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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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## 13 Abstract

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

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

## 28 1. Introduction

29 Per oral administration of drugs is a frequently used way  
30 of giving medicines to children. However, most drugs avail-  
31 able on the pharmaceutical market have not been studied  
32 in children, resulting in widespread off-label use of pharma-  
33 ceuticals in pediatrics. Only 20% of drugs marketed in the

United States have labelling for pediatric use and only five 34  
of the 80 drugs most commonly used in newborns and 35  
infants are approved for pediatric use [1]. In Europe, the 36  
pediatric patient group with the highest incidence of off- 37  
label drug prescriptions is neonates, with 90% of babies 38  
in neonatal intensive care receiving at least one unlicensed 39  
or off-label drug prescription [2]. As the most suitable dos- 40  
age forms for per oral administration to children (syrups, 41  
solutions) are often not available, the pediatrician has to 42  
resort to tablets which in most cases have not been 43  
designed for pediatric applications. Consequently tablets 44  
have to be split (or even crushed) to adjust the dose to 45

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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 (Mettmert, 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 pre-heated 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

142 cured for 30 min at the same conditions as during the coat-  
143 ing process.

### 144 2.3. Evaluation of quinine sulphate pellets

#### 145 2.3.1. Size distribution

146 The particle size distribution of the pellets was deter-  
147 mined by sieve analysis, using a sieve shaker (VE, Retsch,  
148 Haan, Germany) equipped with 800, 700, 500, 300 and  
149 250  $\mu\text{m}$  sieves for 5 min at an amplitude of 2 mm.

#### 150 2.3.2. Sphericity and shape

151 The aspect ratio and shape of the pellets were deter-  
152 mined using an image analysis system. Photomicrographs  
153 of pellets were taken with a digital camera (Camedia C-  
154 3030 Zoom, Olympus, Tokyo, Japan), linked with a stereo-  
155 microscope system (SZX9 DF PL 1.5, Olympus, Tokyo,  
156 Japan). A cold light source (Highlight 2100, Olympus, Ger-  
157 many) and a ring light guide (LGR66, Olympus, Germany)  
158 were used to obtain top light illumination of the pellets  
159 against a dark surface. The images were analysed by image  
160 analysis software (AnalySIS, Soft Imaging System, Mün-  
161 ster, Germany). The magnification was set in a way that  
162 one pixel corresponded to 5.7  $\mu\text{m}$  and around 300 pellets  
163 were analysed for every batch. Each individual pellet was  
164 characterised by aspect ratio (AR) (ratio of longest Feret  
165 diameter and its longest perpendicular diameter) and  
166 two-dimensional shape factor (eR) (as described by  
167 Podczeczek and Newton [11])

$$169 \quad e_r = \frac{2\pi r}{P_m} - \sqrt{1 - \left(\frac{b}{l}\right)^2} \quad (1)$$

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

#### 174 2.3.3. Scanning electron microscopy

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

#### 182 2.3.4. Drug content

183 A sample of coated (20% w/w Eudragit® E PO) pellets  
184 was ground in a mortar. An accurately weighed portion  
185 of powder, equivalent to 100 mg of quinine sulphate, was  
186 dissolved in 100 ml methanol and stirred for 30 min. The  
187 mixture was filtered through a 0.2  $\mu\text{m}$  cellulose acetate filter  
188 (Sartorius, Goettingen, Germany). The quinine sulphate  
189 content was assessed using a HPLC system composed of  
190 a L-7110 pump, a Lichrospher 100 RP-C18 (5  $\mu\text{m}$ ) column  
191 (250  $\times$  4 mm), a L-7480 fluorescence detector (set at 325

and 375 nm as excitation and emission wavelengths, respec-  
tively) and a D-7000 integrator (Merck-Hitachi, Darms-  
tadt, Germany). The mobile phase consisted of a filtered  
and degassed mixture of 0.1 M ammonium acetate, aceto-  
nitrile 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

200 Dissolution tests (USP XXVII) of uncoated and coated  
201 pellets (containing 100 mg quinine sulphate) were carried  
202 out using the basket method (USP Method 1) and an auto-  
203 mated dissolution tester (VanKel, Edison, NJ, USA) at a  
204 rotational speed of 100 rpm. Nine hundred milliliters of  
205 0.1 N hydrochloric acid and demineralised water  
206 ( $37 \pm 0.5$  °C) were used as dissolution media to evaluate  
207 the influence of polymer coating on quinine sulphate  
208 release and to determine the taste-masking efficiency,  
209 respectively. Five milliliter samples were withdrawn from  
210 the dissolution medium over a period of 2 h. The concen-  
211 tration of quinine sulphate was spectrophotometrically  
212 measured using UV detection (Lambda 12, Perkin-Elmer,  
213 Norwalk CT, USA) at 248 and 235 nm for acidic and water  
214 samples, respectively. The dissolution tests were performed  
215 in triplicate. 216

