Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 66 (2007) 460–465
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

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

P.C. Kayumba [a,b], N. Huyghebaert [b], C. Cordella [c], J.D. Ntawukuliryayo [a], C. Vervaet [b], J.P. Remon [b,*]

[a] *Department of Pharmacy, National University of Rwanda, Butare, Rwanda*
[b] *Laboratory of Pharmaceutical Technology, Ghent University, Gent, Belgium*
[c] *Alpha MOS, Toulouse, France*

Received 7 June 2006; accepted in revised form 24 November 2006
Available online 1 December 2006

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

* Corresponding author. Laboratory of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Ghent University, Harelbekestraat 72, 9000 Gent, Belgium. Tel.: +32 9 264 80 56; fax: +32 9 222 82 36.
E-mail address: jeanpaul.remon@ugent.be (J.P. Remon).

0939-6411/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2006.11.018

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

cured for 30 min at the same conditions as during the coating process.

2.3. Evaluation of quinine sulphate pellets

2.3.1. Size distribution

The particle size distribution of the pellets was determined by sieve analysis, using a sieve shaker (VE, Retsch, Haan, Germany) equipped with 800, 700, 500, 300 and 250 μm sieves for 5 min at an amplitude of 2 mm.

2.3.2. Sphericity and shape

The aspect ratio and shape of the pellets were determined using an image analysis system. Photomicrographs of pellets were taken with a digital camera (Camedia C-3030 Zoom, Olympus, Tokyo, Japan), linked with a stereomicroscope system (SZX9 DF PL 1.5, Olympus, Tokyo, Japan). A cold light source (Highlight 2100, Olympus, Germany) and a ring light guide (LGR66, Olympus, Germany) were used to obtain top light illumination of the pellets against a dark surface. The images were analysed by image analysis software (AnalySIS, Soft Imaging System, Münster, Germany). The magnification was set in a way that one pixel corresponded to 5.7 μm and around 300 pellets were analysed for every batch. Each individual pellet was characterised by aspect ratio (AR) (ratio of longest Feret diameter and its longest perpendicular diameter) and two-dimensional shape factor (eR) (as described by Podczeck and Newton [11])

$$e_r = \frac{2\pi r}{P_m} - \sqrt{1 - \left(\frac{b}{l}\right)^2} \quad (1)$$

where r is pellet radius, P_m is perimeter, l is the length of pellet (longest Feret diameter) and b is a pellet breadth (longest diameter perpendicular to the longest Feret diameter).

2.3.3. Scanning electron microscopy

The morphology of the coating surface and the coating thickness were examined by scanning electron microscopy (SEM) (Joel JSM 5600 LV, Jeol, Tokyo, Japan). Pellets were cut into two halves which were platina coated using a sputter coater (Auto Fine Coater, JFC-1300, Jeol, Tokyo, Japan). The coating thickness is expressed as the mean of five pellets, with measurements at three sites per pellet.

2.3.4. Drug content

A sample of coated (20% w/w Eudragit® E PO) pellets was ground in a mortar. An accurately weighed portion of powder, equivalent to 100 mg of quinine sulphate, was dissolved in 100 ml methanol and stirred for 30 min. The mixture was filtered through a 0.2 μm cellulose acetate filter (Sartorius, Goettingen, Germany). The quinine sulphate content was assessed using a HPLC system composed of a L-7110 pump, a Lichrospher 100 RP-C18 (5 μm) column (250 × 4 mm), a L-7480 fluorescence detector (set at 325 and 375 nm as excitation and emission wavelengths, respectively) and a D-7000 integrator (Merck-Hitachi, Darmstadt, Germany). The mobile phase consisted of a filtered and degassed mixture of 0.1 M ammonium acetate, acetonitrile and methanol (40:15:45, v/v), the pH was adjusted to 3.0 using perchloric acid. Quinine sulphate content was calculated by means of a standard calibration curve of concentration (0.25–4 mg/l) versus peak areas.

