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Original Research Article

Development and Evaluation of Praziquantel Solid Dispersions in Sodium Starch Glycolate

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Abstract

Purpose: *To develop and characterize solid dispersions of praziquantel (PZQ) with sodium starch glycolate (SSG) for enhanced drug solubility.*
Methods: *PZQ solid dispersion (SD) was prepared using co-precipitation method by solvent evaporation. The ratios of PZQ to SSG were 2:1, 1:1, 1:2, 1:3 (w/w). PZQ solubility was evaluated in purified water, and PZQ dissolution test was carried out in 0.1N HCl. Structural characterization of the dispersions was accomplished by x-ray diffraction (XRD) and infrared spectroscopy (FTIR) while the external morphology of the SDs, SSG and PZQ were studied by scanning electron microscopy (SEM). Mucoadhesion properties of the SD (1:3) and SSG, on mucin disks were examined using texture profile analysis.*
Results: *The highest solubility was obtained with 1:3 solid dispersion, with PZQ solubility of 97.31 %, which is 3.65-fold greater than the solubility of pure PZQ and physical misture (PM, 1:3). XRD results indicate a reduction in PZQ crystallinity while infrared spectra showed that the functional groups of PZQ and SSG were preserved. SEM showed that the physical structure of PZQ was modified from crystalline to amorphous. The amount of PZQ in PM and SD (1:3) that dissolved in 60 min was 70 and 88 %, respectively, and these values increased to 76 and 96 %, respectively. The solid dispersion reduced the mucoadhesive property of the glycolate.*
Conclusion: *Solid dispersion formulation using SSG is a good alternative approach for increasing the dissolution rate of PZQ.*

Keywords: *Praziquantel, Drug bioavailability, Schistosomiasis, Solid dispersion, Co-precipitation, Sodium starch glycolate*

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INTRODUCTION

Poor bioavailability exerts strong limits to the performance of a drug by the necessity to administer a much higher dose than strictly required from a pharmacologic point of view. For good oral bioavailability drug must be soluble in gastrointestinal fluids, i.e., aqueous soluble and possess permeability properties for good membrane diffusion in order to reach the bloodstream [1].

Oral bioavailability of poorly soluble and highly permeable drugs, whose absorption is controlled by dissolution rate, can be increased by formulation strategies aimed at increasing both

solubility and dissolution rate. Among the several strategies available for improving drug bioavailability, solid dispersions (SD) have been used extensively [2-6]. The SD technique produces a significant increase in surface area and surface wettability as well as solid state modification from crystalline to amorphous form. However, the SD characteristics can be influenced by several factors such as preparation method, carrier type and drug:carrier ratio and pH modifiers [7, 8].

Praziquantel (PZQ) is the first drug of choice in human taeniasis and schistosomiasis treatment. It is classified in Group II of Biopharmaceutical Classification System (BCS) and represents an example of a drug that requires research to improve drug solubility and reduce the high doses used in parasitic disease treatment. Funding of mass chemotherapy programs aimed at reducing the high morbidity rates associated to schistosomiasis is required [9]. SSG is the sodium salt of a carboxymethyl ether of starch, whose molecular weight is typically 500,000 - 11,000,000, and is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. Sodium starch glycolate (SSG) is a very fine, white or off white, free flowing powder; odorless or almost odorless, practically insoluble in water and similarly insoluble in most organic solvents. Solid dispersion of carbamazepine with SSG increased solubility of carbamazepine due to the properties of wetting, significant increase in surface area and control over the particle size of the drug. Solid dispersions of SSG with ibersartan, olanzapine itraconazol, carbamazepina, nalidixic acid, furosemide [2,10] produced higher dissolution rates than with other excipients due probably to their rapid dispersibility in the aqueous dissolution fluids [11-13]. The objective of this study was to investigate the dissolution rate of PZQ from solid dispersions (SD) prepared with SSG and also to structurally characterize the SD by x-ray diffraction (XRD), Fourier transformed infrared spectroscopy (FTIR) and scanning electron microscopy (SEM). The mucoadhesive performance of SD was also evaluated *in vitro*.

EXPERIMENTAL

Materials

Praziquantel (PZQ) with a purity of 99.6% was purchased from Indukern do Brasil Quimica Ltda (Brazil). Sodium starch glycolate was purchased from Blanver, Brazil. Other reagents used were of analytical grade.

