of BNZ in RM β CD by way of its benzene group. As observed previously for SEM and XRD, there were no differences between the binary and the ternary compounds. Despite the possibility of more detailed visualization of some bands typical of BNZ, which were initially 1:1, mol:mol, a decrease in the proportions of CD was noted in the course of formulation.

3.2.4. Dissolution test

The dissolution test enables investigation of the solubility of the drug under study using the ICs obtained in its solid state, and also provides information on the dissolution kinetics, allowing inferences to be made regarding the possible behavior of these systems *in vivo*. It is thus an important tool for investigation of these systems. The dissolution profiles of BNZ and the systems obtained are

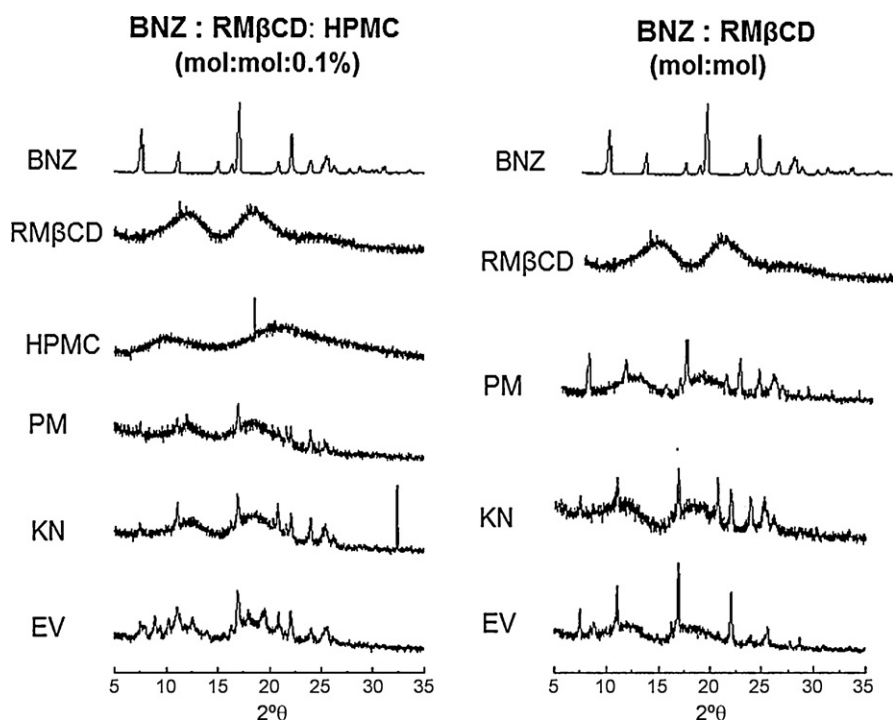


Fig. 2. Diffractograms of BNZ, HPMC, RMβCD, binary and ternary systems.

