International Journal of Pharmaceutics 495 (2015) 536–550

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

# Development of flexible and dispersible oral formulations containing praziquantel for potential schistosomiasis treatment of pre-school age children

Ramona Trastullo[a], Luisa Stella Dolci[b], Nadia Passerini[a], Beatrice Albertini[a,*]

[a] Department of Pharmacy and BioTechnology, University of Bologna, Via S. Donato 19/2, 40127 Bologna, Italy
[b] Department of Chemistry "G. Ciamician", University of Bologna, Via Selmi 2, 40126 Bologna, Italy

ARTICLE INFO

*Article history:*
Received 16 July 2015
Received in revised form 8 September 2015
Accepted 11 September 2015
Available online 16 September 2015

*Keywords:*
Praziquantel
Neglected tropical diseases
Wet granulation
Solid-state characterization
Paediatric dosage form
Extemporaneous aqueous suspensions
Stability

ABSTRACT

Praziquantel (PZQ), an anthelmintic drug used in developing countries for the treatment of schistosome infections, was processed using the fluid bed wet granulation technology to prepare fast dispersible granules, as an appropriate and flexible dosage form for pre-school-aged children. Granulation experiments were performed incorporating PZQ either in the powder mixture, according to the traditional way, or in the liquid phase containing wetting agents. In the powder mixture several excipients were tested: Flowlac 100 as filler, Galeniq 721 (isomalt) and Neosorb P 100 T (D-sorbitol) as sweeteners and PVP K30 as binder; while in the liquid phase Lutrol F68, Cremophor RH 40 or Tween 80 as surfactants were investigated. Different formulations loaded with 10% w/w (batches 1–8) and 20% w/w of PZQ (batches 9–13) were produced The majority of granules displayed good flow properties and uniform drug content. X-ray powder diffraction showed that PZQ remained in its original crystalline state, while differential scanning calorimetry and Fourier transform-infrared analysis evidenced the formation of chemical interactions among the ingredients. The solubilisation test performed in non-sink condition to reproduce the actual condition in which a child of 4 years takes the medicine revealed that granules quickly formed a very fine suspension in water ($d_{V90}$ = 39.9 μm). Although after the granulation process the solubility of raw PZQ was not increased, adding the aqueous suspension to 500 ml of buffer solution of pH 1.5, simulating the fasted state of a child, 50% of the drug was dissolved after 30 min. After granule manipulation with milk and fruit juices, no PZQ degradation was observed during time. Finally, the selected granule formulation provided evidence to be stable even at hot and very humid climate (30 °C/75% RH), at least for the examined time.



## 1. Introduction

Nowadays, there are many challenges associated with formulating paediatric medicines for developing countries and the demand of paediatric medicine still remains at large (Sosnik et al., 2012; Ivanovska et al., 2014). In particular, there is a lack of paediatric-acceptable dosage forms for most neglected tropical diseases as the majority of oral dosage forms is designed for adult patients and lacks in dosing flexibility (World Health Organization, 2007; Conway et al., 2013). Capsules or tablets are the most common dosage forms but also difficult to swallow in small children, especially between the ages of 2 and 6 years (Zajicek et al., 2013). In 2007, four children under 36 months died from choking on albendazole tablets during a deworming campaign in Ethiopia. WHO strongly recommended that manufacturers of anthelminthics for public health programs targeted at pre-school children develop formulations that are appropriate for this age group (World Health Organization, 2007).

Praziquantel (PZQ) is an anthelmintic drug widely used in developing countries for the treatment of schistosome infections. Schistosomiasis is caused by the infection from parasitic worms (*Schistosoma mansoni*,*Schistosoma haematobium*, *Schistosoma japonicum*) and results in chronic diseases such as stunting, wasting, lack of fitness, cognitive impairment, infertility and genital disease (Mutapi et al., 2011). Schistosomiasis affects more than 200 million people worldwide out of a total of 783 million at risk (in 74 developing countries) (Skopp, 2014). The affected population includes 24 million pre-school children and 65 million school-age children, at risk of a total of 72 million and 200 million, respectively. After malaria, it is the second most prevalent disease

* Corresponding author.
*E-mail address:* beatrice.albertini@unibo.it (B. Albertini).

http://dx.doi.org/10.1016/j.ijpharm.2015.09.019
0378-5173/

in African children (Skopp, 2014). PZQ is included in the WHO Model List of Essential Medicines for Children (World Health Organization, 2011). This drug was discovered in the early seventies and is manufactured by several companies such as Bayer (Biltricide®) and Merck (Cesol® or Cisticid®). Nowadays, it is mostly available on the international market as a 600 mg film-coated tablet of 22 mm in length. The dosage is adjusted to the child bodyweight by administering in sets of 150 mg (a quarter of a tablet). The therapeutic regimen for the treatment of schitsosomiasis consists of 20 mg/kg three times a day at intervals of 4–6 h (Bayer HealthCare Pharmaceuticals Inc., 2011) or as a single dose of 40 mg/kg (depending on the parasite) (Sousa-Figueiredo et al., 2012a). It is a one-day treatment. Recently, height intervals instead of bodyweight for tablet division were also considered (Sousa-Figueiredo et al., 2012b). Moreover, it is reported that keeping the tablet or segments in the mouth can reveal a bitter taste, which can promote gagging and vomiting. Therefore, the tablet should be administered with food and swallowed whole with some liquid. From a biopharmaceutical point of view, PZQ is classified a BCS class II drug (high permeability, low solubility and extensive first-pass metabolism) (Lindenberg et al., 2004). Therefore the two main drawbacks of this drug are its bad taste and its poor water solubility, related to the high dose required.

