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RESEARCH ARTICLE

Chitosan microparticles: influence of the gelation process on the release profile and oral bioavailability of albendazole, a class II compound

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Abstract

Encapsulation of albendazole, a class II compound, into polymeric microparticles based on chitosan-sodium lauryl sulfate was investigated as a strategy to improve drug dissolution and oral bioavailability. The microparticles were prepared by spray drying technique and further characterized by means of X-ray powder diffractometry, infrared spectroscopy and scanning electron microscopy. The formation of a novel polymeric structure between chitosan and sodium lauryl sulfate, after the internal or external gelation process, was observed by infrared spectroscopy. The efficiency of encapsulation was found to be between 60 and 85% depending on the internal or external gelation process. Almost spherically spray dried microparticles were observed using scanning electron microscopy. *In vitro* dissolution results indicated that the microparticles prepared by internal gelation released 8% of the drug within 30 min, while the microparticles prepared by external gelation released 67% within 30 min. It was observed that the *AUC* and C_{max} values of ABZ from microparticles were greatly improved, in comparison with the non-encapsulated drug. In conclusion, the release properties and oral bioavailability of albendazole were greatly improved by using spraydried chitosan-sodium lauryl sulphate microparticles.

Keywords

Albendazole, bioavailability, chitosan, dissolution rate, microparticles

History

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Introduction

Albendazole (ABZ) is a benzimidazole carbamate with a broad-spectrum activity against human and animal helminth parasites widely used for the treatment of echinococcosis, hydatid cysts and neurocysticercosis[1,2]. Moreover, ABZ inhibits proliferation of a wide variety of cancer cells including a range of hepatocellular cancer cells and ovarian cancer cells[3,4]. ABZ, included in the World Health Organization Model List of Essential Drugs, belongs to the class II in the Biopharmaceutics Classification Systems (BCS). It is a poorly water soluble (1 μg/mL) and highly lipophilic (log *p* of 2.55) and, as a consequence, it is reported to present low and/or erratic bioavailability after oral administration, leading to a variable oral absorption ($\leq$5%)[5]. Then, several formulation strategies have been investigated to overcome this drawback including solid dispersions[6–8], liposomes[9], cosolvency[10], binary and ternary cyclodextrin complexes[11,12]. In particular, another alternative used to increase the dissolution rate of ABZ is the microencapsulation technology. In this context, chitosan (CH) has been used for the encapsulation of ABZ. CH, a biodegradable, biocompatible, and hydrophilic polymer with positive charge, has the ability to interact with anionic macromolecules or surfactants to form polyelectrolyte complexes[13]. By changing the type and amount of cross-linking agents, as well as, the cross-linking time with the carrier, the drug release rate may be modified and, as a consequence, the pharmacokinetic properties may be improved[14–17]. Simi et al. formulated polyelectrolyte complexes with chitosan (CH)–sodium alginate for colon delivery of ABZ. *In-vitro* studies revealed that ABZ could be successfully delivery to the target organ; however, no *in-vivo* data was provided[18]. Novel magnetic CH–sodium alginate beads prepared for the controlled delivery of ABZ were recently developed by Wang et al. It was shown that the beads possess excellent pH sensitivity in swelling ratio and super paramagnetic property as well as fast magnetic response[19]. In another study, Jain et al. prepared ABZ-Eudragit RL microspheres by the solvent evaporation method using a mixture of acetone and methanol[20], emulsified into liquid paraffin/Span 80. It was found that the polymer concentration and stirring rate influenced the drug loading and particle size of the microspheres. Later, Rai et al. reported the preparation of ABZ–CH microspheres by an emulsion method using glutaraldehyde in toluene as the cross-linking agent[21]. It was found that the influence of CH concentration on *in vitro* drug release from the microspheres was