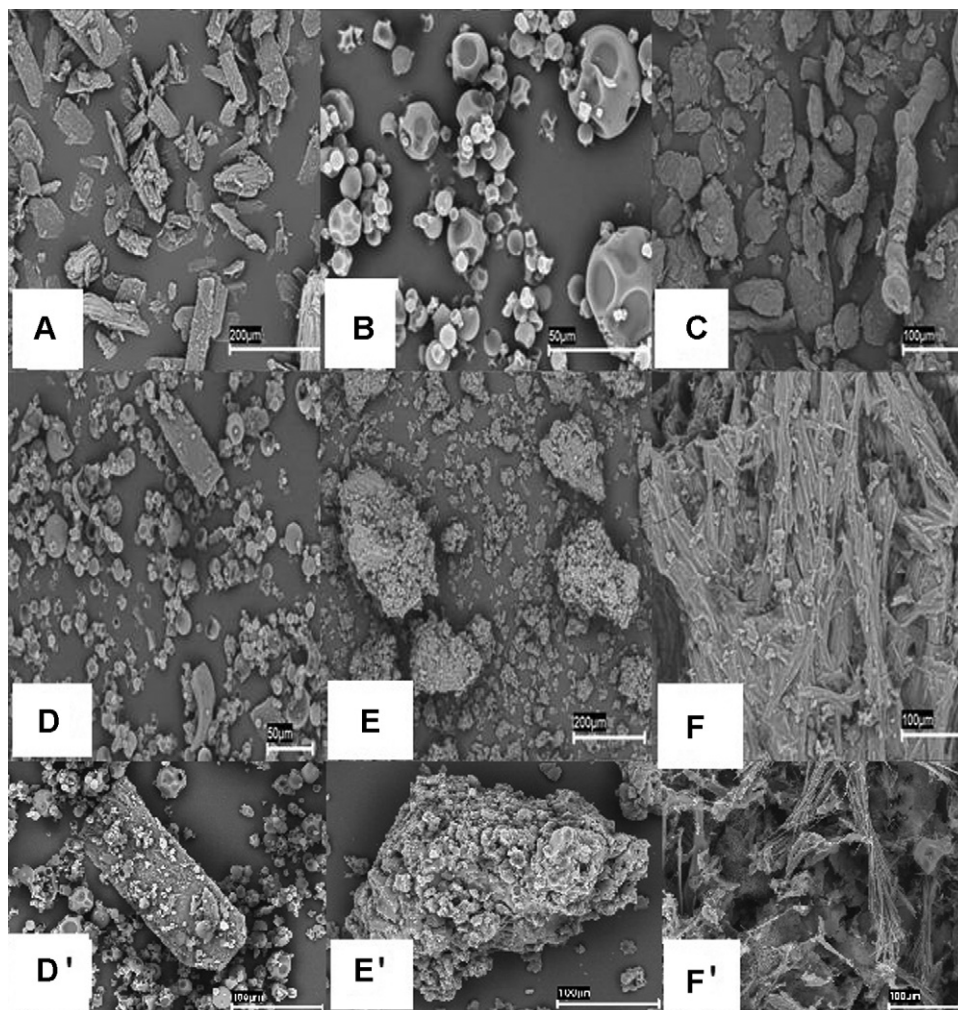


Fig. 3. Micrographs of the: A-BNZ; B-RMβCD; C-HPMC; ternary systems proportion 1:1 (D-PM; E-KN; F-EV); and the binary systems proportion 1:1 (D'-PM; E'-KN; F'-EV).

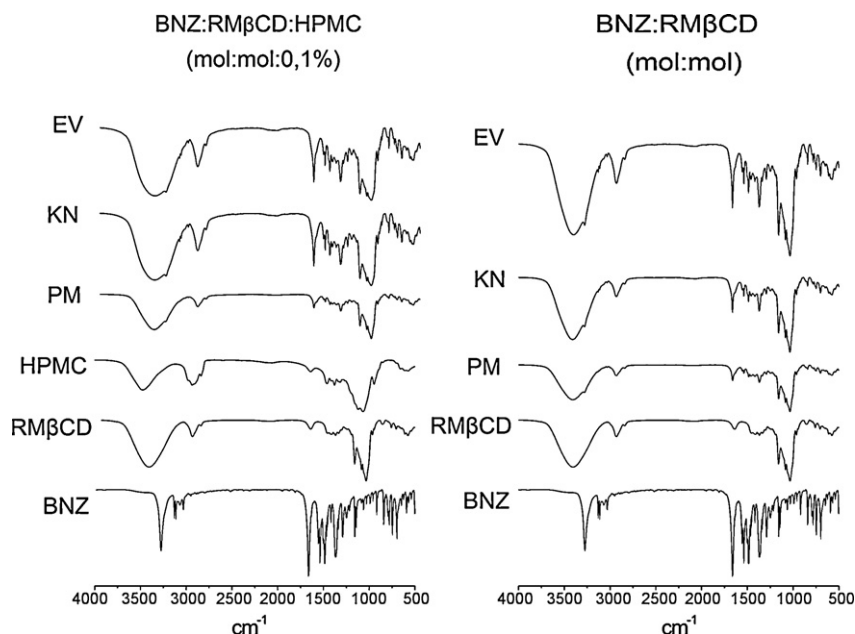


Fig. 4. FT-IR spectra of the binary and ternary systems: BNZ–RMβCD–HPMC sequence: BNZ, RMβCD, HPMC, PM, KN and EV; BNZ sequence: RMβCD, BNZ, RMβCD, PM, KN and EV.

shown in Fig. 5. The calculated 15 and 20 min DE values are given in Table 2.

