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Effect of 70-kDa and 148-kDa dextran hydrogels on praziquantel solubility

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Abstract Praziquantel is an anthelmintic widely used in the treatment of schistosomiasis. Although a highly permeable drug, praziquantel is poorly soluble in water, limiting its bioavailability. Improving the solubility of poorly water-soluble drugs has become an important issue for analysis in pharmaceutical research. The use of dextran hydrogels is an advantageous strategy and the focus of extensive research. In this study, several hydrogels were developed from homologous polymer blends using 70 and 148 kDa dextrans in different proportions containing praziquantel, with the aim of evaluating the effects of polymeric release systems on the solubility of poorly water-soluble drugs such as praziquantel. Nine formulations were prepared, and the solubility of the drug incorporated was assessed. Three of the formations were selected to be characterized by DSC for the study in order to gain a better understanding of the thermal behavior of praziquantel incorporated into dextran hydrogels and the influence of polymers on the solubility of the drug, complemented by XRD and SEM techniques. According to the results, formation of crystallites of praziquantel occurred, probably due to the preparation procedures of the formulations, covering the surface of the polymer matrix and promoting a slight improvement in solubility. These data show that the use of hydrogels for the purposes of improving the solubility of poorly water-soluble drugs represents an effective strategy.

Keywords Praziquantel · Dextran · Homologous polymer blend · Hydrogels · Solubility · Thermal analysis

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Introduction

Praziquantel (PZQ) is a broad spectrum anthelmintic drug, the only product commercialized for the treatment and preventive chemotherapy of all forms of schistosomiasis. This disease is one of the most damaging and prevalent neglected tropical diseases and affects areas such as Africa, Asia and Latin America, infecting around 230 million people and placing a further 600 million at risk of infection [1–5]. The drug is classified as class II in the biopharmaceutical classification system (BCS), under which drugs are ranked into four different classes according to their aqueous solubility and gastrointestinal permeability. Thus, praziquantel is characterized by high membrane permeability and low aqueous solubility, exhibiting erratic or incomplete absorption leading to poor bioavailability [1, 5, 6]. Moreover, high doses should be administered to ensure a sufficient concentration for the drug to reach its target of action. Its high liposolubility and first-pass metabolism after oral administration renders PZQ a less effective substance in combating the parasite [3, 7].

Dissolution of the drug under physiological conditions is determined by its aqueous solubility. Thus, drug solubility is critical to the therapeutic efficacy of a pharmaceutical product, regardless of its route of administration. Controlled drug delivery systems have long been the focus of extensive

research to overcome problems of poorly water-soluble drugs [8, 9]. A strategy investigated for this purpose that has yielded technological advances for the development of delivery systems is the use of polymers in their design [10, 11]. Many drugs formulations have polymers in their composition as excipients, usually polymers of natural origin considered safe in vivo [12]. A group of natural polymers that has probably led to most advances in the development of drug delivery systems technology is the class of polysaccharides, obtainable from various sources such as seaweed, plants, fungi, bacteria, animals and crustaceans [11, 13]. Polysaccharides are hydrophilic, biocompatible, biodegradable, non-immunogenic and non-antigenic. In addition to being safe and stable, these materials have functional groups such as carboxyl, hydroxyl and amino groups, which can be physically or chemically modified to achieve a wide range of properties that may be adapted according to specific needs [12, 14, 15]. Among the various polysaccharides, dextran (DEX) stands out as a bacterial polyanionic carbohydrate that has low protein adsorption and is non-toxic, highly soluble in water, biocompatibility and consists of linear 1,6-glucopyranose units linked with a certain degree of 1,3-branching, found in different molecular weights forming hydrogels [12, 16–19].

Hydrogels can be defined as three-dimensional polymeric networks capable of incorporating large amounts of water or biological fluids, while retaining their structure [20–23]. Polymeric hydrogels have been frequently studied, including dextran hydrogels, because they preserve drugs from harsh environments such as the stomach, and are also able to control the release of drugs [20, 24]. The hydrogels prepared from polysaccharides offer several advantages, including low toxicity, biocompatibility and biodegradability [21].

Pharmaceutical researchers currently use thermal analysis to solve practical problems encountered, for example, at the pre-formulation stage [25, 26]. A thermoanalytical technique commonly adopted in the pharmaceutical research area is differential scanning calorimetry (DSC), employed in the characterization of drugs, in screening studies of compatibility, purity, stability and polymorphism [27]. This technique was chosen for its several advantages such as speed, the need for only small amounts of sample and ease in identifying interactions, polymorphisms, glass transition and changes in crystalline and/or amorphous states [25]. Among the many uses of thermoanalytical techniques, the study of compatibility between drugs and excipients in pre-formulation is one of the fields in which DSC is widely employed [25, 26]. Although not all interactions, whether physical or chemical, are a sign of incompatibility, they are evidence that an event is taking place between these two components and can be used in planning the development of new devices for controlling the release of drugs [26].