Merck has distributed more than 160 million PZQ tablets since 2007 and 38 million school children have been treated via the Merck donation since 2008 (Skopp, 2014). Moreover, since 2003, several mass drug administration campaigns have been implemented in sub-Saharan Africa treating millions of school-aged children for schistosomiasis with PZQ (Sousa-Figueiredo et al., 2012b; Coulibaly et al., 2012). However, younger children (≤6 years) have been consistently excluded from access to such medication, highlighting a PZQ treatment gap for pre-schoolers and infants. WHO considers treatment with PZQ as being safe for children as young as four years of age, but as parasite eggs can be found in children within the first year of life, PZQ is widely used "off-label" (Sousa-Figueiredo et al., 2012b). Hence, a common approach in high endemicity areas is to crush the 600 mg PZQ tablets, mix with water or juice and then administer orally to pre-school-aged children at a dose of 40 mg/kg (Coulibaly et al., 2012). In July 2012, a non-profit private public partnership under Merck Serono's leadership, named Pediatric Praziquantel Consortium, was lunched with the aim to develop a paediatric PZQ formulation for children younger than 6 years old. In particular, orodisperisble tablets of 150 mg PZQ have been developed and are currently in clinical studies (http://www.pediatricpraziquantelconsort.org/home.html). Therefore, this scenario clearly highlights that the current standard PZQ-based medications for pre-school children are not appropriate, making dose adjustment and swallowing a challenging process in small children (Olliaro et al., 2013).

This research project focused on the development of a flexible dosage form suitable for oral administration of PZQ to children from 2 to 6 years old. According to the EMA guideline, powder, granules and pellets received "preferred acceptability" by this age group of children (EMA/CHMP/QWP/805880/2012). In this study granule formulations were investigated. Granules have the further advantage over tablets because they can be given to children as solution or dispersion in beverages or administered with food, thus improving the palatability of the formulations and the adherence to therapy. Moreover, it is reported that the bioavailability of PZQ in adults is significantly influenced by concomitant food intake and that the influence was greater with carbohydrates than with lipids (Castro et al., 2000). As reported, the effect could be related either to some pharmaceutical factors (better tablet disintegration and drug dissolution) or to several biopharmaceutical aspects (changes in hepatic blood flow or in the metabolism of the drug during the first passage through the liver). Therefore, the development of granules dispersible in water or in other common beverages such as fruit juice and milk was investigated. The rationale for the choice of formulating dispersible granules is in line with the characteristics of the drug itself, since it allows to minimize the dissolved PZQ (acceptable palatability) in addition to maintaining the dose flexibility. The obtained granules were characterized as regards the technological properties such as moisture content, flowability, friability, particle size, drug content, solubility and dissolution behavior. The physicochemical properties by means of Fourier transformed infrared (FT-IR) analysis, differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) were also characterized. Finally, granules stability in the solid state (30 °C and 75% RH, trial conditions for climatic zones IVb) (World Health Organization, 2009) and the short-term stability in milk were assessed.

## 2. Materials and methods

### 2.1. Materials

Praziquantel (2-(cyclohexylcarbonyl)-1,2,3,6,7,11b—hexahydro 4H-pyrazino[2,1-a]isoquinolin-4-one) was kindly donated by

**Table 1**
Composition of PZQ loaded-granules.

| Batches | Fluidized powder bed | | | | | | Aqueous binding solution/suspension | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | PZQ | Flowlac 100 | Avicel PH102 | Neosorb P100 | GalenIQ 721 | PVP K30 | PZQ | PVP K30 | Lutrol F68 | Cremophor RH 40 | Tween 80 |
| | Amount (%, w/w) | | | | | | Amount (%, w/w) | | | | |
| 1 | 10 | 35 | 45 | – | – | 5 | – | 5 | – | – | – |
| 2 | | 40 | 30 | – | – | – | 10 | – | 20 | – | – |
| 3 | | 40 | – | – | – | 30 | | – | 20 | – | – |
| 4 | | 40 | 20 | – | – | 10 | | – | 20 | – | – |
| 5 | | – | 20 | 40 | – | 10 | | – | 20 | – | – |
| 6 | | – | 30 | 40 | – | – | | – | – | 20 | – |
| 7 | | – | – | 40 | 30 | – | | – | 10 | 10 | – |
| 8 | | – | – | 30 | 45 | – | | – | – | 15 | – |
| 9 | | – | – | 25 | 40 | – | 20 | – | – | 15 | – |
| 10 | | – | – | 25 | 35 | – | | | | 15 | 5 |
| 11 | | | – | 35 | 30 | – | | – | 5 | 10 | – |
| 12 | | 20 | – | 35 | – | 10 | | – | – | 15 | – |
| 13 | | 35 | – | 20 | – | 10 | | – | 15 | – | – |