2.3.5. Dissolution testing

Dissolution tests (USP XXVII) of uncoated and coated pellets (containing 100 mg quinine sulphate) were carried out using the basket method (USP Method 1) and an automated dissolution tester (VanKel, Edison, NJ, USA) at a rotational speed of 100 rpm. Nine hundred milliliters of 0.1 N hydrochloric acid and demineralised water (37 ± 0.5 °C) were used as dissolution media to evaluate the influence of polymer coating on quinine sulphate release and to determine the taste-masking efficiency, respectively. Five milliliter samples were withdrawn from the dissolution medium over a period of 2 h. The concentration of quinine sulphate was spectrophotometrically measured using UV detection (Lambda 12, Perkin-Elmer, Norwalk CT, USA) at 248 and 235 nm for acidic and water samples, respectively. The dissolution tests were performed in triplicate.

2.3.6. Evaluation of taste-masking efficiency

As an alternative to human sensory evaluation, the taste-masking properties of the formulations were evaluated via a sensor-based system, the Astree Electronic Tongue (Alpha M.O.S., Toulouse, France). Therefore, an amount of quinine sulphate pellets (uncoated and coated with 10%, 20% and 30% (w/w) Eudragit® E PO) corresponding to 100 mg quinine sulphate was added to a beaker containing 100 ml water. After a specific time interval (1–5 min) the liquid was filtered (0.45 μm) to remove the pellets and any undissolved material, and the solutions were analysed by the Astree Electronic Tongue equipped with the Bitterness Prediction Module (BPM). The BPM uses a 7-sensor array (specifically developed to evaluate bitterness) and a statistical model between instrumental and human sensory scores (elaborated using a set of bitter reference compounds). Based on the model (Partial Least Square analysis) the bitterness score of the samples (used as a marker for quinine sulphate release and coating integrity) is determined on a scale ranging from 1 to 20 (corresponding to a bitterness qualified as ''non detectable'' and ''unacceptable'', respectively) (Fig. 1). A detailed review of the Electronic Tongue system has been published by Vlasov et al. [12].

3. Results and discussion

Pellets were selected as dosage forms for flexible pediatric dosing as their multiparticulate nature allows precise adjustment of the dose depending on the body weight of the child, provided that a simple dosing system for these

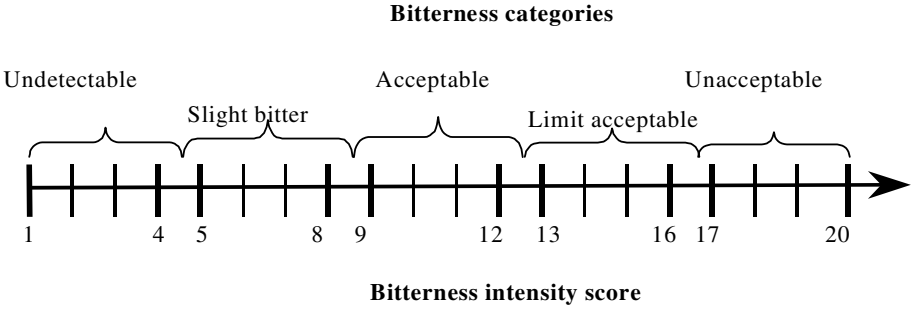

Fig. 1. Bitterness intensity score and corresponding bitterness categories.

pellets is available. More specifically the size range of 300–700 μm was selected for the pellets as preliminary tests showed that larger particles had a less acceptable mouth feel when mixed with fluids or semisolids. When smaller pellets were used a fraction of these tended to remain in the mouth which would induce an unacceptable bitter taste since the taste-masking film would dissolve some time after drug administration.

Although pellets having a high drug fraction could be formulated using extrusion/spheronisation, the drug dose was fixed at 20% (w/w) as at high drug concentration the total amount of pellets per dosing would be too small.

Fig. 2 summarizes the size distribution of the pellets containing 20% quinine sulphate produced via extrusion/spheronisation using extrusion screens having different perforation diameters (400 and 600 μm). As shown, most of the pellets produced ranged between 500 and 700 μm. The 400 μm screen was more suitable to produce 300–700 μm pellets as 95.9% of the pellets were within this interval. The 600 μm screen yielded only 66.4% pellets within the required range as in excess of 30% of the particles was larger than 700 μm. The aspect ratio and two-dimensional shape factor of the pellets produced with the 400 μm screen were 1.15 ± 0.08 and 0.52 ± 0.1, respectively, making them suitable for coating.