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evaluated in simulated gastrointestinal fluids. ABZ released from CH microparticles was up to nearly 80% in 24 h. Although the emulsification process using organic solvents have been widely applied for the preparation of microparticles, such chemicals would meet some problems caused by toxicity[22]. Thus, an alternative encapsulation procedure, such as spray drying process, is a suitable methodology in order to avoid the mentioned drawbacks. It is highly reliable, reproducible, and offers the possibility of controlling the particle size and morphology[23,24]. Recently, spray-dried ABZ microparticles using a variety of polymers, such as hydroxypropylmethylcellulose (HPMC), polyvinylalcohol (PVA), and polyvinylpyrrolidone (PVP) were prepared and *in-vitro* characterized. It was concluded that the loss of ABZ crystalline state contributed to increase the drug dissolution rate[25]. However; no studies on the impact of the oral bioavailability from those ABZ spray-dried microparticles were performed. Therefore, the aim of this work was to evaluate whether CH, a cationic carrier, and sodium laurylsulphate (SLS), an anionic crosslinking agent, may interact to form a polymeric network in order to modify the dissolution rate and oral bioavailability of ABZ. The preparation of ABZ–CH–SLS microspheres was performed by spray-drying, following two procedures based on an internal or external gelation processes. The microparticles were characterized by X-ray powder diffractometry (XRD), infrared spectroscopy (IR) and scanning electron microscopy (SEM) techniques. In addition, *in-vitro* dissolution profiles and further oral bioavailability studies in rats were carried out. To our knowledge, *in-vitro* and *in-vivo* studies of ABZ–CH spray dried microparticles prepared by internal and external gelation, have not been elucidated to date.

Materials

ABZ, SLS and CH (molecular weight <300 000 Da, degree of deacetylation >85%) were supplied by Aldrich Chemical Co. (Milwaukee, WI). All other chemicals were of analytical grade.

Methods

Preparation of ABZ–CH microparticles by internal gelation (M-1)

The M-1 methodology is shown in Figure 1. Briefly, ABZ (100 mg) was dissolved at room temperature in glacial acetic acid (30 mL) and then, distilled water was added to obtain a final concentration 30% v/v. A given amount of CH (0.5% w/v) was dispersed in the acetic acid-ABZ solution and stirred by 5 min. To the resulting solution, 100 mL of SLS (0.2% w/v) were added and the solution was stirred by 20 min. Then, the final solution was fed to the nozzle via peristaltic pump using a Büchi Mini dryer B-290 (Flawil, Switzerland). The following parameters remained constant: airflow rate 38 m^3/h, feed rate 5 mL/min, and aspirator set at 100%. The spray-drying inlet temperature was set at 130 °C; the outlet temperature was recorded at 70 °C. After spray-drying for 40 min, the powders were removed from the collector vessel and stored at 40 °C. For the preparation of blank microparticles, without ABZ, the following procedure was carried out: CH (0.5% w/v) was dispersed in the acetic acid solution (10 mL) and stirred by 5 min. To the resulting solution, 50 mL of SLS (0.2% w/v) were added and the solution was stirred by 20 min. Then, the final solution was fed to the nozzle via peristaltic pump using a Büchi Mini dryer B-290 (Flawil, Switzerland) applying the spraying parameters already described.

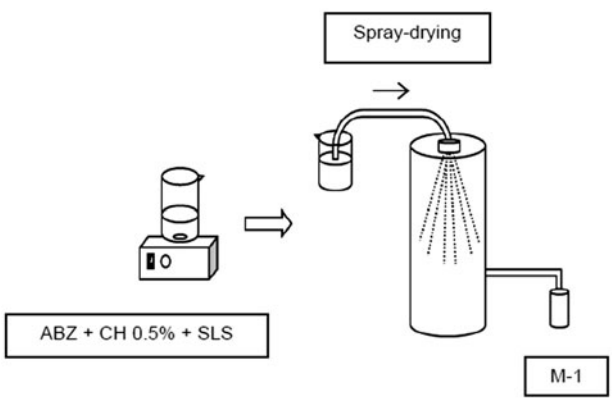


Figure 1. Internal gelation spray drying procedure (M-1).

Preparation of ABZ–CH microparticles by external gelation (M-2)

The M-2 methodology is shown in Figure 2. Briefly, ABZ (100 mg) was dissolved at room temperature in glacial acetic acid (30 mL) and then, distilled water was added to obtain a final concentration 30% v/v. A given amount of CH (0.5% w/v) was dispersed in the acetic acid-ABZ solution and stirred by 5 min. This solution was fed to the nozzle via peristaltic pump following the parameters detailed above. After spray-drying for 20 min, the powders were removed from the collector vessel and added to a solution of 100 mL of SLS (0.2% w/v). The mixture was magnetically stirred by 2 h and fed to the nozzle via peristaltic pump using a Büchi Mini dryer B-290 using the parameters already detailed. For the preparation of blank microparticles, the same procedure was carried out as follow: CH (0.5% w/v) was dispersed in the acetic acid solution (10 mL) and stirred by 5 min. This solution was fed to the nozzle via peristaltic pump applying the parameters detailed above. After spray-drying for 20 min, the powders were removed from the collector vessel and added to a solution of 50 mL of SLS (0.2% w/v). The mixture was magnetically stirred by 2 h and fed to the nozzle via peristaltic pump using a Büchi Mini dryer B-290, as already described.

