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Extemporaneous benznidazole oral suspension prepared from commercially available tablets for treatment of Chagas disease in paediatric patients

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Abstract

OBJECTIVE To develop an extemporaneous 1% benznidazole (BNZ) suspension, with masked taste and adequate stability starting from available commercial tablets. The quality of compounding was evaluated through content uniformity measurement and physical and microbiological stability evaluation, under different storage conditions during 90 days.

METHODS Six batches of 1% BNZ suspension were prepared using safe excipients currently available in a galenic area of Hospital Pharmacy and then stored at 5 and 25 °C for 90 days. The BNZ content was determined by UV spectrophotometry. Physical stability was defined as the absence of colour, odour and/or flavour changes and the re-suspension of solid phase by a reasonable amount of simple 15-s shaking. The compliance with microbiological attributes of non-sterile pharmaceutical products was also evaluated.

RESULTS An oral liquid suspension, containing 1% of BNZ, was developed from commercially available BNZ tablets. The formulations stored for 90 days were easily re-dispersed after a simple 15-s shaking, ensuring the pouring of a liquid volume containing the desired dose of BNZ. All samples were within the acceptable range of BNZ concentration with minimal standard deviations. There were no detectable changes in colour, odour, viscosity, pH and microbial growth, complying with official quality requirements. The quality attributes were not affected by storage, room or refrigeration conditions or by the frequent opening or closing of the multidose containers.

CONCLUSION Paediatric oral liquid suspension containing 1.0% of BNZ was easily prepared starting from commercial tablets, being an interesting alternative for optimising the paediatric treatment of Chagas disease.

keywords benznidazole, chagas disease, compounding, oral paediatric suspension

Introduction

American trypanosomiasis or Chagas disease, a protozoan infection caused by the kinetoplastid *Trypanosoma cruzi*, constitutes a significant health problem in developing nations; it is still one of the major causes of morbidity and mortality from cardiovascular diseases in Latin America despite nearly one century of ongoing research [1, 2]. According to WHO, an estimated 20 million people are infected with this parasite and another 40 million are at risk of acquiring the disease. WHO considers Chagas a silent and chronic neglected disease [3]. The *T. cruzi* parasite is transmitted mainly by insect vectors; yet, congenital and transfusion-transmitted infections occasionally develop. However, in recent years, an increase in the congenital infection prevalence was detected, both in endemic and non-endemic regions, affecting between 1 and 10% of newborn babies from infected mothers [4].

In Argentina alone, during the last decade (2001–2010), the infection prevalence in pregnant women/patients dropped from 6.8 to 4.8%. An estimated 1300 congenitally infected babies are born every year who, if detected early, can be treated and cured. The average of infection prevalence in children under 14 years was 2.3% in 2010; fortunately, 90% of children treated in the acute phase and 70% treated in the chronic phase of Chagas disease are cured [5].

Benznidazole (BNZ) (Figure 1) developed more than 40 years ago is one of the two active compounds with a significant trypanocidal activity in the acute and early chronic phases [6]. BNZ is available only as 50- and 100-mg conventional tablet. Its poor water solubility (below 0.4 mg/ml) prevents the formulation of oral solution, and unfortunately, BNZ is not available in a convenient easy-to-take liquid dosage form [7]. Consequently, patients who are not able to swallow solid medicines, for

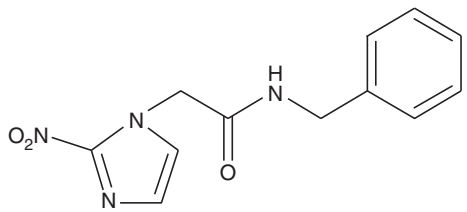

Figure 1 Molecular formula of benznidazole.

example neonates, infants, the elderly, may present with a special need. To assist the paediatric population, these tablets are usually split, crushed and dispensed in packets to be dispersed in fruit juice or milk. However, this situation may trigger some unwanted consequences, such as improper dosage, incomplete dissolution and further risks of developing side effects [8, 9].

Thus, there is a need to develop a convenient suspension starting from the available tablets in order to supply safe and reliable paediatric dosages. In this field, several approaches were reported, such as liquid solutions using co-solvents or suspensions [10–12], liposomes [13, 14], microparticles [15] and nanoparticles [16], which are still in early stages of development. However, low priority was set among governments and the pharmaceutical industry for funding the development of new dosage forms suitable for the treatment of this protozoan infection in young children [17].