In previous studies by our research team [28], dextran 70 kDa hydrogel containing praziquantel was developed and DSC proved important for elucidating and furthering knowledge about the changes in the solubility of praziquantel and the mechanism of drug release. According to DSC curves, a weak interaction between the drug and the polymer was observed, which could lead to slightly lower solubility, influence the swelling profile and, consequently, prolong praziquantel release [28]. Drawing on the data obtained, the aim of this study was to evaluate the possibility of an improvement in solubility of the poorly water-soluble drug. For this purpose, several hydrogels were developed from homologous polymer blends, utilizing 70 kDa dextran (DEX-70) and 148 kDa dextran (DEX-148), containing praziquantel, which were subsequently characterized and assessed for praziquantel solubility.

Materials and methodology

Materials

Dextran 70000 (TCI®), absolute ethanol 99.5 % (Synth®), Dextran 148000 (Sigma®) and praziquantel (Shangai Pharmaceutical®) were used as received.

Methodology

Preparation of hydrogels and physical mixture

The incorporation of praziquantel into hydrogels (HG) was achieved by the solvent casting process, as in the method developed by Campos [28]. Briefly, PZQ was dissolved by stirring in a water–ethanol solution at a ratio of 7:5 (ethanol: water). The dextrans were then added separately under stirring. First, DEX-70 was added and, after its solubilization, DEX-148 was then added and solubilized. Subsequently, these mixtures were placed in a freezer at −5 °C for 24 h. After this period, the samples were left to dry by freeze-drying for over 24 h. Following this step, samples at ratios of 1:1:1, 1:2:1, 1:1:2, 1:2:2, 1:1:3, 1:3:1, 1:2:3, 1:3:2 and 1:3:3 (PZQ:DEX-70:DEX-148) were obtained. Separately, physical mixtures (PM) were prepared by weighing PZQ, DEX-70 and DEX-148 at ratios of 1:1:1, 1:2:1, 1:1:2, 1:1:3, 1:3:1 and 1:2:2 (PZQ:DEX-70:DEX-148), and mixing. After mixing, the samples were sieved and stored.

Determination of praziquantel content

The content of PZQ incorporated into the formulations was determined by adding a proportional mass of sample (polymer + drug) that contained 50 mg of drug. These

samples were initially solubilized in 10 mL ethanol. An aliquot of 1 mL diluted with 10 mL of water was then taken and the amount of PZQ determined by UV spectrometry at 263 nm. The experiment was performed in triplicate and the results expressed as mean values.

Solubility assays

The solubility of the incorporated PZQ in water was determined by dispersing aliquots of hydrogels containing 10 mg of PZQ in 10 mL of water, according to the approach adapted from work carried out by Nepal et al. [29] and Vippagunta et al. [30]. These samples were stirred for 24 h, centrifuged at 3400 rpm for 10 min and the amount of dissolved PZQ determined by UV spectrophotometry at 263 nm. The experiments were performed in triplicate and results expressed as mean values.

Differential scanning calorimetry (DSC)

For thermal characterization of PZQ, DEX, PZQ/DEX physical mixture and PZQ/DEX hydrogels, a DSC-2910 differential scanning calorimeter (TA Instruments®), capable of operating from room temperature up to 600 °C, was employed. DSC curves were obtained from 1.9 to 2.1 mg of samples in aluminum crucibles heated at 10 °C min^{-1} under a nitrogen atmosphere flowing at 25 mL min^{-1}.

X-ray diffraction (XRD)

The identification of the crystalline structure and/or amorphous forms of PZQ, DEX, PZQ/DEX physical mixture and PZQ/DEX hydrogels was carried out in diffraction patterns obtained from X-ray diffraction on a Siemens® model D5000 goniometer at a speed of 0.05/min under Cu-Kα radiation ($\lambda = 1.5406$ Å) and scanning X-ray wide angle 2θ from 4° to 60°.

The average crystallite size of praziquantel in the hydrogels based on XRD data was obtained using Scherrer's Eq. (1), according to work carried out by Abdullah and Khairurrijal [31] and Uvarov and Popov [32].

$$D = \frac{K\lambda}{\beta \cos\theta} \quad (1)$$

where D is a measure of crystal size in nanometers, K is the Scherrer constant, whose value used in calculations was 0.9, λ is the X-ray wavelength, β is the peak width (full width of half maximum: FWHM) expressed in radians, and θ is the angle of the peak, chosen for the calculation that is usually the most intense. In this case, the most intense peak was that approaching an angle of 20°.