Encapsulation efficiency

Encapsulation efficiency (EE) was determined by dissolving 30 mg sample in 0.1 N HCl. The suspension was incubated, for 24 h, at room temperature under magnetic stirring (300 rpm) to dissolve the particles. The amount of ABZ in each sample was determined by measuring the absorbance spectrophotometrically (LKB-Pharmacia Ultrospec II, Cambridge, UK) at 291 nm, according to Equation (1):

$$\text{Encapsulation efficiency}\,(\%) = 100 \times (W_{ABZ}/W_t) \quad (1)$$

Where W_{ABZ} is the actual ABZ content and W_t is theoretical ABZ content in the microparticles. Each experiment was performed in triplicate[26].

Dissolution studies

Dissolution studies were performed in 900 mL HCl 0.1 N at 37 °C, according to U.S. Pharmacopeia (USP) Apparatus 2 (SR8 8-Flask Bath, Hanson Research, Chatsworth, CA) with paddle rotating[27] at 50 rpm. Samples of ABZ alone, M-1 and M-2 equivalent to 100 mg of the drug were spread on the surface of the dissolution medium and the time 0 was recorded. At appropriate time intervals (10, 20, 30, 40, 50, 60, 90 and 120 min), 5 mL of samples were withdrawn, and filtered (pore size 0.45 mm). The amount of released ABZ was determined by UV analysis, as described in ''Encapsulation efficiency'' section. The results presented are mean values of three determinations. Preliminary tests demonstrated that there was no change in the λ max of ABZ due to the presence of the carriers dissolved in the dissolution medium.

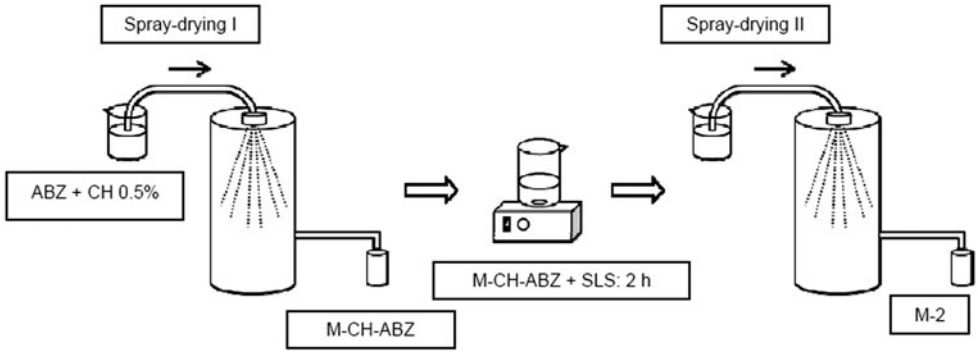


Figure 2. External gelation spray drying procedure (M-2).

Batch reproducibility

In vitro dissolution specifications are established to ensure batch-to-batch consistency and to signal potential problems with *in vivo* bioavailability.

The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f_2 = 50 \log \left\{ \left[1 + (1/n) \sum t = 1^n (R_t - T_t)^2 \right]^{-0.5} 100 \right\} \quad (2)$$

where n is the number of time points, R_t is the dissolution value of the reference batch at time t, and T_t is the dissolution value of the test batch at time t.

For curves to be considered similar, f_2 values should be close to 100. Generally, f_2 values greater than 50 (50−100) ensure sameness or equivalence of the two curves.

Three batches of the formulations were prepared and their release characteristics were evaluated. *In vitro* release data pertaining to reproducibility studies were compared by f_2 metric (similarity factor) values in accordance with previous report[28].

Scanning electronic microscopy

Morphology and surface of the microparticles were analyzed by SEM (AMR 1000 Scanning Microscope, Wetzlar, Germany). Samples were previously sputter-coated with a gold layer. The pictures were taken at an excitation voltage of 20 Kv.