Preparation of solid dispersion

PZQ and SSG were used at SD ratios of 2:1, 1:1, 1:2 and 1:3. A sufficient amount of ethanol was used to dissolve PZQ while SSG was dispersed in water. The mixture of PZQ solution with SSG dispersion was produced by mechanical agitation for 5 min. When a clear solution was obtained, the sample was evaporated under reduced pressure at 65 ºC (Tecnal® TE-210 rotary evaporator) and dried in a freeze-dryer (Edwards Modulyo® Freeze-Dryer). The co-precipitate (solid dispersion) was crushed in a porcelain mortar with a pestle and stored in a silica desiccator pending use. The viscosity of the SSG dispersion was measured (DV-E Brookfield viscometer) before mixing with the PZQ solution.

Preparation of physical mixtures (PM) of PZQ and SSG

PZQ and SSG powder mixtures (PM) at ratios of 2:1, 1:1, 1:2 and 1:3 were prepared by first sifting the individual powders through a 425 µm aperture screen and mixing together by trituration in a mortar with a pestle. The mixture was stored in a silica desiccator pending use.

Solubility studies

The solubility of PZQ was determined in purified water. Briefly, 15 ml of water was added to SD or PM (containing an equivalent of 15 mg of PZQ) in a test tube. The tube was sonicated 40KHZ for 30 min (Unique – Mod 2800A) and then shaken in a water bath (25 °C) for 48 h. A portion of the solution (10 ml) was withdrawn, centrifuged at 2,200 *g* for 20 min, filtered (0.45µm pore size) and centrifuged again at 7,000 *g* for 10 min twice. The upper portion (1 ml) was then taken, diluted with 9 ml of ethanol and the diluted solution subsequently and analyzed spectro-photometrically for PZQ content at 263 nm.

In vitro release studies

The release rate of pure PZQ, PZQ in SD and in PM was determined using a dissolution test (method II, USP 32). The dissolution test was performed in 900mL of 0.1M HCl with 0.2 %w/v of sodium lauryl sulphate, at 37 ± 0.5 ^{o}C, rotating at 50 rpm, for 120 min. PZQ sample of 0.5mg.mL^{-1} were taken for dissolution studies at regular intervals. Withdrawing samples were filtered through a membrane filter (Allcrom, 0.22 µm pore size). The withdrawn sample, in each case, was replaced with an equivalent volume of

fresh dissolution medium at 37 °C. Absorbance of the samples was measured spectrophotometrically at 263nm.

Scanning electron microscopy

The external morphology of SD, PM and PZQ was studied by scanning electron microscopy (SEM). The samples were prepared for SEM by lightly sprinkling the powder onto a double-sided adhesive tape affixed to an aluminum stub. The stubs were then coated with gold to a thickness of about 300 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The samples were then randomly scanned and photomicrographs taken with a scanning electron microscope (JSM-6360).

X-ray diffraction analysis

Diffraction patterns (PXRD) of all the samples were obtained using X-ray diffraction on a D 5000- Siemens device (filtered Ni, Cu.Kα radiation). The samples were scanned at increments of 0.02° from 5º to 40º at a diffraction angle of 2θ. The voltage and currents used were 40 kV and 50 mA.

Fourier transform infrared spectroscopy

The infrared spectra of pure PZQ and SD, PM were obtained by the KBr disk method recorded on a Fourier transform infrared (FTIR) spectrophotometer (Perkin Elmer, Spectrum One). The spectra were obtained by scanning at b 400 to 4,000 cm^{-1} at a resolution of 2cm^{-1}. KBr pellets were prepared by gently mixing 1 mg of the sample with 200 mg KBr.

Mucoadhesive test

The mechanical properties of SD (1:3) and SSG were examined using texture profile analysis (TA.XT plus, Stable Micro Systems, UK) [14]. In the test, compressed mucin disc was affixed to a metal platform using double-sided adhesive tape and then affixed onto a cylindrical probe with double-sided adhesive tape. The mucin disc was hydrated with phosphate buffer (pH 7.4) for 60 s. The test was performed in compression mode at a speed of 0.5 $mm.s^{-1}$ under a force of 2 mN. To come into contact with the mucin disc, the probe containing the sample was moved vertically at a speed of 2.0 $mm.s^{-1}$. After 10 min of contact, the probe was moved in the opposite direction at the same speed. The maximum force required to separate the probe from the mucin disk was monitored by the in-built software (Texture Exponent Lite). The total force required (Wad) was calculated from the area of the plot of force versus distance. The analysis was performed in duplicate.