Scanning electron microscopy (SEM)

Microscopic analysis of PZQ, dextrans, physical mixtures and hydrogels was performed using a JEOL JSM-7500F Field EMISION SEM/Analytical Field Emission SEM electron microscope. Samples were prepared on a metal stub with an adhesive and coated under vacuum with gold. The images were taken at a magnification of 1000×.

Results

Preparation of hydrogels

Hydrogels have been extensively studied as drug delivery systems. One use of hydrogels in drug delivery is for enhanced dissolution of the pharmaceuticals and consequent improvement in their bioavailability. Poorly water-soluble drugs that can benefit from this application include praziquantel as well as many other class II drugs. These drugs are characterized by having high permeability in the gastrointestinal tract, but being poorly soluble in physiological fluids whose main component is water. Therefore, these drugs have low bioavailability, impairing drug action and requiring the use of larger doses to achieve therapeutic plasma levels. Dextran is a non-toxic, safe, biocompatible, biodegradable, hydrophilic polymer for forming gels, making it ideally suited for use in hydrogels.

Hydrogels were prepared according to the methodology used in previous work. Drug and polymer were solubilized in a hydroalcoholic solution and then submitted to a solvent casting process [28]. In this process, the ethyl alcohol helps in solubilization of the drug and affects the crosslinking process of the polymer, contributing to the occurrence of weak molecular interactions between the polymer chains. The water, on the other hand, facilitates hydrogel formation and incorporation of the drug, concluding the process of obtaining formulations [28]. Thus, it can be seen that the process of obtaining hydrogels was successful, proving a practical, inexpensive and efficient method of achieving this type of drug delivery system.

Determination of praziquantel content

Figure 1 shows the values obtained in the assays. It can be seen that the 1:1:1 and 1:3:2 formulations had the highest concentration of drug incorporated of 0.63 and 0.57 mg mL^{-1}, respectively. The 1:1:2 and 1:3:1 formulations were found to have similar concentrations. However, at some of the high concentrations of praziquantel found in samples 1:2:1 and 1:2:3, concentrations lower than the theoretical drug content (0.5 mg mL^{-1}) of 0.41 and 0.40 mg mL^{-1}, respectively, were evident.

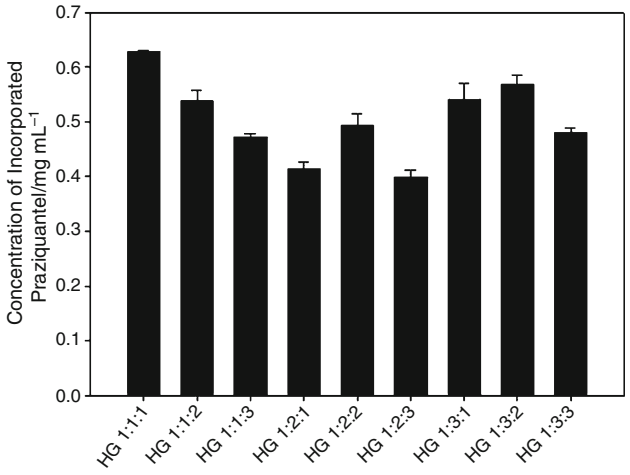

Fig. 1 Concentration of praziquantel incorporated into the formulations

The 1:1:1 formulation was selected to evaluate the solubility of praziquantel, serving as a minimum parameter regarding the effects of the proportion of polymers on the biopharmaceutical and physicochemical properties. Conversely, the 1:2:2 sample was selected to assist studies of the maximum parameter. In addition, hydrogels 1:1:2, 1:1:3, 1:2:1 and 1:3:1 were selected and helped determine the influence of a higher proportion of dextrans 70 and 148 kDa on the properties of the drug.

Solubility assays

Figure 2 shows the results obtained in solubility studies of PZQ for different samples. The solubility of PZQ was 0.26 mg mL^{-1} and served as a parameter to assess the influence of polymeric carriers on this drug property.