BNZ in isolation exhibited a low dissolution rate, with 29.4% of the drug dissolving within 60 min. For the systems, the influence of the HPMC in terms of an increase in dissolution was, generally speaking, not that effective, in contrast to the results obtained in a liquid medium, where there was a considerable increase in solubility of BNZ in the presence of HPMC. This may be related to the slight impact or non-uniformity of the HPMC in the formulation, as well as the influence of the processes used to obtain the systems.

The best results were therefore obtained with the BNZ:RMβCD binary systems. The exception was the KN systems with proportions of 1:1.00; 1:0.66 and 1:0.33 with 0.1% HPMC. However, there is no significant difference that would justify the use of HPMC, since, in both cases, the percentage of the drug dissolved in these proportions was higher than 90% within 60 min.

In contrast to the HPMC, the methods used to obtain the system had a significant influence on the release of BNZ, as can be seen from the dissolution profiles (Fig. 6) and the DE (Table 2).

The binary and ternary systems obtained by way of EV enabled total dissolution of the BNZ, corroborating the DE data. It can thus be concluded that the HPMC did not interfere in the BNZ–RMβCD

complex as the proportion of cyclodextrine did. The use of smaller proportions of RMβCD is thus recommended, since this reduces the cost of obtaining the binary system. Although the phase solubility diagram suggests that the formation of the complex occurs in a proportion of 1:1, only the presence of CD in the systems provides an increase in the wetting process and solubility of the drug, by way of a decrease in the surface tension between the medium and the BNZ. This also explains the results obtained in the PM, which achieved a dissolution rate of 80% of the drug, demonstrating the positive effect of the CDs, despite their crystalline characteristics, as can be seen in the results for XRD and SEM.

The kneaded systems also achieved satisfactory rates of dissolution, with an average percentage of $94.4 \pm 2.42\%$ of the drug dissolved in the medium for the BNZ:RMβCD systems and $92.24 \pm 9.86\%$ for the BNZ:RMβCD:HPMC systems. Although these percentages are lower than those for the EV system, the kneading process has the important advantages of being simple, high-yielding, and easy to scale up, since this is the method most commonly used in the pharmaceutical industry (Lima, Soares-Sobrinho, Corrêa-Júnior, & Rolim-Neto, 2008). This, together with the percentage dissolution of over 80%, justifies the use of this method.

Table 2
Dissolution efficiency after 15 and 20 min of proportions of BNZ:RMβCD with and without 0.1% HPMC.

Proportions BNZ:CD (mol:mol)	System components	EV ^b		KN ^c		PM ^d	
		DE ₁₅ ^a	DE ₂₀ ^a	DE ₁₅ ^a	DE ₂₀ ^a	DE ₁₅ ^a	DE ₂₀ ^a
1:1.00	BNZ–RMβCD–HPMC	83.4	88.7	60.9	69.6	49.5	56.5
	BNZ–RMβCD	83.5	87.7	77.7	81.6	46.9	54.4
1:0.66	BNZ–RMβCD–HPMC	81.4	86.0	61.9	69.3	51.0	57.5
	BNZ–RMβCD	84.4	89.4	68.4	73.0	46.1	54.3
1:0.33	BNZ–RMβCD–HPMC	80.9	86.9	53.4	61.5	50.9	57.6
	BNZ–RMβCD	84.5	89.0	66.2	73.0	47.9	56.9
1:0.17	BNZ–RMβCD–HPMC	83.8	88.0	22.5	30.7	24.0	33.2
	BNZ–RMβCD	48.9	58.5	41.6	53.2	14.4	48.1

^a Dissolution efficiency.

^b Evaporated.

^c Kneaded.

^d Physical mixture.