X ray powder diffraction

X-ray diffraction patterns from the microparticles were recorded on a X'Pert Phillips MPD difractometer (Eindhoven, The Netherlands) using CuKα radiation ($\lambda = 1.540562$ Å), a voltage of 40 kV, 20 mA current and steps of 0.02° on the interval $2\theta = 10°$–$40°$. Low peak broadening and background were assured by using parallel beam geometry by means of an X-ray lens and a graphite monocromator placed before the detector window.

Fourier-transform infrared spectroscopy

Fourier-transform infrared spectra of CH, SLS and CH–SLS blank microparticles were obtained by a FT-IR-Prestige-21 Shimadzu spectrometer (Tokyo, Japan) using the KBr disk method (2 mg sample in 100 mg KBr). Scanning range was 800–3800 cm^{-1} with a resolution of 1 cm^{-1}.

Bioavailability studies

Male Wistar rats (250–300 g) were used in all experiments. The animals were allowed to access to standard laboratory diet and water *ad libitum*, freely prior to the experiment and received care in compliance with international regulations. The protocol was approved by the Animal Care and Use Committee of the National University of Rosario (Permit Number: 648/2012). The number of animals used in the experiment was 3 ($n = 3$). Aqueous dispersions of M-1 and M-2 microparticles containing 1.5 mg ABZ/mL were prepared for this study. For comparison, ABZ suspended in distilled water (ABZ-W) containing ABZ 1.5 mg/mL was prepared and used as a reference. The formulations were administered orally via bucco-gastric tube. After drug administration, blood samples were collected from the tail vein at the following time intervals: 0.25, 0.5, 0.75, 3, 5 and 24 h. Then, the blood samples were heparinized and centrifuged individually. Blood samples were collected into heparinized tubes, centrifuged at 4 °C for 10 min at 6800 rpm and the plasma samples were stored at −20 °C until HPLC analysis.

Drug analysis

Two-hundred microliters of plasma was added to 1 mL of methanol (Mallinekradt Chemicals) in a glass test tube and stored at −20 °C. Then, the residual protein was separated through centrifugation (12 000 × *g*, 4 °C for 12 min). Samples were concentrated to dryness in a vacuum concentrator and then reconstituted with 500 µL of mobile phase until being analyzed by a validated HPLC method. Plasma samples were analyzed using an Agilent 1100 HPLC with UV detector (Alpharetta, GA). Fifty microliters of each previously extracted sample was injected and the analytes eluted (flow 1.2 mL/min) from the analytical column using a linear gradient method as reported[7] Dib et al. The main metabolite, albendazole sulfoxide (ABZSO), was identified by the retention time of pure reference standard[29,30]. The concentration versus time curves for ABZSO in plasma for each individual animal after the different treatments were fitted with PK Solution 2.0 (Summit research services, Ashland, OH). A biexponential concentration–time curves for ABZSO after the oral treatment were used. The peak concentration (C_{max}) and time to peak concentration (T_{max}) were displayed from the plotted concentration-time curve of each administered formulation. The $AUC_{0-\infty}$ was calculated as the sum of AUC_{0-24} and $AUC_{24-\infty}$. Also, the AUC_{0-24} was calculated by the trapezoidal rule method and $AUC_{24-\infty}$ was estimated as the quotient between C_{24} and K_e.

Statistical analysis

Results are presented as mean ± standard deviation and the number of animal treatment was three for each formulation. Statistical significance of the differences between values was assessed by analysis of variance (ANOVA) followed by Schefe's multiple range tests. A p value less than 0.05 were considered statistically significant (Statgraphics, Statistical Graphics System, Rockville, MA).

Results and discussion

Microparticles preparation

According to literature survey, the preparation of CH–SLS complex as carrier for ABZ using the spray-drying procedure with internal and external gelation has not been reported to date. The formation of the corresponding microparticles is through the interaction of the NH_3^+ cation, and the anionic groups from SLS. The interaction between the opposite charges is the main reason of the new network polymeric formation and further precipitation of the microparticles, without any agglomeration[31]. Figures 1 and 2 show the formulations developed according the following procedures:

Internal gelation procedure: In this case, the microparticles were obtained by mixing under magnetic stirring during 20 min the ABZ–CH solution and the anionic SLS. Then, the resulting mixture was spray dried to yield the corresponding ABZ–CH–SLS microparticles (M-1).