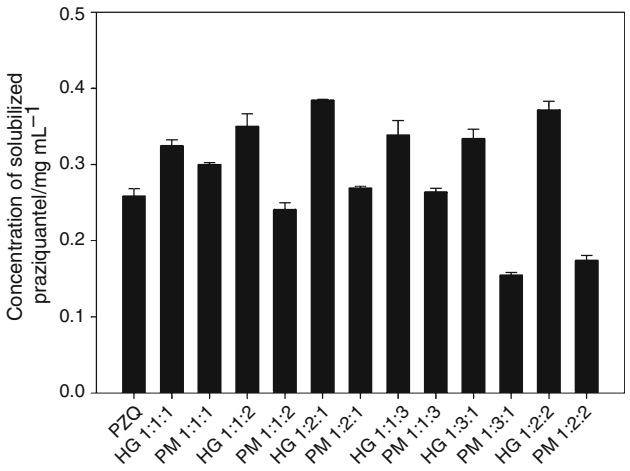

Fig. 2 Concentration of praziquantel solubilized in water after 24 h at 25 °C

Figure 2 depicts an increase in solubility of hydrogels. All hydrogel samples showed a significant solubility increase in relation to free drug and physical mixtures. However, special attention should be paid to the formulations HG 1:2:1 and HG 1:2:2, which incorporated PZQ concentrations of 0.38 and 0.37 mg mL^{-1}, respectively, representing an increase of about 0.12 mg mL^{-1}. By contrast, the physical mixture of the same proportions exhibited drug concentrations of 0.27 mg mL^{-1} for PM 1:2:1 and 0.17 mg mL^{-1} for PM 1:2:2, confirming substantial improvement in PZQ solubility.

Given these results, the HG 1:2:1 and HG 1:2:2 samples were selected for use, along with their physical mixtures, as parameters. Moreover, the HG 1:1:1 sample was selected for a comparative parameter as regards the amount of polymer relative to drug and, thereby, evaluated the influence of polymer amount on dissolution of the drug and its profile.

Differential scanning calorimetry (DSC)

DSC curves for amorphous dextrans 70 and 148 kDa (Fig. 3a) showed augmented endothermic peaks at approximately 50 and 39 °C, respectively. These events are attributed to evaporation of weakly bound water entrapped in the polymer chains, which have a large number of hydroxyl groups, as reported by Stenekes et al. [33] and Zhang and Chu [34]. Loss of water avoids the plastificant effect and increases the strength of the interactions between polymer chains due to hydrogen bonds involving hydroxyl groups. These interactions were responsible for the high glass transition temperature (T_g) of dextran of over 220 °C.

In Fig. 3b, praziquantel exhibits a sharp endothermic peak at 141.07 °C, evidencing its crystalline nature and proving that this was the drug since the temperature corresponds to the melting point of the drug [35–38].

Figure 3b also shows the DSC curves of the physical mixtures and PZQ. Notably, physical mixtures showed a broad endothermic peak similar to that observed in the polymers, an indication of the presence of weakly bound water that evaporated during the DSC procedure. Furthermore, a long endothermic sharp peak is evident at 141 °C in all physical mixtures, indicating the presence of praziquantel without major changes, since the peak is not shifted significantly relative to that observed for free PZQ. Also in Fig. 3b, a broad endothermic peak can be seen in the hydrogel samples. Again, this broad peak is attributed to the presence of water molecules bound within the polymer. A praziquantel endothermic peak can also be observed. Table 1 shows the expected and found enthalpies for the samples of hydrogels and physical mixtures. A reduction in the amount of energy required to break the crystals was observed for praziquantel samples compared with the free drug.

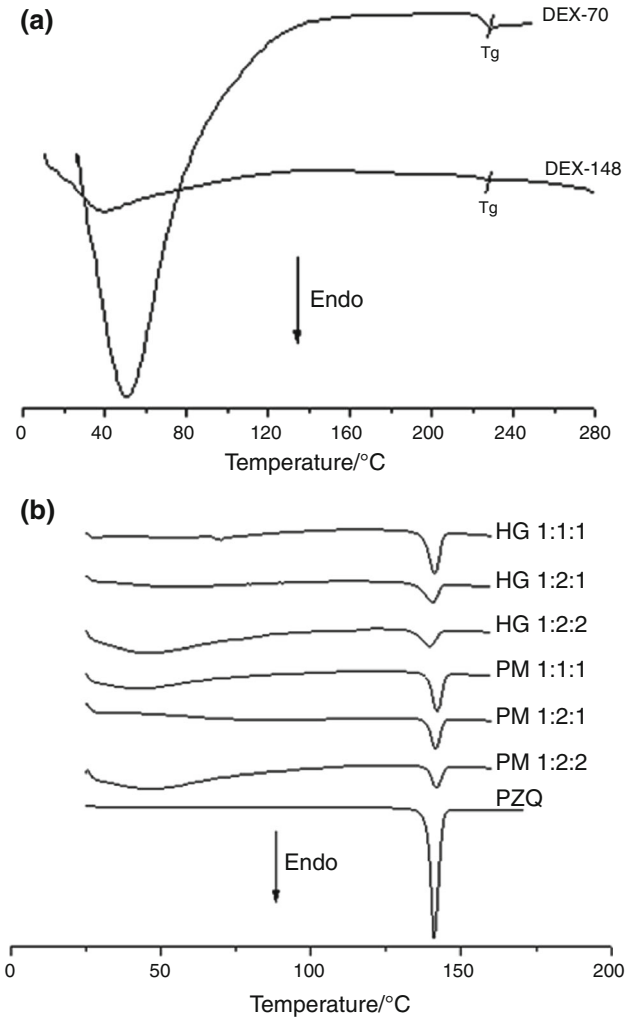

Fig. 3 DSC curves of dextrans 70 and 148 kDa (**a**) and praziquantel, physical mixtures and hydrogels (**b**)

