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Research paper

Quinine sulphate pellets for flexible pediatric drug dosing: Formulation development and evaluation of taste-masking efficiency using the electronic tongue

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Abstract

The purpose of this study was to develop a taste-masked quinine sulphate dosage form as a flexible pediatric formulation tool. Pellets were produced as they offer more flexibility to body weight dose adaptation and therefore represent an alternative to tablet breaking in pediatrics. Quinine sulphate pellets were produced via extrusion-spheronisation. Next pellets were coated using Eudragit® E PO to obtain a taste-masked formulation. Using 15% dibutyl sebacate (based on polymer weight) as a plasticizer in the formulation caused rapid pellet agglomeration during storage at 40 °C and 75% relative humidity. Using stearic acid (15% based on polymer weight) as plasticizer yielded pellets which were less sensitive to sticking. Quinine sulphate release in water within the first 5 min of dissolution testing: 9.2%, 5.9% and 2.1% of the drug dose was released from pellets coated with 10%, 20% and 30% (w/w) Eudragit® E PO, respectively. These observations correlated well with the bitterness score of the formulations determined via the Astree electronic tongue and its Bitterness Prediction Module, showing that 20% (w/w) Eudragit® E PO was required to obtain a homogeneous film and to delay quinine sulphate release sufficiently to mask the bitterness after drug administration. In acid medium immediate quinine sulphate release was obtained.

Keywords: Pediatric formulation; Quinine sulphate; Pellets; Extrusion-spheronisation; Electronic tongue; Taste-masking; Eudragit® E PO

1. Introduction

Per oral administration of drugs is a frequently used way of giving medicines to children. However, most drugs available on the pharmaceutical market have not been studied in children, resulting in widespread off-label use of pharmaceuticals in pediatrics. Only 20% of drugs marketed in the United States have labelling for pediatric use and only five of the 80 drugs most commonly used in newborns and infants are approved for pediatric use [1]. In Europe, the pediatric patient group with the highest incidence of off-label drug prescriptions is neonates, with 90% of babies in neonatal intensive care receiving at least one unlicensed or off-label drug prescription [2]. As the most suitable dosage forms for per oral administration to children (syrups, solutions) are often not available, the pediatrician has to resort to tablets which in most cases have not been designed for pediatric applications. Consequently tablets have to be split (or even crushed) to adjust the dose to

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the body weight of the patient. However, dosing due to the poor reproducibility of tablet breaking [3–6] could compromise the efficiency of the treatment.

In contrast, multiple unit dosage forms (pellets or mini-tablets) offer a flexible dosing system. Since each individual unit contains a small amount of drug, the drug dose can be easily adjusted by measuring a specific volume (i.e. weight) of these multiparticulates depending on the patient's body weight.

Since quinine is re-emerging as an important drug in the treatment of multiple-drug resistant *Plasmodium falciparum* malaria and no pediatric formulations of quinine sulphate are commercially available, the concept of multiparticulate dosage forms was explored, the aim of this work being the development of quinine sulphate pellets via extrusion-spheronisation.

Next to the dosing flexibility, pellets offer the advantage that they can be sprinkled on food, mixed with fluids (water, milk or jelly) or directly swallowed, improving patient compliance [7].

An additional formidable challenge for an oral quinine sulphate formulation is the extremely bitter taste of the drug (a 0.025% (w/v) solution was classified at the highest score on a bitter taste scale, only solutions below 0.001% were considered as having an acceptable bitter taste [8,9]). Therefore, efficient taste-masking is required to ensure patient compliance and effective pharmacotherapy, especially in pediatric applications. Although several strategies are available for taste-masking [10], coating of the quinine sulphate pellets with a polymer (Eudragit® E PO) was selected since the spherical shape of the pellets promotes the efficiency of the coating process.

2. Materials and methods

2.1. Materials

Quinine sulphate was purchased from BUFA (Uitgeest, The Netherlands). The microcrystalline cellulose grades (Avicel® PH 101 and Avicel® CL611) were obtained from FMC (Cork, Ireland). The coating polymer Eudragit® E PO was obtained from Röhm Degussa (Darmstadt, Germany), sodium lauryl sulphate and stearic acid from Federa (Brussels, Belgium), dibutyl sebacate from Sigma Aldrich (Bornem, Belgium) and magnesium stearate from Alpha Pharma (Nazareth, Belgium). Demineralised water was used as granulation liquid and as dispersion medium for coating purposes.

2.2. Production of taste-masked quinine sulphate pellets

2.2.1. Extrusion-spheronisation

Quinine sulphate was blended with a mixture of Avicel® PH 101 and Avicel® CL 611 (ratio PH101/CL611: 1/3). The batch size was 300 g of dry materials and the quinine sulphate load was 20% (w/w). The powders were dry mixed for 5 min at 60 rpm in a planetary mixer (Kenwood Major Classic, Hampshire, UK). The mixture was wetted with demineralised water (40–43% of the total mass) and granulated for 5 min using the same equipment and mixing speed. The wet mass was extruded at an extrusion speed of 60 rpm by means of a single-screw extruder (Model DG-L1, Fuji Paudal, Osaka, Japan) equipped with a domed screen having perforations of 400 or 600 μm diameter. The extrudates were spheronised (at 750 rpm during 8 min) in a spheroniser (Caleva Model 15, Sturminster Newton, UK) using a friction plate with cross-hatched geometry. The pellets were dried overnight in a forced-air oven (Memmert, Belgium) at 40 °C.

2.2.2. Coating of quinine sulphate pellets

An aqueous-based dispersion of Eudragit® E PO (11.4% w/w) was used for quinine sulphate pellets, coating. Eudragit® E PO is a cationic copolymer consisting of butylmethacrylate–(2-dimethylaminoethyl) methacrylate–methylmethacrylate (1:2:1), soluble below pH 5, swellable and permeable above pH 5. It can prevent the release of drug in saliva (pH 6.8–7.4) and readily dissolves in gastric fluids (pH 1.0–1.5). Sodium lauryl sulphate (SLS, 10% w/w based on dry polymer weight) was used as emulsifier and two plasticizers (10–15% w/w based on dry polymer weight), stearic acid (StA) or dibutyl sebacate (DBS) were evaluated. Magnesium stearate (35% w/w based on dry polymer weight) was added as antisticking agent. Sodium lauryl sulphate and the plasticizer were dispersed in part of the water and homogenized by means of a magnetic stirrer. Next Eudragit® E PO was added progressively. The mixture was homogenized for 30 min by means of a magnetic stirrer. Magnesium stearate was homogeneously suspended in the remaining part of water using a high–shear mixer (Silverson, Bucks, UK) for 10 min. Afterwards, the magnesium stearate suspension was added to the polymer dispersion and homogenized for an additional 30 min using a high–shear mixer. The coating suspension was passed through a 250 μm sieve before use. Gentle stirring was continued during the entire coating process using the magnetic stirrer.

Three hundred grams pellets (300–700 μm) were preheated for 30 min to 30 °C and coated in a fluid bed used in the bottom-spray mode with the Wurster setup (GPCG1, Glatt, Binzen, Germany). The coating conditions are presented in Table 1. After coating, the pellets were

Table 1
Parameters during the coating process of quinine sulphate pellets in GPCG1-fluid bed (Glatt)

Coating process parameters	Set values
Product load (g)	300
Nozzle diameter (mm)	0.8
Spray rate (g/min)	3.5–4.6
Atomizing air pressure (bar)	1.5
Inlet air temperature (°C)	30–35
Bed temperature (°C)	27–30