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Praziquantel systems with improved dissolution rate obtained by high pressure homogenization

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ABSTRACT

Praziquantel (PZQ), an antihelmintic agent commonly administered to humans and cattle, has low aqueous solubility, which compromises its bioavailability and efficacy. The purpose of this study was to develop a new formulation, in order to improve PZQ dissolution rate. PZQ dispersions have been developed by high-pressure homogenization (HPH) using different stabilizers, selected upon PZQ saturation solubility. After the screening, two promising formulations were developed, combining poloxamer 188 with polyvinylpyrrolidone or maltodextrin. Characterization studies including particle size distribution, crystallinity, morphology, drug content, and in vitro dissolution profiles, were performed over selected formulations. The scanning electronic micrographs revealed that the morphology of suspended particles corresponded to elongated shapes, with an average particle size close to the micron range. X-ray powder diffractometry and differential scanning calorimetry results confirmed the drug crystallinity, before and after the HPH process. Besides, differential scanning calorimetry revealed the absence of interactions between PZQ and excipients. The dissolution rate of PZQ dispersions was significantly enhanced compared with raw PZQ, either in phosphate buffer or hydrochloric acid, mainly due to particle size reduction, thus improved saturation solubility.

1. Introduction

The antihelmintic Praziquantel (PZQ) is a broad-spectrum agent classified as a pyrazinoisoquinoline [1]. PZQ presents a considerably high activity against trematodes and tapeworms, including all *Schistosoma* species and *Taenia solium*, which is the agent responsible for cysticercosis disease in its larval phase [2]. Although it is considered an effective, safe, and low-cost drug, its usefulness is limited due to its low water solubility (only 0.04 g/100 mL) and its important first pass effect [3–5]. Nevertheless, this agent is widely used in developing countries for the treatment of various parasitic diseases that cause morbidity, both in man and in cattle [6]. An improvement of those unfavorable properties would promote a more effective and rational pharmacotherapeutic scheme.

PZQ is classified in the Biopharmaceutical Classification System (BCS) as a class II active pharmaceutical ingredient, which implies that the drug presents low aqueous solubility and high permeability through the intestinal membrane [7]. Moreover, due to its low solubility and high metabolism, in the Biopharmaceutics Drug Disposition Classification System (BDDCS), it is also classified as a type II drug [8]. It is well known that only the dissolved fraction of the drug will be available to be absorbed, and exert a therapeutic effect. Due to those unfavorable properties, these drugs may present significant oral absorption problems, which could lead to a compromised bioavailability [9]. A possible approach for overcoming the low water solubility issue is to reduce the drug particle size, especially below the micrometer range, leading to the enhancement of the specific surface area, the saturation solubility and, thus, the dissolution rate [10]. The Noyes-Whitney equation clearly states the dependence between these variables [11]. Moreover, the influence of PZQ systems with reduced particle size on the cysticerci metabolism was previously established [12].

A well-established procedure to reduce particle size is high-pressure homogenization (HPH), a top-down methodology, which is widely applied in food, cosmetic, and pharmaceutical industries [13]. The advantages of this technology include ease of operation and industrial scaling up, ability to be applied to several active pharmaceutical ingredients, avoidance of harsh solvents, and reduction of product contamination [14]. Moreover, compared with other size reduction techniques, HPH has no drug loading evaluation concern, since all active pharmaceutical ingredients added will be present in the final

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formulation. Nevertheless, the reduced size of the nanoparticles and the associated high surface energy entails a high probability of obtaining systems with physical instability, which is the major drawback of this technique [15].

The suspension, consisting of a drug, a stabilizing agent, and a liquid dispersion medium, is forced through a very small gap under pressure, with a significantly high velocity. During the process, particle size reduction is achieved because of shear and cavitation forces, and interparticle collisions. Smaller particle size and narrower distributions can be obtained by the increase of pressure and/or number of cycles in the HPH process [10]. Critical points of this technique include the suitable selection of stabilizer type, and concentration of both drug and stabilizer, in order to achieve an adequate size reduction and improve the physical stability of obtained formulations [16,17].The most common approaches to impart repulsive forces or energy barriers are steric and/or electrostatic techniques. Steric stabilization can be obtained by adsorption of polymers (e.g., cellulose derivatives, polyvinylpyrrolidone, polyvinyl alcohol) or non-ionic surfactants (e.g., poloxamers, polysorbates) to the surface of the particle. On the other hand, electrostatic stabilization is achieved by adsorbing ionic surfactants (e.g., SLS) onto the particle surface [16,18]. However, in the case that dispersions of nanoparticles are intended to be post-processed as a dry powder, long-term stability of the liquid formulation is not a major concern. Finally, the characterization of the obtained system is crucial in the effective development of these formulations [10].

Multiple strategies have been carried out attempting to improve the solubility and dissolution rate of PZQ, e.g. solid dispersions, inclusion complexes with α-, β- and γ-cyclodextrins, solid lipid nanoparticles and polymeric nanoparticles, Poly (− caprolactone) implants, co-crystals by grinding methodology, microparticles, granules or coprecipitates [19–28]. Although these systems exhibited several advantages, important drawbacks could also be detected in the applied techniques, such as a greater process complexity, the use of organic solvents, a higher excipient proportion, and a drug loading estimation requirement or some matrix effects. However, to the best of our knowledge, the development of a suitable system for PZQ by HPH has not been studied.