There was no impact of pellet size on the release rate from uncoated quinine sulphate pellets in 0.1 N hydrochloric acid: drug release from all pellet fractions (300–500 μm, 500–700 μm and 700–800 μm) was complete within 10 min. The mean quinine content was 96.8 ± 1.8 % ($n = 6$), complying with the USP 27 interval of 90–110% required for quinine sulphate content.

Coating of the 300–700 μm pellet fraction using a Eudragit® E PO-based dispersion was possible. However, using 15% DBS (based on polymer weight) as a plasticizer in the formulation caused pellet agglomeration after one week storage at 40 °C and 75% relative humidity. A high concentration of plasticizer decreased the minimum film formation temperature of the polymer, correlating with an increase in tackiness of the film [13]. In addition to the low T_g when Eudragit® E PO was plasticized with DBS (~10 °C) [14], this agglomeration process was accelerated by the plasticizing effect of water when it is absorbed by the polymer film during storage at high relative humidity [15]. Similar agglomeration phenomena have been observed following storage at high temperature and relative humidity of pellets coated with acrylic and cellulosic polymer films [16]. Reducing the plasticizer concentration to 10% did not prevent pellet agglomeration during storage and in addition this plasticizer concentration resulted in a higher drug release rate during the initial stages of the dissolution test (Fig. 3). This observation was due to the suboptimal plasticizer concentration, resulting in cracks in the film which allowed the dissolution medium to penetrate

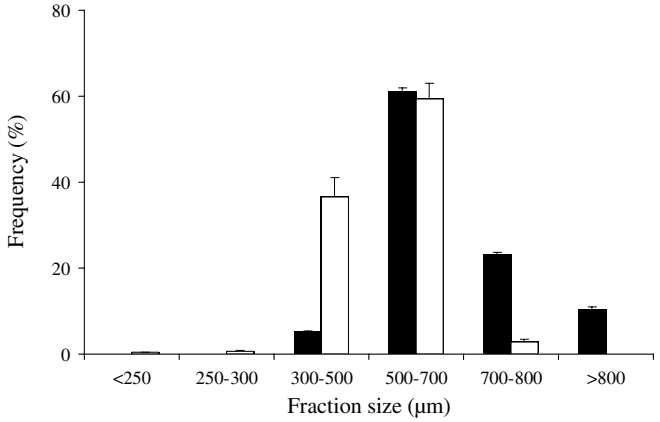

Fig. 2. Size distribution of the pellets containing 20% quinine sulphate and produced via extrusion/spheronisation using extrusion screens having 400 μm (□) and 600 μm (■) perforations, diameter.

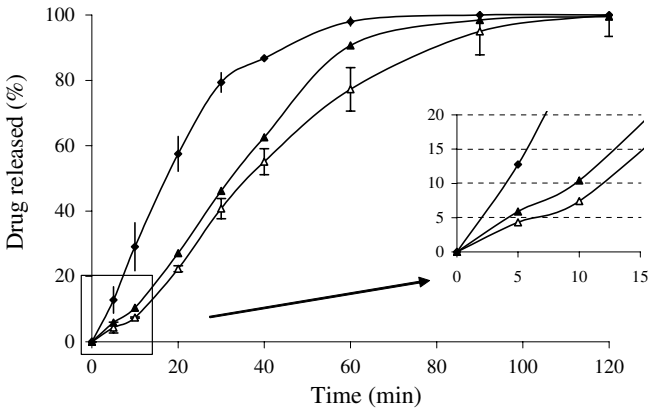

Fig. 3. Release (%) of quinine sulphate in water ($n = 3$), from pellets coated with 20% (w/w) Eudragit® E PO using 15% (△) dibutyl sebacate, 10% (◆) dibutyl sebacate and 15% stearic acid (▲) as plasticizer.