Statistical analysis

Two-way analysis of variance (ANOVA) and *t* test were employed for statistical analysis of PZQ dissolution rate and solubility data. $P \leq 0.05$ was considered as indicative of statistically significant difference. The study was conducted using the software Microcal Origin v. 7.0 (OriginLab Corp) .

RESULTS

The SD preparations were relatively simple and the SD mass was sufficiently friable to be ground easily.

Solubility and *in vitro* release of PZQ

Figure 1 shows PZQ solubility in purified water. Letters *a* and *b* compare the solubility of pure PZQ with PZQ in PM or SD. Letters *c* and *d* compare the solubility of PZQ between the PMs and respective SDs. Equal letters indicate no statistical difference whereas different letters show a statistical difference *for* $p \leq 0.05$. In case of PMs, drug solubility seemed to decreased with increase in concentration of PZQ, and none of them achieved the solubility of PZQ SDs. No statistical difference between the solubility of PZQ pure and the PMs was found. Moreover, a statistically significant difference was found between the solubility of PZQ pure and SDs as well as between physical mixtures and the SDs corresponding.

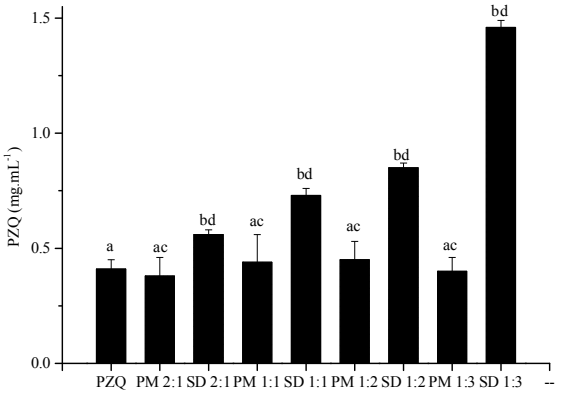

Figure 1: Solubility of pure PZQ, PM and SD in water after 48 h of agitation. Letters *a* and *b* compare the solubility of pure PZQ with the solubility of PZQ in PM and SD. Letters *c* and *d* compare the solubility of PZQ in PM and corresponding SD. Different letters represent statistically significant difference at $p \leq 0.05$. Data are expressed as mean ± SD (n = 3).

Figure 2 shows the dissolution profile of pure PZQ and of PZQ in SD (1:3) and PM (1:3)

formulations. Dissolved PZQ for PM and SD in 60 min (PZQ, PM 1:3) was 70 and 88 %, respectively. After 120 min (SD, 1:3), the figures increased to 76 and 96 %, respectively. Over the same time period (120 min.), dissolution of pure PZQ was only 64 %.

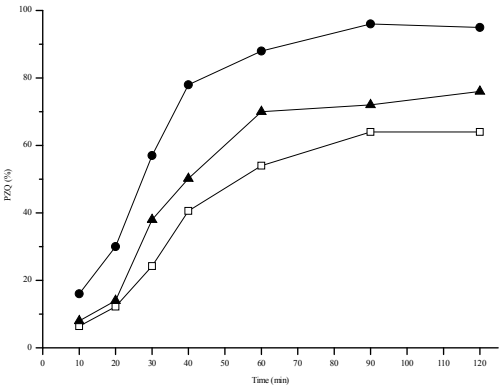

Figure 2: Dissolution profile of pure PZQ (□), 1:3 solid dispersion (●) and 1:3 physical mixture (▲). Data are expressed as mean ± SD (n = 6)

Structural and molecular and morphological characterization of formulations

The XRD diffractograms of SD, PM and the individual components are are shown in Fig 3. The polymer clearly exhibited an amorphous profile while PZQ was crystalline as evidenced by intense diffraction peaks). The diffraction pattern of PM was simply the superimposition of those of the individual components. On the other hand, the diffractogram of SD shows a change in the crystal structure of PZQ, revealing a transition from a crystalline to an amorphous state.