The purpose of this study was to formulate novel dispersions of PZQ and selected stabilizers using the HPH technique, in order to improve the solubility and dissolution rate of the drug. The obtained formulations were subsequently characterized, regarding technological and crystallographic properties, such as particle size distribution, drug content, in vitro dissolution profiles, particle morphology, differential scanning calorimetry, and X-ray powder diffraction. Finally, all these properties were compared with the raw materials and their physical mixtures.

These novel systems, developed with a not complex and scalable technique, would promote the adoption of this technology in order to improve the properties of PZQ and parasitic diseases treatment.

2. Materials and methods

2.1. Materials

Pharmaceutical-grade PZQ was purchased from Todo Droga (Argentina), and complied with the British Pharmacopoeia requirements [29]. Selected stabilizers, including poloxamer 188 (P188 – Lutrol F68®), polyvinylpyrrolidone K30 (PVP – BASF), sodium lauryl sulfate (SLS – Lab. Cicarelli), and maltodextrin (MDX-Todo Droga), were pharmaceutical-grade quality. Dissolution media were prepared using analytical-grade potassium dihydrogen phosphate (Anedra-Research AG, Argentina), sodium hydroxide (Cicarelli, Argentina), and hydrochloric acid (HCl - Anedra Research AG, Argentina). Different types of water were used: triple distilled for the formulation of PZQ dispersions, deionized for dissolution media preparation, and Ultrapurified Milli-Q® (Millipore SAS, France) for dilution of samples during particle size analysis. For PZQ assay, ethanol analytical grade (Dorwil, Argentina) was used.

2.2. Methods

2.2.1. Physical mixtures preparation

For physical mixtures (PM) preparation, PZQ and stabilizers were thoroughly mixed in a glass mortar, considering the same drug/stabilizer ratios (w/w) as for the PZQ dispersions.

2.2.2. Saturation solubility studies

The HPH process is sensitive to the proper selection of stabilizers and drug concentration [16]. Excipients were selected based on their stabilization properties (i.e., steric [PVP, MDX], electrostatic [SLS] or a combination of polymeric/surface active agents [P188]). These four water-soluble compounds are approved as inactive ingredients by the U.S. Food and Drug Administration (FDA), and commonly used for the formulation of drug delivery systems [30]. In general, they exhibit good binding ability on the surface of drug particles, and affinity to hydrophobic and hydrophilic areas [31]. In particular, it has been reported that interactions between PZQ and PVP are mostly van der Waals forces [32].

Moreover, the solubility of the formulated drug in the stabilizer solution plays an important role in the particle size increase during storage, in terms of Ostwald ripening [33]. Therefore, the stabilizer should have a slight effect on drug solubility [33]. For that reason, it is critical to determine the solubility of the drug in different stabilizer solutions, in order to establish the PZQ supersaturation concentration required. Binary stabilizer solutions were prepared at a total concentration of 1% (w/v). These binary solutions consisted of a combination of P188 with SLS, PVP or MDX, in a 1:1 ratio. Moreover, P188 was used individually (1% w/v). An excess of PZQ was added to 7 mL of stabilizer solutions (n = 3), and the mixtures were stirred for 96 h at 40 °C (the highest temperature reached by the dispersion during the HPH process). The concentration of PZQ was determined at 264 nm (Varian Cary 50Conc, Varian Instruments, Australia), after centrifugation (3500 rpm, 15 min) and filtration (0.45-μm pore-size nylon membrane, Microclar, Argentina) of the samples. At the PZQ maximum absorption wavelength, no interference signals were recorded for stabilizer solutions. Statistical evaluation of solubility results was performed using Analysis of Variance (ANOVA) followed by LSD multiple comparisons. Significance was tested at the 0.05 level of probability (p).

2.2.3. Preparation of PZQ dispersions

PZQ (2 g), as supplied, was dispersed within the stabilizer solution at a concentration of 1% (w/v), in a final volume of 200 mL. The drug:stabilizer ratio was 1:1 (w/w), i.e. the concentration of stabilizer was 1% (w/v) in the case of F1, and 0.5% per each stabilizer in the case of F2-F4 (Table 1). The suspensions were stirred at 1000 rpm for 10 min. To avoid obstruction of the homogenization valve, a first size-reduction step was needed [10]. Therefore, mixtures were pre-homogenized at 22,000 rpm for 10 min (PRO Scientific PRO250). The obtained suspensions were then processed by HPH (APV 1000, Denmark) for 60 cycles at 950 bar.

Table 1
Formulated PZQ systems.

Sample	Stabilizer mixture[a]
F1	P188
F2	P188-SLS
F3	P188-MDX
F4	P188-PVP

[a] API concentration of 1% (w/v) and a PZQ:stabilizer mixture ratio of 1:1.