External gelation procedure: First, the ABZ–CH acidic solution was spray dried to yield a solid product. Then, these ABZ–CH microparticles were dispersed in an aqueous solution and mixed under magnetic stirring during 120 min with SLS. Finally, the solution was spray dried to yield the corresponding ABZ–CH–SLS microparticles (M-2).

The EE was 82 and 85% for M-1 and M-2, respectively (Table 1). Regarding the efficacy of the methodology, ABZ–CH microparticles prepared by internal gelation (M-1) were obtained with high yields (85%) while the corresponding microparticles prepared by external gelation (M-2) were obtained in moderate yields (60%). In this case, the loss of material may be attributed to the manipulation related with the second step process, as well as, to the adherence of the powder to the walls of dryers during the spraying process[24].

SEM characterization

The morphology and surface topography of ABZ–CH–SLS microparticles were examined by SEM (Figure 3). Both M-1 and M-2 microparticles were found to be almost spherical possessing a compact structure on the surface. As observed, the morphology and surface of M-1 and M-2 were very similar, despite of the different gelation processes, indicating that the spray drying methodology was a convenient approach for the preparation of these types of microparticles.

Table 1. Range of size, Q_{30}, EE and yield of ABZ–CH microparticles.

Microparticles	Encapsulation efficiency (%)	Yield (%)	Q_{30} (%)*
M-1	82.45 ± 1.96	84.12 ± 3.87	7.76 ± 2.76
M-2	84.70 ± 3.34	59.89 ± 4.67	66.23 ± 3.12
ABZ(pure drug)	–	–	19.45 ± 3.23

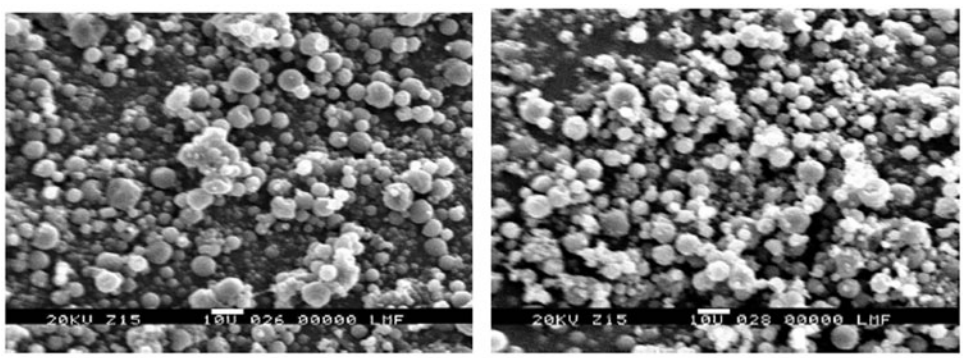
*Q_{30}, percent of ABZ dissolved at 30 min.

X-ray powder analysis

Powder X-ray diffraction patterns for ABZ and the microparticles are shown in Figure 4. The spectrum for ABZ exhibited several reflection peaks revealing its crystalline nature in the range of 10–30° 2θ. The crystalline peaks located at 7.3°, 11.8°, 18.5° and 24.7° (2θ) are attributed to ABZ crystals[25]. The diffractograms of M-1 and M-2 displayed amorphous patterns, indicating that the drug underwent a transition from a crystalline to an amorphous state. In comparison with the drug alone, all the peaks of ABZ were absent in case of the microparticles. According to these results, the amorphous fraction of ABZ may be considered to be mainly responsible for the dissolution enhancement, as shown in Figure 4. In addition, it should be note that a similar transition of ABZ degree of crystallinity was observed[25] by Alanazi et al.