X-ray diffraction (XRD)

Figure 4 shows the XRD patterns of praziquantel, dextrans, physical mixtures and hydrogels. A wide range of small peaks visible in Fig. 4a indicate the presence of amorphous material in the case of dextran [39]. In Fig. 4b, PZQ exhibits a crystalline structure, evidenced by the narrow and intense peaks at approximately 6° and 8°, plus a series of peaks between 10° and 25°, as observed by Cheng et al. [40] and Passerini et al. [1]. Also in Fig. 4b, there is a difference between the XRD patterns of the physical mixtures and hydrogels.

The average crystallite size of praziquantel in hydrogels was calculated by the Scherrer equation. The average size of PZQ crystals was 80.06 nm, while the crystallites of physical mixtures PM 1:1:1, PM 1:2:1 and PM 1:2:2 measured 198.74, 54.25 and 393.79 nm, respectively. The HG 1:1:1 hydrogel had an average crystallite size of 33.78 nm and HG 1:2:1 a size of 58.65 nm. However, the size of the crystallites of the HG 1:2:2 sample could not be determined, probably due to the high amount of polymer, where the peak chosen proved almost imperceptible in the XRD pattern of the sample (Fig. 4).

Scanning electron microscopy (SEM)

Figure 5 shows SEM photomicrographs of praziquantel, dextrans, physical mixtures and hydrogels at a magnification of 1000×. The differences between these, physical mixtures and hydrogels, are evident. The PZQ has a crystalline form found in clusters in the form of small prisms (Fig. 5a), as observed by Cheng et al. [39]. DEX-70 is in the form of spherical particles that are amorphous in nature

Table 1 DSC data

Samples	T_{onset}/°C	T_{peak}/°C	*ΔH_{exp}/J g^{-1}	**ΔH_{obt}/J g^{-1}	Percentage difference between ΔH_{exp} and ΔH_{obt}/%
HG 1:1:1	137.39	141.07	37.63	33.30	11.55
PM 1:1:1	138.82	142.02	29.92	24.47	18.2
HG 1:2:1	135.08	140.59	18.60	18.23	1.99
PM 1:2:1	138.50	141.54	22.47	19.38	13.8
HG 1:2:2	134.29	139.25	17.76	16.66	13.8
PM 1:2:2	138.70	141.76	19.95	14.66	6.19
PZQ	137.70	141.20	–	89.87	26.5
DEX-70	–	–	–	–	–
DEX-148	–	–	–	–	–

* ΔH_{exp}—expected enthalpy

** ΔH_{obt}—obtained enthalpy

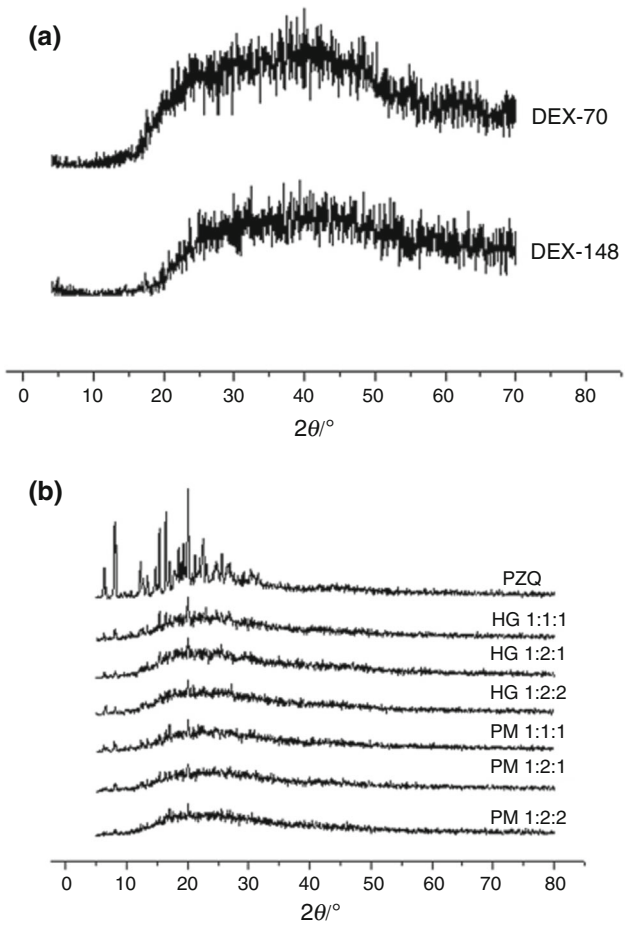

Fig. 4 XRD patterns of dextrans 70 and 148 kDa (**a**) and praziquantel, physical mixtures and hydrogels (**b**)

(Fig. 5b), while DEX-148 shows a similar structure to flakes, also amorphous in nature (Fig. 5c). In Fig. 5d–f, deposition of crystals adhered to the surface of the polymer particles can be observed. In Fig. 5g–i, clear signs of change in the characteristics of PZQ and dextrans can be noted.