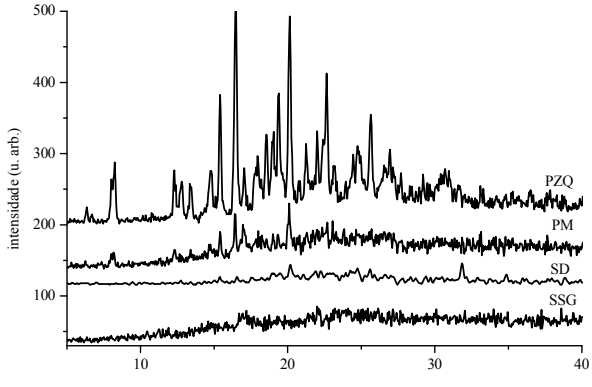

Figure 3: X-ray diffractohrams of pure PZQ , SSG, and 1:3 ratio of PM and SD

The FTIR of pure PZQ, SD and PM are shown in Figure 4. For PZQ, the wide band in the region 3600 - 3400 cm^{-1} indicate a characteristic stretching of the O-H group which, in this case, can be attributed to the presence of water molecules. In the region 3000 - 2900 cm^{-1}, vibration absorption bands of C-H connections are seen, reflecting the symmetrical and asymmetric axial deformations of CH_2 and CH_3 groups. Stretching bands overlaid at 1651 cm^{-1} represent two carbonyls (C = O) stretching absorption. At 1437 cm^{-1}, CH_2 angular stretching symmetrical bands appear with a band overlap partially observed at 1651 cm^{-1} for two connections stretching among carbons of the aromatic ring. Between 1350 and 1000 cm^{-1}, axial deformation occurs with band overlapping of C-N and C-H symmetrical angular stretching of CH_2. With regard to SSG spectrum (Figure 4B), a broad band in the region spanning 3600 - 2900 reflects the OH stretching group of this compound molecule. At 1600 - 1000 cm^{-1}, overlapping bands reflect asymmetric and symmetrical stretching of C-O-C group The scanning electron photomicrographs (SEM) of PZQ, SD and SSG are displayed in Figure 5. Pure PZQ particles were crystalline (A) and SSG (B) spherical and non-porous, being oval or spherical granules, 30 - 100 µm in diameter but with some in the size range of 10 - 35 µm (diameter). SD (C) show structural change in the particles, with SSG particles losing their spherical shape and appear to increase volume. SD particles also presented filamentous shape and PZQ lost its original crystalline form.

Mucoadhesive adhesive properties of solid dispersion

SSG dispersed well in cold water and settled in the form of a highly hydrated layer; it exhibited a viscosity of 4.21 mPa. After mixing SSG dispersion with PZQ solution, the viscosity decreased to 3.36 mPa. The mucoadhesion of SSG and SD (1:3) was 1497 ± 170 and 1058 ± 109 µJ, respectively. The forces (N) required to detach the formulations from mucin disc was 1735 ± 0.888 and 0.852 ± 0.177, respectively.

DISCUSSION

In this study, the solubility of PZQ in the SDs increased with increase in SSG concentration reaching a maximum at PZQ:SSG ratio of 1:3. This can be attributed to the swelling of SSG, which has a tendency to absorb water and retain it, resulting in up to 250 % increase in particle diameter when exposed to water [15]. This volume increase in their particle diameter could serve as an impediment to drug release and could explain the decrease in drug solubility observed with an increase in their respective concentrations [16]. In this study, increase drug solubility may be due to significant reduction of