FTIR analysis

As already described[32,33], FT-IR is a very useful technique to evaluate the interactions of blank polyelectrolyte complexes between CH and compounds of opposite charge. In agreement with Elsayed et al., in this study, the FT-IR analysis of CH, SLS and CH–SLS blank microparticles were performed to evaluate whether the gelation process between CH and SLS would lead to the formation of a novel polymeric structure[31]. As seen in Table 2 the main signals of CH are due to stretching vibrations of OH groups in the range from 3750 cm^{-1} to 3000 cm^{-1}, which are overlapped to the stretching vibration of N–H; and C–H bond in $–CH_2$ ($\nu_1 = 2920\ cm^{-1}$) and $–CH_3$ ($\nu_2 = 2875\ cm^{-1}$) groups, respectively. The absorption band of the carbonyl stretching of the secondary amide (amide I band) at 1645 cm^{-1}, and the bending vibrations of the N–H (amide II band) at 1599 cm^{-1}. The C–H bending vibrations are detected in the region of 1421–1380 cm^{-1}. The characteristic broad signals at the region of 1092–988 cm^{-1} are attributed to carbohydrate ring (C–OH, C–O–C and CH_2–OH)[31]. On the other hand, the spectra of SLS shows the typical alkyl chain band (CH_3 and CH_2) in the region of 2900–2800 cm^{-1}, the asymmetric $–SO_3–$ stretching signals at 1219 and 1084 cm^{-1}, and an asymmetric signal in the region of 1000–930 cm^{-1} (C–O–C). As shown in Table 2, it was observed in the CH–SLS blank microparticles, prepared by internal gelation (M-1 without ABZ), that the absorption band at



M-1 M-2

Figure 3. Scanning electron microscopy (SEM) ABZ (raw material) and the microparticles.

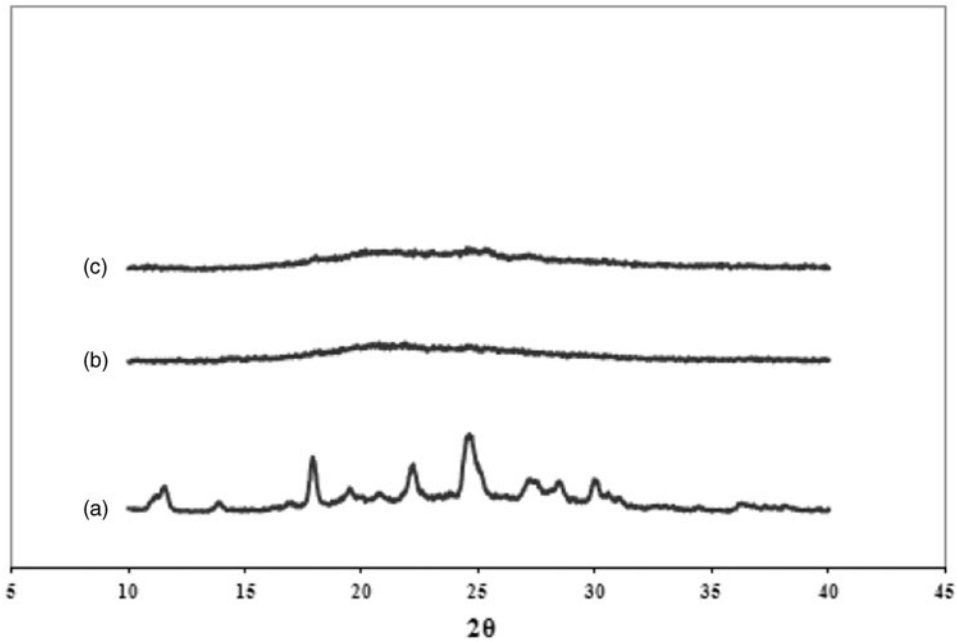


Figure 4. X-ray diffraction patterns: ABZ – pure drug (a), M-1 (b), M-2 (c).

Table 2. FT-IR data of CH, SLS and CH–SLS blank microparticles.

	CH	SLS	CH–SLS blank microparticles*	CH–SLS blank microparticles†
IR band (cm^{-1})/Description	3750–3000 ν(O–H)			
	2920 ν(C–H)			
	2875 ν(C–H)			
	1645 ν(C=O)			
	1599 ν(C=O)		1631 ν(C=O)	1622 ν(C=O)
	1421, 1380 δ(C–H)		1486, 1384 δ(C–H)	1470, 1380 δ(C–H)
	1092–988 ν(C–OH, C–O–C, CH_2OH)			
		2960–2800 ν(CH_3, CH_2)		
		1219–1084 ν(–SO_3–)	1113 ν(–SO_3–)	1100 ν(–SO_3–)
		1000–930 ν(C–O–C)		

*CH-SLS blanck microparticles prepared by means of M-1 procedure (internal gelation) without ABZ.
†CH-SLS blanck microparticles prepared by means of M-2 procedure (external gelation) without ABZ.