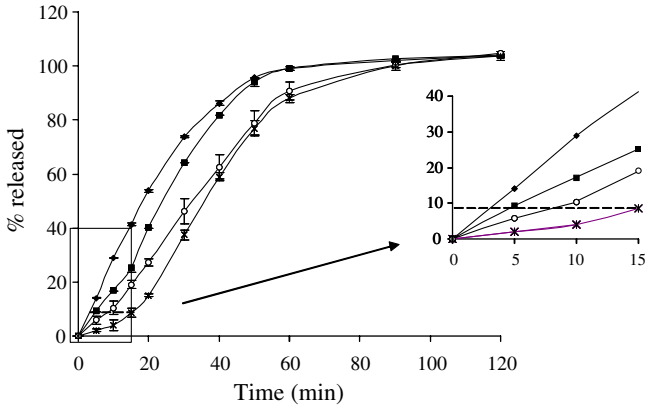

Fig. 4. Release of quinine sulphate in water ($n = 3$), from uncoated pellets (◆) and coated pellets with 10 (■), 20 (○) and 30% (×) (w/w) Eudragit® E PO. Dashed line (~9.4 mg/l quinine sulphate) indicating the upper limit concentrations without bitter taste mouth feel according to Suzuki et al. and Katsuragi et al. [8,9].

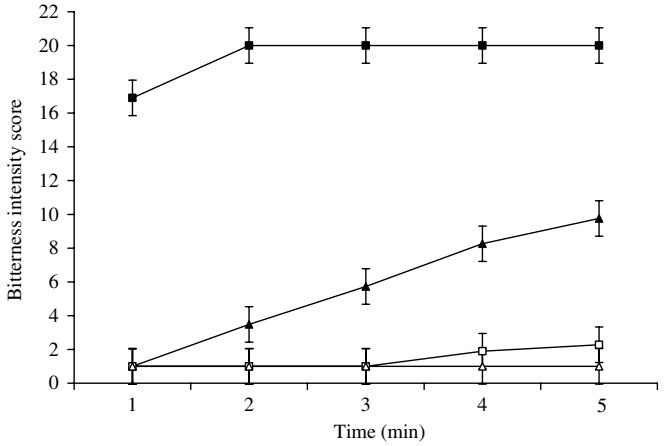

Fig. 5. Bitterness score (±SD, $n = 6$) of quinine sulphate pellets in function of time. Bitterness of quinine sulphate pellets (uncoated (■) and coated with 10 (▲), 20 (□) and 30% (△) (w/w) Eudragit® E PO) was measured using the Astree electronic tongue and its Bitterness Prediction Module.

into the pellet and dissolve the drug. This correlated well with the loss of the taste-masking properties of the formulation. Substituting DBS as a plasticizer by StA (15% based on polymer weight) yielded pellets which were less sensitive to sticking. This might be due to the higher glass transition temperature (T_g) when Eudragit® EPO is plasticized by StA (26 °C) [14]. Adding stearic acid to the coating dispersion had no effect on the taste-masking potential as confirmed by the dissolution profiles (Fig. 3). As a delay in the onset of drug release was essential to obtain a taste-masking effect, the dissolution profiles of the coated pellets in water (Fig. 4) confirmed the ability of a Eudragit® E PO-based coating to delay quinine sulphate release from pellets. These release data in water (pH ~ 7) suggested that Eudragit® E PO can sufficiently delay the release of quinine sulphate in saliva whose pH is between 6.8 and 7.4 [17]. Whereas about 14% of quinine sulphate was released from uncoated pellets within the first 5 min, the initial release was reduced depending on the amount of coating: 9.2%, 5.9% and 2.1% drug released from pellets coated with 10%, 20% and 30% (w/w) Eudragit® E PO, respectively. Based on papers of Suzuki et al. [8] and Katsuragi et al. [9] a drug release below 9% resulted in a solution with an acceptable bitter taste (i.e. quinine sulphate solutions having a concentration below 10 mg/l). However, based on the dissolution profiles it was impossible to assess which pellet formulations will have an acceptable taste perception for the patient during in vivo application (due to the different experimental conditions, e.g. volume and mixing hydrodynamics). Therefore, pellets were evaluated under conditions which are a better representation of the conditions during administration of these formulations: immersion in 100 ml water (pellets are mixing with food or fluids before administration) during 5 min. The bitterness score of the resulting quinine sulphate solutions was evaluated in function of time using the bitterness prediction module of the electronic tongue (providing a direct correlation with the in vivo bitterness perception via a model established with a taste panel) (Fig. 5). Without coating the bitterness