Discussion

Initial analysis of the solubility data (Fig. 2) reveals a significant increase in solubility in all samples of hydrogels compared to PZQ and physical mixtures, most prominent in HG 1:2:1 and HG 1:2:2 formulations. In both these cases, results indicate that PZQ has possibly undergone a change in its crystal structure. Analysis of the DSC curves (Fig. 3) shows that as the proportion of polymer increases, the heat flow decreases, i.e., less energy is used to melt PZQ. This indicates, therefore, the formation of crystallites, a fact confirmed by the results observed in X-ray diffraction (Fig. 4). The XRD patterns for hydrogels show weaker peaks than the free drug, being indicative of decreasing drug crystal size. This decrease is supported by the results obtained by the Scherrer equation used to determine the size of PZQ crystals in hydrogels based on XRD data. A reduction in praziquantel crystal size was observed when incorporated in the polymeric matrix of hydrogels. The HG 1:2:2 sample remained the most noteworthy because it was not possible to determine the size of its crystals, probably due to the large amount of polymers and very small crystals that were ultimately well incorporated into the matrix. Furthermore, these data confirm the assumptions based on the DSC curves. Other data confirming DSC results include the SEM photomicrographs (Fig. 5). These depict a polymer matrix filled and covered with fine PZQ crystallites which becomes more perceptible as the ratio of the polymers increases, as exemplified by HG 1:2:1(Fig. 5h) and HG 1:2:2 (Fig. 5i). These changes most likely occurred due to the influence of the procedure for obtaining hydrogels, which served to reduce the energy required to disrupt PZQ crystals and influenced the increase in solubility of the drug. Moreover, the smaller, well-dispersed crystals formed favored surface contact, thereby increasing the solubility of PZQ. A similar effect was observed by Torres, Torrado and Torrado [36] who, in their study of solid dispersions, prepared PZQ/PVP and noted the formation of lamellar structures of PVP-containing filaments identified as PZQ crystals, which showed an increase in solubility of the drug, particularly for the 1:5 formulation. Thus, it can be assumed that the greater the amount of both polymers, the smaller the PZQ crystals become.

Further key information obtained from the DSC curves is given in Table 1. The temperature peak, onset temperature, as well as found and expected enthalpies for PZQ mass present in the samples can be observed. The low enthalpies indicate a change in the crystal structure of praziquantel for crystallites that are probably dispersed in the polymer matrix, supporting the hypothesis based on the DSC curves. As noted in previous work conducted by Campos et al. [28], molecules in PZQ crystals are firmly linked to each other by strong intermolecular bonds, whereas in hydrogels and physical mixtures these bounds are weaker. This is due to the wider separation of PZQ molecules in the polymeric network of dextran. Therefore, the amount of energy required for fusion of the hydrogels containing PZQ is lower than for the free drug [28]. Thus, it can be inferred that this reduction in PZQ peak, and consequently in the amount of energy required for melting to occur, is due to the formation of crystallites, which ultimately may have influenced the solubility of the drug in the hydrogels, as observed in the solubility assay.