1599 cm^{-1} of CH shifts to 1631 cm^{-1}, the C–H vibrations shifted to 1486 and 1384 cm^{-1}, and the stretching vibration of –SO_3– at 1219 and 1084 cm^{-1} moved to a broad band at 1113 cm^{-1}. Similarly, the CH–SLS blank microparticles prepared by external gelation (M-2 without ABZ) showed that the C=O band shifted from 1599 cm^{-1} to 1622 cm^{-1}, the C–H vibrations shifted to 1470 and 1380 cm^{-1}, and the stretching vibration of –SO_3– at 1219 and 1084 cm^{-1} moved to a broad band at 1100 cm^{-1}. In both cases, the shifting of the main peaks of CH and SLS demonstrate electrostatic attractive interactions between them, suggesting the formation of a polyelectrolyte complex[31].

Dissolution studies

The drug dissolution rate was studied under non sink conditions, by fitting a sigmoidal equation with three parameters.

$$\%\,\text{drug release} = \alpha/1 + \exp\left[-(x-\beta)/\gamma\right] \quad (3)$$

where α: % drug release (time $\rightarrow\infty$) (upper asymptote) is the value that tends the percentage of drug dissolved at infinite time. β: t 50% time corresponding the percentage of drug dissolved is equal to half the maximum. γ: parameter related with the dissolution rate.

The dissolution behavior fitted a sigmoidal release profile, characterized by slower release at initial stage followed by increased release rate at later stage. The results showed a bimodal release profile for M-1 and M-2 (Figure 5), probably due, in part, to the formation of a novel polymeric structure, observed by FT-IR, and the morphology of the ABZ microparticles obtained by means of spray drying technique. ABZ is poorly soluble in water (1 μg/mL) and it is well demonstrated in the extent of drug dissolved after 60 min (7%). On the other hand, the release of ABZ from the microparticles prepared by internal gelation (M-1) was 11% within 60 min, while nearly 24% of drug was released after 180 min indicating that the internal gelation process between CH and SLS is capable of controlling the drug release. In contrast, when SLS was added to the ABZ–CH microparticles (external gelation process) 80% of the drug was released within 60 min, while after 180 min nearly 100% of the drug was released. It can be postulated that the addition of the surfactant to the already formed CH microparticles, produced a gelation on the surface of the particle. Then, the surfactant properties of SLS resulted in a greater wetting and increase the surface available for dissolution by reducing the interfacial tension between the hydrophobic drug and the dissolution media. It should be mention that the results obtained herein are opposite to other works, in which, the

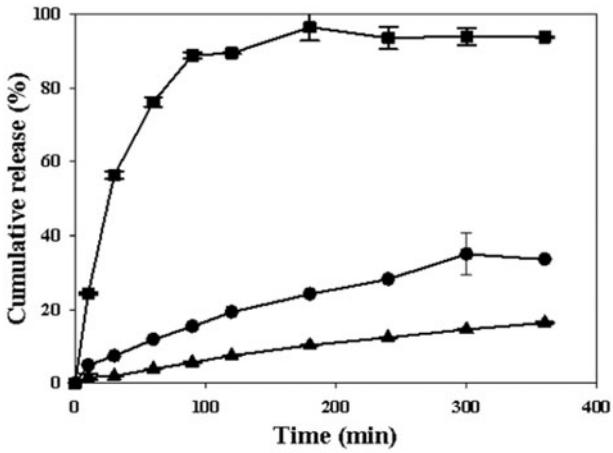


Figure 5. Dissolution profile of ABZ in HCl 0.1 N at 37 °C ($n = 3, \pm$ SD) of 100 mg ABZ pure drug (▲) and the same dosage prepared according to M-1 (●) and M-2 (■).

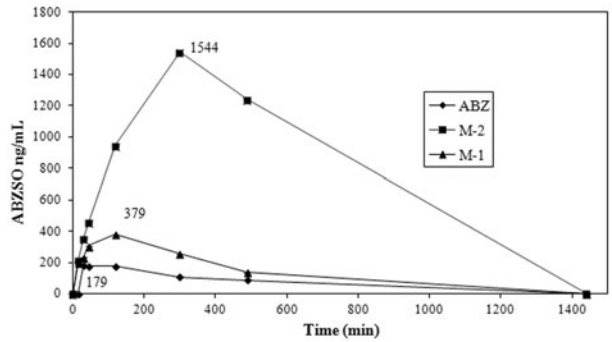


Figure 6. Plasma concentration of ABZSO after the oral administration of ABZ (pure drug), M-1 and M-2.

extension of the crosslinking time produced a more crosslinked structure and, as a consequence, a more sustained drug release[15,16,34–38]. In particular, it is worthy of mention that M-2 formulation was able to increase the ABZ dissolution rate more than six times in comparison with the non encapsulated drug (Table 1).