To improve the paediatric treatment with the available solid dosage form and minimise the risk associated with improper dosage, this work focuses in the development of an extemporaneous 1% BNZ suspension with masked taste and adequate stability, starting from the available commercial tablets. It is expected that the formulated suspension can be prepared and dispensed by the Pharmacy Services of paediatric hospitals; therefore, safe excipients currently available in a galenic area of Hospital Pharmacy were selected.

Materials and methods

All generally recognised as safe excipients (GRAS) such as wetting agents, suspending agents, sweeteners, flocculant agents, antimicrobial preservatives, colourants and flavours were selected.

Suspensions were prepared from commercially available tablets, containing 100 mg of BNZ (batch RJ0357 Radanil®; Roche, Argentina) and the following chemical substances were used: Tween® 80 (batch 182/09, Parafarm®, Argentina), sodium carboxymethylcellulose (4000 cP, batch 00340300332/010, Parafarm®), acesulfame potassium (batch 20070203, Parafarm®), nipagin (Parafarm®), nipasol (Montreal®, Argentina), banana flavour (batch 0200145451, Parafarm®), strawberry flavour (batch BN00017824, Parafarm®), sunset yellow colourant (batch T7680709, Parafarm®), NaCl pa (batch 59599, Cicarelli®, Argentina), HCl 1 N (batch 21607-2, Anedra®, Argentina) and KCl (batch 59259, Cicarelli®).

Preparation of 1.0% BNZ suspension

Six batches of 900 ml of 1% BNZ suspension were prepared in accordance with the composition detailed in Table 1 and following this procedure: 90 commercial tablets of 100 mg BNZ were crushed in a mortar and then mixed with 0.9 g of Tween® 80 and about 90 ml of distilled water. In parallel, 6.3 g of sodium carboxymethylcellulose was sprinkled on 400 ml of distilled water and dispersed under moderate heating until homogenisation. Next, this dispersion was introduced into the mortar and the rest of powder excipients were added under constant mixing. The entire blend was transferred to a graduated cylinder of 1.0 l, and the remaining volume of distilled water was slowly incorporated. Finally, each batch of the suspension was bottled in 18 light-resistant glass containers of 50 ml (total: 108 containers of 50 ml) and stored under two pre-determined conditions: refrigerated and room temperature.

Stability evaluation

Each batch was divided into two groups of 54 containers and stored under room and refrigeration conditions, (25 ± 2) and (5 ± 2) °C, respectively. All samples were

Table 1 Qualitative and quantitative formula of 1.0% BNZ suspension

Component	Proportion (g)	Functional category
BNZ (eq. 10 tablets)	1.00	Active pharmacy ingredient
Polysorbate-80	0.10	Wetting and suspending agents
NaCl	0.90	
Sodium carboxymethylcellulose (4000 cP)	0.70	
Methylparaben	0.02	Antimicrobial preservatives
Propylparaben	0.02	
Acesulfame-K	0.05	Sweetening agent
Banana flavour (powder)	2.00	Flavouring agents
Strawberry flavour (powder)	2.00	
Sunset yellow colourant	*s.q.*	Colourant
Distilled water *s.q.t.*	100.00	Vehicle

s.q., sufficient quantity; s.q.t., sufficient quantity to.

labelled and stored for 90 days. To evaluate content uniformity and physical stability, samples of each suspension batch were collected on days 0, 7, 15, 30, 60, and 90 and all measurements were taken in triplicate; the results were expressed as the average with the standard deviation.

Physical stability evaluation. Physical stability was defined as the absence of colour, odour and flavour changes and the evaluation of re-suspension of cake solid phase by a reasonable amount of simple 15-s shaking [18]. Physical stability was assessed by visual examination, optical microscopy, determination of dynamic viscosity and measurement of the sedimentation volume of suspensions (V_s).

A morphological analysis of BNZ-suspended particles was conducted by means of 10 × optical microscopy (Olympus, BX41TF, Jp) with photographic digital camera. The photographs were analysed using Infinity Analyze software (Release 5.0.2) for Windows.

Thus, dynamic viscosity (η) of formulation was assayed on days 0, 15 and 90, using a rotational viscometer (VT500; Haake, Germany) equipped with NV-cylinder and NV-cup sensors. The upward and downward flow curves were performed at the interval of 0–60 r.p.m. and 60–0 r.p.m. in 60 s each segment. η was measured at constant shear rate of 60 r.p.m. during 60 s, and results were expressed in centipoise (cP).

The V_s of suspensions was calculated by the ratio between the measure of volume of the dispersion at different stored times (V_f) *vs.* the original volume of suspension (V_0) bottled in the container, according to eq. 1:

$$V_s = V_f / V_0 \quad (1)$$

V_s was determined at predefined times: 0, 24 and 48 h and after 7, 14 and 90 days of storage.