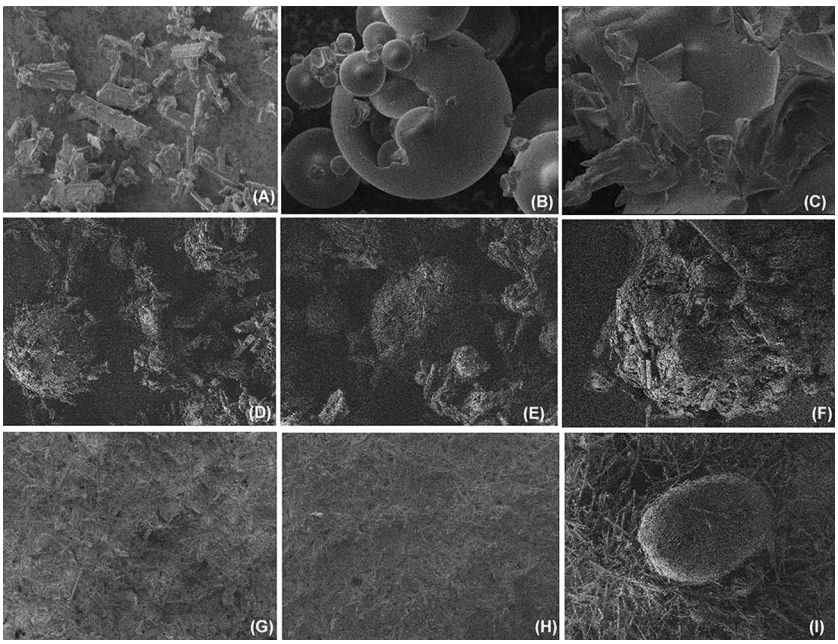

Fig. 5 Photomicrographs of praziquantel (**a**), dextran 70 kDa (**b**), dextran 148 kDa (**c**), physical mixture 1:1:1 (**d**), physical mixture 1:2:1 (**e**), physical mixture 1:2:2 (**f**), hydrogel 1:1:1 (**g**), hydrogel 1:2:1 (**h**) and hydrogel 1:2:2 (**i**), obtained by scanning electron microscopy at $\times 1000$ magnification

Conclusions

Thermal analysis by DSC was found to be a powerful tool for the characterization of hydrogels and for compatibility studies between drug and polymers, proving a rapid and reliable method for use in scientific research within the pharmaceutical field. From the results obtained, it can be affirmed that the crystallites are formed by the procedure employed for obtaining the hydrogels and that their smaller size and consequent greater surface area improved solubility compared to PZQ crystals in their natural form and to other formulations containing a single polymer presented in our earlier study [28].

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References

1. Passerini N, Albertici B, Perissuti B, Rodriguez L. Evaluation of melt granulation and ultrasonic spray congealing as techniques to enhance the dissolution of praziquantel. Int J Pharm. 2006;318:92–102.
2. Cioli D, Pica-Mattoccia L. Praziquantel. Parasitol Res. 2003;90:S3–9.
3. Souza ALR, Andreani T, Oliveira RN, Kill CP, Santos FK, Allegretti SM, Chaud MV, Souto EB, Silva AM, Gremião MPD. In vitro evaluation of permeation, toxicity and effect of praziquantel-loaded solid lipid nanoparticles against *Schistosoma mansoni* as a strategy to improve efficacy of the schistosomiasis treatment. Int J Pharm. 2014;463:31–7.
4. Sadhu PS, Kumar SN, Chandrasekharam M, Pica-Mattoccia L, Cioli D, Rai VJ. Synthesis of new praziquantel analogues: potential candidates for the treatment of schistosomiasis. Bioorg Med Chem Lett. 2012;22:1103–6.
5. Almeida AE, Souza ALR, Cassimiro DL, Gremião MPD, Ribeiro CA, Crespi MS. Thermal characterization of solid lipid nanoparticles containing praziquantel. J Therm Anal Calorim. 2012;108:333–9.
6. Breda SA, Jimenez-Kairuruz AF, Manzo RH, Oliveira ME. Solubility behaviour and biopharmaceutical classification of novel high-solubility ciprofloxacin and norfloxacin pharmaceutical derivates. Inter Pharm. 2009;371:106–13.
7. Chaud MV, Tamascia P, Lima AC, Paganelli MO, Gremião MPD, Freitas O. Solid dispersions with hydrogenated castor oil increase solubility, dissolution rate and intestinal absorption of praziquantel. Braz J Pharm Sci. 2010;46:473–81.
8. Leong KW, Langer R. Polymeric controlled drug delivery. Adv Drug Deliv Rev. 1987;1:199–233.
9. Thakur RRS, McMillan HL, Jones DS. Solvent induced phase inversion-based in situ forming controlled release drug delivery implants. J Control Release. 2014;176:8–23.
10. Kim S, Kim J, Jeon O, Kwon IC, Park K. Engineered polymers for advanced drug delivery. Eur J Pharm Biopharm. 2009;71:420–30.
11. Alvarez-Lorenzo C, Blanco-Fernadez B, Puga AM, Concheiro A. Crosslinked ionic polysaccharides for stimuli-sensitive drug delivery. Adv Drug Deliv Ver. 2013;65:1148–71.
12. Prezotti FG, Cury BSF, Evangelista RC. Mucoadhesive beads of gellan gum/pectin intended to controlled delivery of drugs. Carbohydr Polym. 2014;113:286–95.
13. Petronijevic Z, Maluckov B, Smelcerovic A. Crosslinking of polysaccharides with activated dimethylsulfoxide. Tetrahedron Lett. 2014;54:3210–4.
14. Mocanu G, Nichifor M. Cationic amphiphilic dextran hydrogels with potential biomedical applications. Carbohydr Polym. 2014;99:235–41.
15. Cutiongco MFA, Tan MH, Ng MYK, Visage CL, Yim EKF. Composite pullulan-dextran polysaccharide scaffold with interfacial polyelectrolyte complexation fibers: a platform with enhanced cell interaction and spatial distribution. Acta Biomater. 2014;10:4410–8.
16. Beloqui A, Solinís MA, Rieux A, Préat V, Rodríguez-Gascón A. Dextran-protamine coated nanostructured lipid carriers as mucus-penetrating nanoparticles for lipophilic drugs. Int J Pharm. 2014;468:105–11.