Batch reproducibility

Three batches of each formulation were prepared and the dissolution rate was performed as previously decrypted in the section ''Dissolution studies''. No significant difference was observed in the release profiles of the formulations between different batches, as indicated by f_2 metric (similarity factor). The obtained f_2 values were higher than 50%. Due f_2 values higher than 50% are indicatives no significant differences between batches, this study indicated that the formulation methodologies employed were found to be suitable for formulation of ABZ microparticles.

Bioavailability studies

ABZ presents poor intestinal absorption (<5%) due to its low aqueous solubility being this property a major determinant of the variability in plasma levels and efficacy[7]. Thus, the increase of ABZ dissolution rate becomes crucial for achieving improved pharmacokinetic parameters. As described in this study, the ABZ dissolution profile was remarkably enhanced in the M-2 formulation in comparison with the M-1 formulation. To evaluate the relationship between the ABZ dissolution rate and the plasma concentration values, pharmacokinetic studies were carried out. The plasma concentration versus time profile after 24 h and the pharmacokinetic parameters are showed in Figure 6 and detailed in Table 3. The analysis showed that ABZ, as a parent drug, was not detected in plasma. ABZSO, the active metabolite, was detected in plasma during the 24 h. From the data, it can be concluded that there was a significant difference in the rate of absorption of ABZ from the assayed formulations. The results showed that the C_{max} of ABZ after oral administration of M-1 and M-2 formulations were 2.20- and 9-fold higher than the drug dispersed in water (ABZ-W), respectively. After oral administration of the ABZ-loaded microparticles M-2, the peak plasma ABZSO concentration and the time required to reach the highest ABZSO concentration were both higher than those obtained after administration of non encapsulated ABZ.

Table 3. Comparative pharmacokinetic variables for ABZSO after the oral administration of ABZ (parent drug), M-1 and M-2.

	$AUC_{0-\infty}$ (μg min/mL)	C_{max} (μg/mL)	T_{max} (min)
Group 1 (ABZ)	47 ± 9	0.17 ± 0.08	120
Group 2 (M-2)	404 ± 20*	1.54 ± 0.07*	300
Group 3 (M-1)	149 ± 6†	0.37 ± 0.05†	120

Statistical significance of the differences between values was assessed by analysis of variance (ANOVA) followed by Schefe's multiple range tests. A p value less than 0.05 was considered statistically significant.
*Different from group 1 and 3.
†Different from group 1.

The T_{max} of M-2 formulation was observed to be greater than the other polymeric formulation, due to the structure originated by the external gelation procedure, which might act as a barrier for the *in vivo* drug behavior from the system[39–41]. Following a trend observed in the dissolution assay, there was a significant enhancement on oral bioavailability of ABZ from M-1 and M-2 microparticles. Clearly, an increase of 300% in the *AUC* data from M-1 was obtained. M-2 showed an *AUC* almost 900% higher than the pure drug and the T_{max} was observed after 5 h of the oral dose. The comparative plasma pharmacokinetics plots revealed significant increased concentrations and *AUC* values after the oral administration of the microparticles formulations. It is worthwhile to mention that the improvement of the bioavailability of ABZ may result in better outcome of treatment by modifying the dose regimen.

Conclusions

CH–SLS microparticles for the oral administration of ABZ were prepared by internal and external gelation by means of spray-drying methodology. FT-IR analysis suggested the formation of a novel polymeric structure between CH and SLS, after the interaction between CH and SLS. A markedly influence of the gelation process on the drug release rate was observed for both ABZ–CH–SLS formulations. Particularly, M-2 microparticles, prepared by external gelation, was able to increase the ABZ dissolution rate more than six times in comparison with the non-encapsulated drug. A significant improvement on the oral bioavailability of ABZ from the prepared microparticles, in comparison with the drug alone, was successfully achieved. Therefore, the polymeric carrier yielded from the ionic interaction between CH and SLS may be employed as a promising alternative for the delivery of ABZ.

Declaration of interest

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