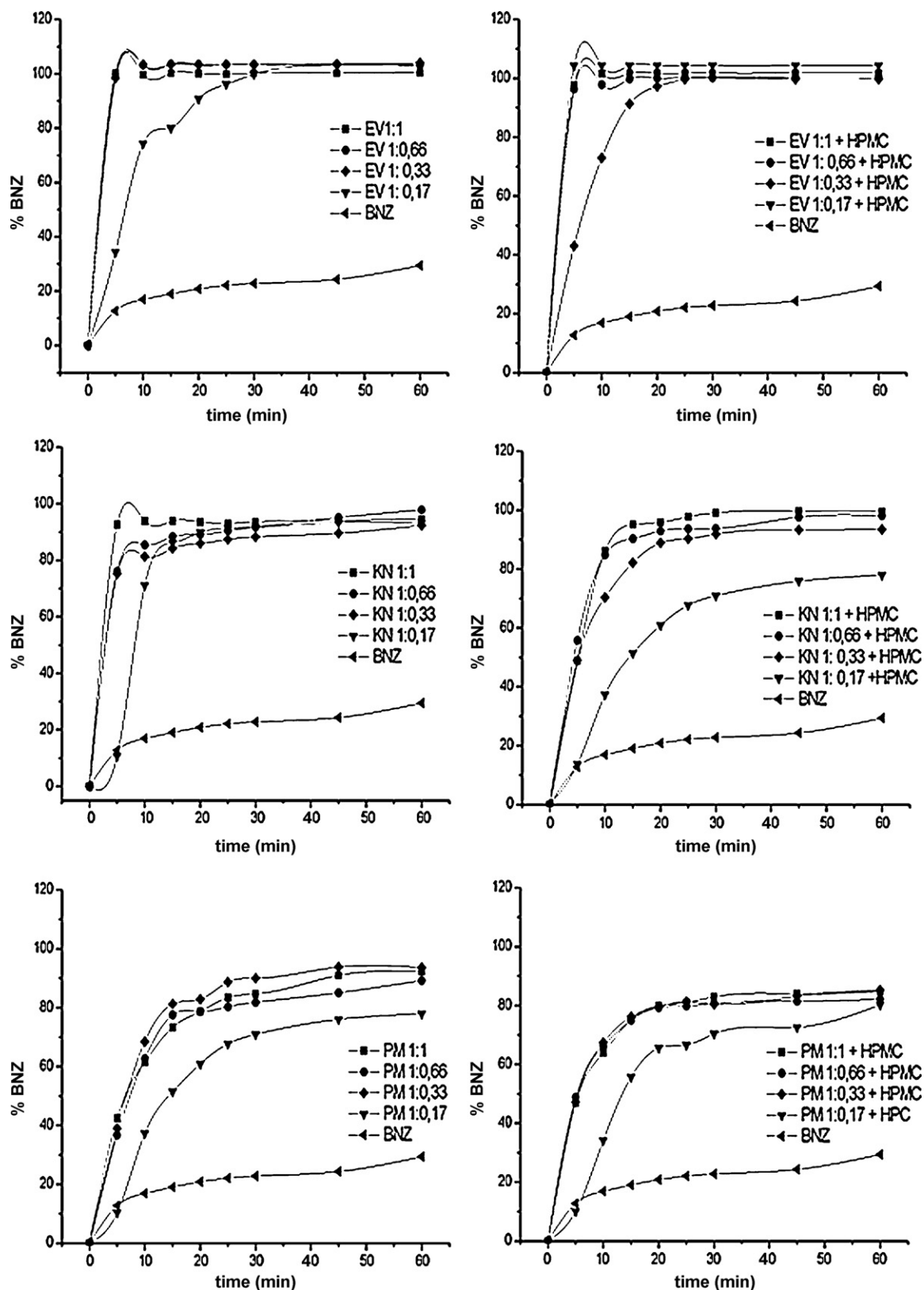


Fig. 5. Dissolution profiles for different BNZ:RM β CD proportions with and without 0.1% HPMC.

4. Conclusion

According to these results, the solid systems of cyclodextrin and benznidazole obtained using EV and KN showed a significant increase in solubility of BNZ, providing drug dissolution of more

than 80%. Although the greatest increase in solubility of the BNZ in ternary systems compared to binary systems in liquid state, the same influence was not observed in the solid state. This result is due to the low percentage of polymer contained in the systems. However, the ternary systems containing 0.1% HPMC did not

prove to have significant advantages over the binary systems of BNZ–RM β CD in solid state. In addition, the KN method and the 1:0.17 proportion of BNZ–RM β CD proved to be the most adequate for the development of a formulation, in view of the possibility of scaling this up to industrial levels of production and the low concentration of CD used, which also helps to cut the cost of development of a formulation.

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