17. Coviello T, Matricardi P, Marianecci C, Alhaique F. Polysaccharide hydrogels for modified release formulations. J Cont Release. 2007;119:5–24.
18. Lloyd LL, Kennedy JF, Methacanon P, Paterson M, Knill CJ. Carbohydrate polymers as wound management aids. Carbohydr Polym. 1998;37:315–22.
19. Hiemstra C, van der Aa LJ, Zhong Z, Dijkstra PJ, Feijen J. Novel in situ forming, degradable dextran hydrogels by Michael addition chemistry: synthesis, rheology, and degradation. Macromalecules. 2007;40:1165–73.
20. Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev. 2012;64:49–60.
21. Hamidi M, Azadi A, Rafiei P. Hydrogel nanoparticles in drug delivery. Adv Drug Deliv Rev. 2008;60:1638–49.
22. Peppas NA, Bures P, Leobandung W, Ichikawa H. Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm. 2000;50:27–46.
23. van Nostrum CF, Hennink WE. Novel crosslinking methods to design hydrogels. Adv Drug Deliv Rev. 2012;64:223–36.
24. Hiemstra C, van der Aa LJ, Zhong Z, Dijkstra PJ, Feijen J. Rapidly in situ-forming degradable hydrogels from dextran thiols through Michael Addition. Biomacromalecules. 2007;8:1548–56.
25. Chadha R, Bhandari S. Drug-excipient compatibility screening—role of thermoanalytical and spectroscopic techniques. J Pharm Biomed Anal. 2014;87:82–97.
26. Nunes RS, Semaan FS, Riga AT, Cavalheiro ETG. Thermal behavior of verapamil hydrochloride and its association with excipients. J Therm Anal Calorim. 2009;97:349–53.
27. Oliveira MA, Yoshida MI, Gomes ECL, Mussel WN, Viana-Soares VD, Pianetti GA. Análise Térmica aplicada à caracterização da sinvastatina em formulações farmacêuticas. Quim Nova. 2010;33:1653–7.
28. Campos FS, Cassimiro DL, Crespi MS, Almeida AE, Gremião MPD. Preparation and characterization of Dextran-70 hydrogel for controlled release of praziquantel. Braz J Pharm Sci. 2013;49:75–83.
29. Nepal PR, Han H, Choi H. Enhancement of solubility and dissolution of Coenzyme Q10 using solid dispersion formulation. Int J Pharm. 2010;383:147–53.
30. Vippagunta SR, Maul KA, Tallavajhala S, Grant DJW. Solid-state characterization of nifedipine solid dispersions. Int Pharm. 2002;236:111–23.
31. Abdullah M, Khairurrijal. Derivation of Scherrer relation using an approach in basic physics course. J Nanosains Nanotek. 2008;1:28–32.
32. Uvarov V, Popov I. Metrological characterization of X-ray diffraction methods at different acquisition geometries for determination of crystallite size in nano-scale materials. Mater Charact. 2013;85:111–23.
33. Stenekes RJH, Talsma H, Hennink WE. Formulation of dextran hydrogel by crystallization. Biomaterials. 2001;22:1891–8.
34. Zhang Y, Chu CC. Thermal and mechanical properties of biodegradable hydrophilic-hydrophobic hydrogels based on dextran and poly(lactic acid). J Mater Sci-Mater M. 2002;13:773–81.
35. El-Subbagh HI, Al-Badr AA. Praziquantel. Anal. Prof Drug Subst and Exc. 1998;25:464–500.
36. Torre P, Torrado S, Torrado S. Preparation, dissolution and characterization of Praziquantel solid dispersion. Chem Pharm Bull. 1999;47:1629–33.
37. Liu Y, Wang X, Wang JK, Ching CB. Structural characterization and enantioseparation of the chiral compound praziquantel. J Pharm Sci. 2004;39:3039–46.
38. Mainardes RM, Gremião MPD, Evangelista RC. Thermoanalytical study of praziquantel loaded-PLGA nanoparticles. Rev Bras Ciênc Farm. 2006;42:523–30.
39. Yuan W, Geng Y, Wu F, Liu Y, Guo M, Zhao H, Jin T. Preparation of polysaccharides glassy microparticles with stabilization of proteins. Int J Pharm. 2009;366:154–9.
40. Cheng L, Lei L, Guo S. In vitro and in vivo evaluation of praziquantel loaded implants based on PEG/PCL blends. Int J Pharm. 2010;387:129–38.