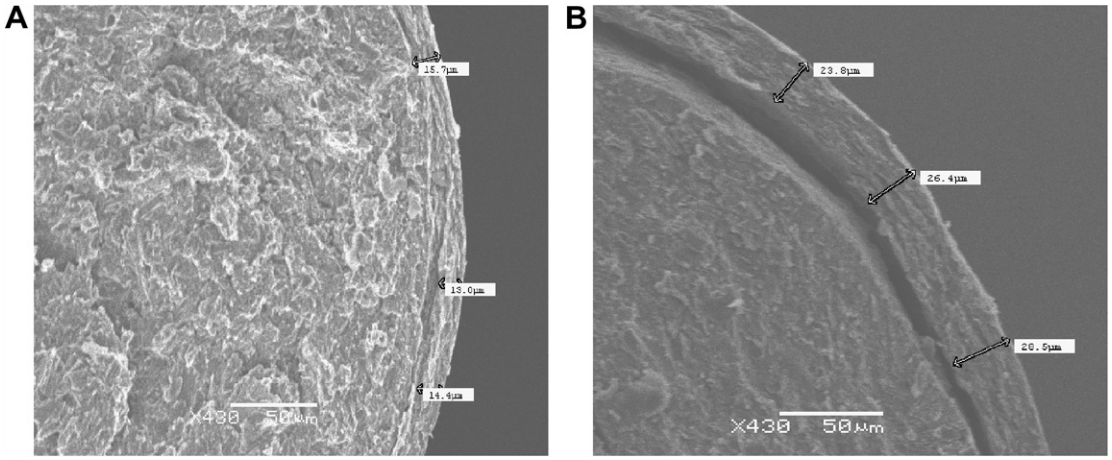

Fig. 6. SEM picture of a cross-section of a pellet coated with (A) 10 and (B) 20% (w/w) Eudragit® E PO.

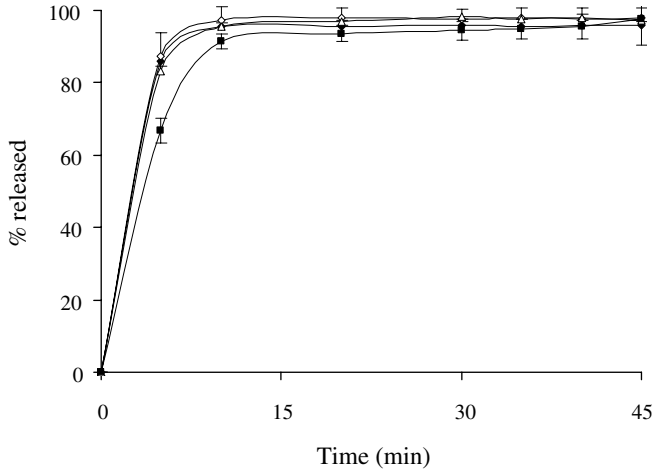

Fig. 7. Release of quinine sulphate in 0.1 N hydrochloric acid ($n = 3$), from uncoated pellets (◇) and coated pellets with 10 (◆), 20 (△) and 30% (■) (w/w) Eudragit® E PO.

reached an unacceptable level (intensity score $\geqslant 16.5$) within the first minute. Using a 10% (w/w) Eudragit® E PO coat, quinine sulphate release was delayed, yielding a bitterness score of 3.5 (undetectable) and 9.8 (acceptable) after 3 and 5 min, respectively. When applying $\geqslant$20% (w/w) Eudragit® E PO to the pellets no bitterness was detected (score < 4.5) even after 5 min. The standard deviation of these measurements (taking into account all 7 sensors) was lower than 3%, indicating a very good repeatability of the results. As a delay in drug release of even a few minutes has been reported to prevent the sensation of an unpleasant taste [18], the drug release of quinine sulphate pellets coated with 20% (w/w) Eudragit® E PO is considered as sufficiently delayed for the patient to swallow the pellets without experiencing any discomfort due to quinine bitterness.

SEM pictures (Fig. 6) confirmed the potential of the 20% (w/w) Eudragit® E PO-formulation for taste-masking purposes since the film (coating thickness: 26.1 ± 1.5 μm) appeared smooth and continuous, constituting a barrier between the formulation and dissolution medium. In contrast, at a coating level of 10% (w/w) Eudragit® E PO the film appeared thin and discontinuous, suggesting that taste-masking might not be sufficient. The Eudragit® E PO coating has no impact on the quinine sulphate release profile in acid medium as the dissolution profiles of uncoated and coated pellets were similar, more than 80% quinine sulphate was released within the first 10 min independent of the coating thickness (Fig. 7).