Content uniformity evaluation. Content uniformity as function of time was assessed following BNZ concentrations in the samples after re-dispersion of the stored formulation by simple 15-s shaking. BNZ concentrations were determined by UV spectrophotometry (Evolution 300; Termo Scientific, Switzerland), at 324 nm. To carry out the study, a sample of 1 ml of suspension of each batch was dissolved in HCl 1N; then, a one-tenth dilution in the same medium was spectrophotometrically assayed.

pH measurement. The pH values were recorded with a digital pH meter (SevenMulti S40; Mettler-Toledo, Switzerland) with an Ag/AgCl-reference electrode (DG-115-SG), calibrated with commercial reference buffer solutions of pH 4.01 and 7.00 (Anedra®, Argentina) in automatic temperature compensation mode.

Microbiological stability evaluation. Microbiological assessment of BNZ suspension was carried out on day 0, 30, 60 and 90 on the samples stored at room temperature. The samples were subjected to microbiological evaluation in order to determine whether they meet the microbiological attributes of non-sterile pharmaceutical products, which was set as total aerobic microbial count below 10^2 cfu/ml, total combined yeasts/moulds count below 2 cfu/ml and the absence of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli* and *Salmonella spp*. Microbial examination of non-sterile product was performed according to the methods given in the text on *microbiological examination of non-sterile products: Microbial Enumeration Test <61> and Test for Specified Microorganism <62>*. Limit content of microorganisms was performed according to the criteria given in the texts: *<1111>* USP-30 NF-25 and ANMAT N° 7667 disposition [18, 19]. The term 'growth' has been used in a special sense herein, that is to designate *the presence and presumed proliferation of viable microorganisms*. These studies were made on the Applied Chemistry Center (CEQUIMAP), Faculty of Chemical Sciences, National University of Cordoba.

Dissolution test. Dissolution tests of suspensions, on day 0 and 90, were carried out using *Apparatus 2*, paddles, USP-disolutor (Smart-AR7; Sotax, Switzerland), at 75 r.p.m. with 900 ml of HCl 0.1 N at 37.0 ± 0.5 °C as a dissolution medium. Aliquots of 4 ml of dissolution media were taken out at pre-determined times (15, 30, 45, 60, 90 and 120 min), and these volumes were replaced with fresh medium. The BNZ concentration dissolved was spectrophotometrically assayed. Dissolution tests of commercial tablets containing 100 mg of BNZ were used as a reference. The results were expressed as the average of three determinations with their SD.

Results and discussion

An oral liquid suspension, containing 1% of BNZ, was developed from commercially available BNZ tablets, using excipients recognised as safe for paediatric formulations [20] and currently available in a hospital pharmacy. The suspension was prepared through an easy and reproducible process under current good manufacturing practices of pharmaceutical compounding [21]. The formulation composition is reported in Table 1.

In a previous pre-formulation study (data not shown), different proportions of polysorbate-80 and sodium carboxymethylcellulose were assayed, using recommended concentration ranges [22], to evaluate the capacity of wetting in the dispersed phase. The resulting viscosity of the formulation, the sedimentation and the re-suspension of the solid phase by a reasonable amount of shaking were evaluated.

Stability evaluation

Table 2 shows content uniformity and physical stability descriptors of suspensions at 90 days of assay and at two different storage temperatures (5 and 25 °C). The suspension was orange-yellow with particles uniformly dispersed, and no changes of colour, odour and flavour were detected.

As well known, suspensions are unstable thermodynamic systems. Hence, suspended particles would sediment at a certain sedimentation rate, which is being the main reason why they have to be shaken before use, so as to ensure content uniformity [23]. A cake solid phase that cannot be resuspended by a reasonable amount of shaking is a primary indication of instability in a suspension. The official compendia do not specify values of V_s as quality requirement. However, with higher values of V_s and minimal variations of V_s over time, the formulation has been considered to remain in flocculated state assuring the easiness of re-suspension of sedimented particles [24, 25]. The presence of relatively large particles may suggest that excessive crystal growth has taken place.

The determination of V_s in the formulations showed a slight decrease in V_s between 0 and 7 days (Table 2). Afterwards, V_s remained relatively unchanged up to day 90. Figure 2 shows the morphological characterisation of the suspended BNZ particles. The sample displayed a uniform distribution with adequate particle sizes in the range of 35–63 μm [24], and the shape and size of suspended particles remained stable during storage.