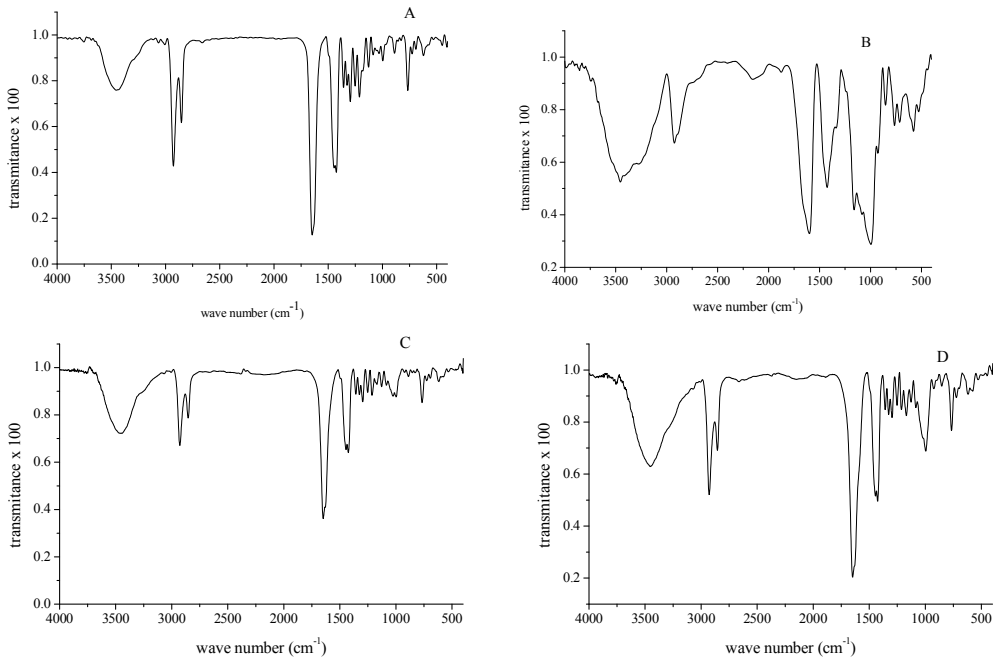

Figure 4: FTIR spectra of pure PZQ (A); SSG (B); 1:3 SD (C); and 1:3 PM (D)

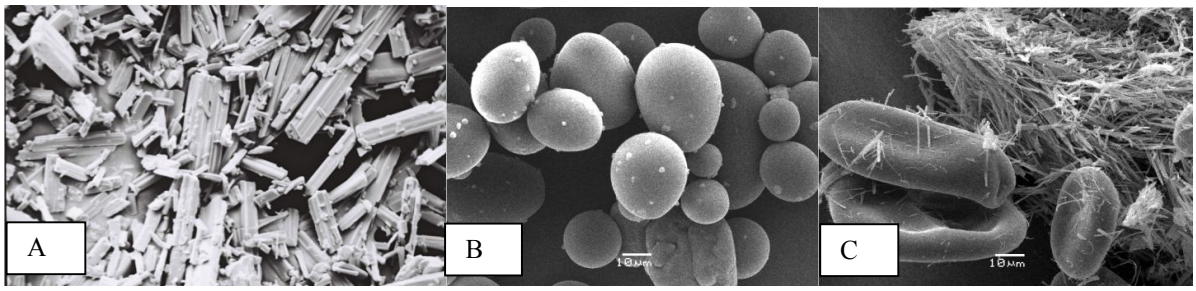

Figure 5: Scanning electron photomicrographs (x 1000) of pure PZQ (A); SSG (B) and SD 1:3 (C)

the crystallinity of the drug, as shown by x-ray diffraction results.

Increase in dissolution was partly dependent on reduction in drug crystallinity and is consistent with solubility results. The greater solubility of PZQ in PM than that of the pure drug is an indication of increased drug wettability promoted by SSG. The results show that PZQ dissolution in SD was significantly greater than in PM. Enhancement of dissolution of PZQ from solid dispersion (SD) can be attributed to several factors which affect the mechanism of dissolution in solid dispersion. These include reduction of drug crystallinity, i.e., amorphization, increased wettability and dispersibility [4,5,17].

PZQ is crystalline while SSG is amorphous. However,. This result helps explain the higher solubility and dissolution rate of PZQ in SD. The smaller diffraction peaks of SD compared with those of pure PZQ and PZQ in PM can be attributed principally to the conversion of PZQ from a crystalline to amorphous state.

IR indicates that bonding, if present, might not have been strong as to suppress the spectral band of PZQ. In both SD and PM, the characteristic stretching of the functional drug groups was preserved, indicating the physical and chemical integrity of PZQ remained intact. It is therefore presumed that formation of solid dispersion or physical mixture does not cause any physical and/or chemical interaction between PZQ and SSG at molecular level.

Mucoadhesion is used to increase the residence time of drug at a specific site [20]. Generally, the polymer chains need to be mobile to interpenetrate the mucus glycoprotein chains and contribute to the consolidation of the mucoadhesive phenomenon. SSG, chemically described as the sodium salt of a carboxymethyl ether of starch, presents, in addition to hydroxyl group, only one cluster for ionization and interaction with mucin. Although PZQ easily permeates the intestinal mucosa, its bioavailability is limited by the rate of dissolution. However, mucoadhesion associated with

increased solubility of PZQ in solid dispersion is a strategy that can result in improved bioavailability of PZQ.

CONCLUSION

This study shows that the dissolution rate of PZQ can be enhanced greatly by the solid dispersion technique. The mucoadhesive ability of the SSG was confirmed for the SD 1:3 formulation. The results of this study, like those of a few others exploring solid dispersion strategy, indicate that solid dispersion is a viable solution for pharmaceutical companies to enhance the life cycle of the existing products in which poor solubility is a major concern. The SD of PZQ with mucoadhesive and hydrodispersible carriers also represents a useful strategy for increasing the bioavailability of poorly water-soluble drugs.

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