4. Conclusion

Quinine sulphate pellets were successfully produced via extrusion/spheronisation and were coated with Eudragit® E PO polymer for taste-masking purposes. Based on dissolution tests and in vitro evaluation of bitterness via the Astree electronic tongue, the taste-masking efficiency of pellets coated with 20% (w/w) Eudragit® E PO was confirmed, sufficient to delay release of a bitter taste during administration and providing immediate release in the gastro-intestinal tract. The electronic tongue provided valuable information about the evolution of bitterness intensity in function of time, which was essential for selecting of the optimal formulation among pellets having different coating thickness. Based on these data quinine sulphate taste-masked pellets are proposed in pediatrics as alternative to tablet breaking and can be used as flexible dosage form for dose adaptation to a child's body weight, provided that a simple system for accurate dosing is available.

References

[1] Milap C. Nahata, Pediatric drug formulation: challenges and potential solutions, Ann. Pharmacother. 33 (1999) 247–249.
[2] I. Choonara, S. Conroy, Unlicensed and off-label drug use in children: implication for safety, Drug Saf. 25 (2002) 1–5.
[3] H.G. Kristensen, G.H. Jorgensen, J.M. Sonnegaard, Mass uniformity of tablets broken by hand, Pharmeuropa 7 (1995) 298–302.
[4] P. Gupta, K. Gupta, Broken tablets: does the sum of the parts equal the whole? Am. J. Hosp. Pharm. 45 (1988) 1498.
[5] S. Myriam, A. Philippe, J.E. Fontan, F. Brion, Splitting tablets in half, Am. J. Hosp. Pharm. 15 (1994) 548–550.
[6] J.T. Mc Devitt, A.H. Gurst, Y. Chen, Accuracy of tablet splitting, Pharmacotherapy 18 (1998) 193–197.
[7] J. Breitkreutz, T. Wessel, J. Boos, Dosage forms for peroral drug administration to children, Pediatr. Perinat. Drug Ther. 3 (1999) 25–33.
[8] H. Suzuki, O. Hiraku, T. Yuri, I. Masaroni, M. Yoshiharu, Development of oral acetaminophen chewable tablets with inhibited bitter taste, Int. J. Pharm. 251 (2003) 123–132.
[9] Y. Katsuragi, Y. Mitsui, T. Umeda, K. Otsuji, S. Yamasawa, K. Kurihara, Basic studies for the practical use of bitterness inhibitors: selective inhibition of bitterness by phospholipids, Pharm. Res. 14 (1997) 720–724.
[10] H. Sohi, Y. Sultana, R.K. Khar, Taste masking technologies in oral pharmaceuticals: recent developments and approaches, Drug Dev. Ind. Pharm. 30 (5) (2004) 429–448.
[11] F. Podczeck, J.M. Newton, A shape factor to characterize the quality of spheroids, J. Pharm. Pharmacol. 46 (1994) 82–85.
[12] Y. Vlasov, A. Legin, A. Rudnitskaya, Electronic tongues and their analytical application, Anal. Bioanal. Chem. 373 (2002) 136–146.
[13] M. Wesseling, F. Kuppler, R. Bodmeier, Tackiness of acrylic and cellulosic polymer films used in the coating of solid dosage forms, Eur. J. Pharm. Biopharm. 47 (1999) 73–78.
[14] H.U. Petereit, New aspects of moisture protection and insulation of solid dosage forms with Eudragit® E PO, 33rd International Eudragit workshop, Darmstadt, Germany, 2001.
[15] H.U. Petereit, W. Weisbrod, Formulation and process considerations affecting the stability of solid dosage formulated with methacrylate copolymers, Eur. J. Pharm. Biopharm. 47 (1999) 15–25.
[16] K. Thoma, K. Bechtold, Influence of aqueous coatings on the stability of enteric coated pellets and tablets, Eur. J. Pharm. Biopharm. 47 (1999) 39–50.
[17] A.M. Pedersen, A. Bardow, B.S. Jansen, B. Nauntofte, Saliva and gastrointestinal functions of taste, mastication, swallowing and digestion, Oral Dis. 8 (2002) 117–129.
[18] J. Klancke, Dissolution testing of orally disintegrating tablets, Dissol. Technol. 10 (2003) 6–8.