According to Stoke's Law [26], increasing the viscosity of an aqueous vehicle will reduce the sedimentation rate of the suspended particles, thereby increasing the physical stability of the formulation. Criteria for acceptable viscosity levels of liquid oral preparations are not defined in official compendia. On the one hand, viscosity should be as high as possible to minimise particle sedimentation rate and prevent agglomeration and irreversible solid-cake sedimentation; on the other hand, it should be low so as to ensure the pouring of a liquid volume containing the desired dose [24, 25]. Figure 3 shows the flow curves of shear stress as a function of rotational speed for fresh and stored suspensions. Under assayed conditions, both the upward and downward curves presented identical pathways, suggesting a pseudoplastic flow with narrow or negligible thixotropy (a time-dependent recovery of the flow). The aged suspensions showed viscosity values slightly lower than those for freshly prepared ones. How-

Table 2 Stability parameters of 1.0% BNZ suspensions up to 90 days. Data expressed as average of three determinations with standard deviation (*SD*)

Parameters	Storage temp. (°C)	Storage time (days)					
		0	7	15	30	60	90
BNZ (% ± *SD*)*	25	104.1 ± 0.6	102.9 ± 0.7	102.3 ± 0.8	101.0 ± 0.7	100.4 ± 0.7	99.5 ± 0.7
	5		100.9 ± 0.8	100.7 ± 0.5	100 ± 1	99 ± 1	98 ± 1
pH ± SD	25	5.63 ± 0.06	5.63 ± 0.05	5.56 ± 0.05	5.54 ± 0.07	5.53 ± 0.06	5.50 ± 0.06
	5		5.59 ± 0.05	5.51 ± 0.05	5.57 ± 0.04	5.55 ± 0.04	5.55 ± 0.04
η† (*cP* ± *SD*)	25	71 ± 3	–	69 ± 3	–	–	64 ± 4
	5		–	67 ± 3	–	–	59 ± 3
Microbial growth‡	25	Negative	–	–	Negative	Negative	Negative
V_s	25	0.25 ± 0.01§	0.20 ± 0.01	0.19 ± 0.01	–	–	0.20 ± 0.02

There are no official acceptable levels defined for V_s and η values. Minimum or no changes of V and η values along the time set as criteria for physical stability.

*BNZ amount in the suspensions, expressed as % of initial concentration. BNZ concentration no less than 90% and no more than 110%, considered as criteria for acceptable levels of stability [18].

†η is the dynamic viscosity of suspensions, expressed as centipoises (cP).

‡Negative microbial growth according to the criteria given in the text <1111> USP-30 NF-25 and ANMAT N° 7667 disposition [18, 19].

§Sedimentation volume (V_s) of suspensions measured 20 h after preparation.

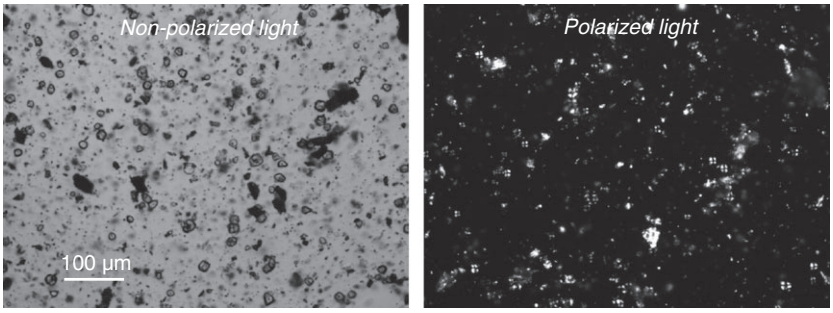

Figure 2 Optical microscopy images (10 ×) of BNZ suspensions prepared from commercially available tablets.

ever, the minimal changes observed on viscosity behaviour do not lead to quality attribute changes in the formulation.

In all cases, the stored suspensions were easily re-dispersed after a simple 15-s shaking, ensuring the pouring of a liquid volume containing the desired dose.

Content uniformity evaluation

According to USP-pharmacopoeia, the general criteria for acceptable levels of drug content uniformity in suspensions are not less than 90.0% and not more than 110.0% of the labelled amount of BNZ [18]. The content uniformity evaluation showed an acceptable re-dispersion of BNZ concentration, and all samples were within the acceptable range of BNZ concentration with minimal standard deviations (Table 2). Although it is well known that BNZ is chemically stable in aqueous media [12], under assayed conditions no significant decrease in BNZ concentration was detected; at least 98% of total BNZ could be quantified in an appropriate dosage volume (5 ml) for a period of at least 90 days. The suspension pH remained unchanged, showing slightly acid values between 5.0 and 6.8, generally recommended for oral liquid dosage forms [18].

Microbiological stability

The samples were subjected to microbiological evaluation in order to determine whether they fulfil the microbiological specifications of non-sterile pharmaceutical products, which is set as the total aerobic microbial count below 10^2 cfu/ml, the total combined yeast/mould count below 2 cfu/ml and the absence of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli and Salmonella spp*. All suspensions batches stored at room temperature (most unfavourable condition) showed no microorganism developed both on day 0 and after 90 days of storage (expressed as 'negative' in Table 2). The microbial examination test denoted the absence of microbial growth for the total aerobic microbial, the total combined yeast/mould,

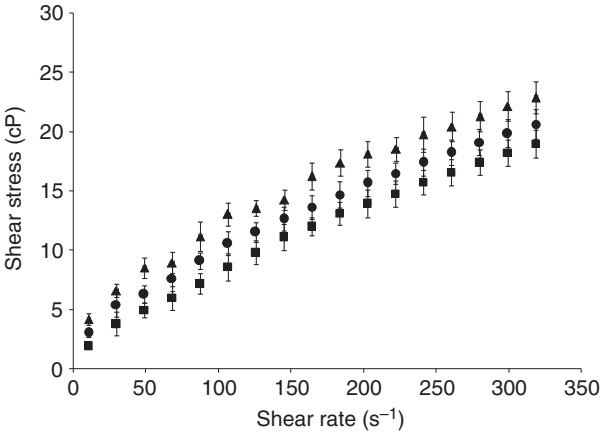

Figure 3 Flow curves of BNZ suspension prepared from commercially available tablets: (▲) fresh suspension, (●) suspension stored at 5 °C and (■) suspension stored at 25 °C.

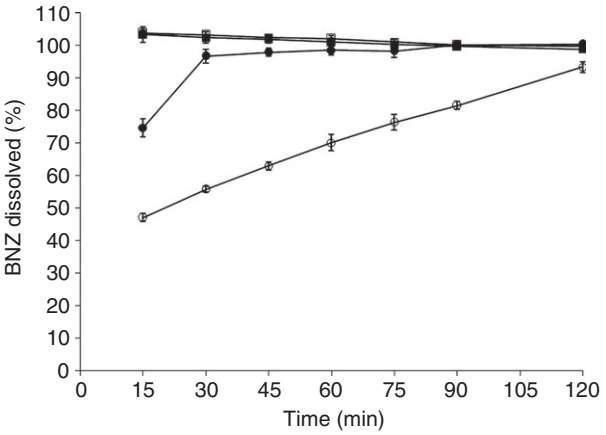

Figure 4 Dissolution profiles of BNZ suspensions, freshly prepared (□) and stored for 90 days at 25 °C (■) at 5 °C (▲); in comparison with intact (○) and crushed (●) commercially tablets (USP-apparatus 2, 75 r.pm., 900 ml HCl 0.1 M at 37 °C).

and the specific pathogens (*Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli and Salmonella spp*.) complying with official quality requirements [18, 19].

In vitro dissolution studies

Comparative *in vitro* BNZ dissolution performance from suspensions vs. available tablets was assayed and dissolution profiles are plotted in Figure 4. A faster dissolution rate of BNZ formulated as suspension showed a complete release ($Q_{100\%}$) before 15 min, while BNZ dissolution from intact commercial tablets did not exceed 50% of BNZ released at the same time. A faster but incomplete BNZ dissolution was obtained from milled powder of commercial tablets ($Q_{100\%} \geq 30$ min) simulating the current dosing practice.

The rapid and complete dissolution of BNZ from suspension could ensure more uniform drug absorption through the gastrointestinal tract and a potential increase in bioavailability which would result in greater efficacy than that in current paediatric treatments.

Finally, the results of this work indicate that BNZ reformulation as suspension ensures a more correct and convenient BNZ dosage form than the ones currently used in the Hospital Pharmacy Services, containing an amount of the drug in an appropriate volume of suspension for the administration of 0.5–0.7 ml/kg in newborns, babies or children. The formulation effectively disguises the unpleasant taste of BNZ, improving paediatric formulation acceptance and treatment adherence.

Conclusions

Paediatric oral liquid suspension containing 1.0% of BNZ was easily prepared starting from commercial tablets. The compounding shows adequate stability at least by 90 days, keeping all quality attributes required. The developed formulation is an interesting alternative, in terms of efficacy, safety and reliability, to be prepared in a Hospital Pharmacy Service for optimising the paediatric treatment of Chagas disease.

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