#### 2.3.6. Evaluation of taste-masking efficiency

217 As an alternative to human sensory evaluation, the taste-  
218 masking properties of the formulations were evaluated via a  
219 sensor-based system, the Astree Electronic Tongue (Alpha  
220 M.O.S., Toulouse, France). Therefore, an amount of quin-  
221 ine sulphate pellets (uncoated and coated with 10%, 20%  
222 and 30% (w/w) Eudragit® E PO) corresponding to 100 mg  
223 quinine sulphate was added to a beaker containing 100 ml  
224 water. After a specific time interval (1–5 min) the liquid  
225 was filtered (0.45  $\mu\text{m}$ ) to remove the pellets and any undis-  
226 solved material, and the solutions were analysed by the  
227 Astree Electronic Tongue equipped with the Bitterness Pre-  
228 diction Module (BPM). The BPM uses a 7-sensor array  
229 (specifically developed to evaluate bitterness) and a statisti-  
230 cal model between instrumental and human sensory scores  
231 (elaborated using a set of bitter reference compounds).  
232 Based on the model (Partial Least Square analysis) the bit-  
233 terness score of the samples (used as a marker for quinine  
234 sulphate release and coating integrity) is determined on a  
235 scale ranging from 1 to 20 (corresponding to a bitterness  
236 qualified as “non detectable” and “unacceptable”, respec-  
237 tively) (Fig. 1). A detailed review of the Electronic Tongue  
238 system has been published by Vlasov et al. [12]. 239

## 3. Results and discussion

240 Pellets were selected as dosage forms for flexible pedi-  
241 atric dosing as their multiparticulate nature allows precise  
242 adjustment of the dose depending on the body weight of  
243 the child, provided that a simple dosing system for these  
244

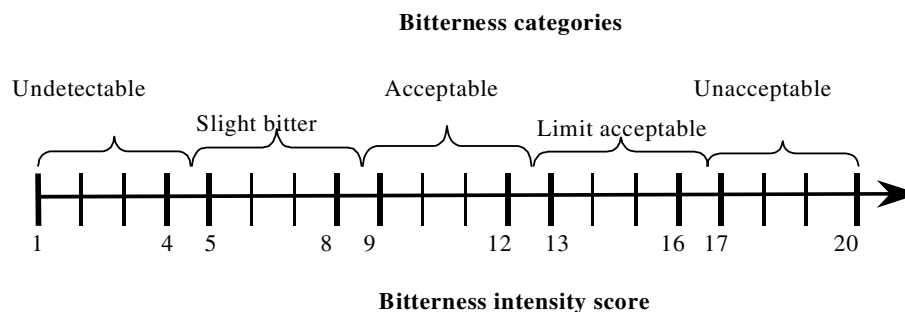


Fig. 1. Bitterness intensity score and corresponding bitterness categories.

pellets is available. More specifically the size range of 300–700  $\mu\text{m}$  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  $\mu\text{m}$ ). As shown, most of the pellets produced ranged between 500 and 700  $\mu\text{m}$ . The 400  $\mu\text{m}$  screen was more suitable to produce 300–700  $\mu\text{m}$  pellets as 95.9% of the pellets were within this interval. The 600  $\mu\text{m}$  screen yielded only 66.4% pellets within the required range as in excess of 30% of the particles was larger than 700  $\mu\text{m}$ . The aspect ratio and two-dimensional shape factor of the pellets produced with the 400  $\mu\text{m}$  screen were  $1.15 \pm 0.08$  and  $0.52 \pm 0.1$ , 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  $\mu\text{m}$ , 500–700  $\mu\text{m}$  and 700–800  $\mu\text{m}$ ) was complete within 10 min. The mean quinine content was  $96.8 \pm 1.8\%$  ( $n = 6$ ), complying with the USP 27 interval of 90–110% required for quinine sulphate content.

Coating of the 300–700  $\mu\text{m}$  pellet fraction using a Eudragit<sup>®</sup> 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<sup>®</sup> E PO was plasticized with DBS ( $\sim 10$  °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 sub-optimal plasticizer concentration, resulting in cracks in the film which allowed the dissolution medium to penetrate

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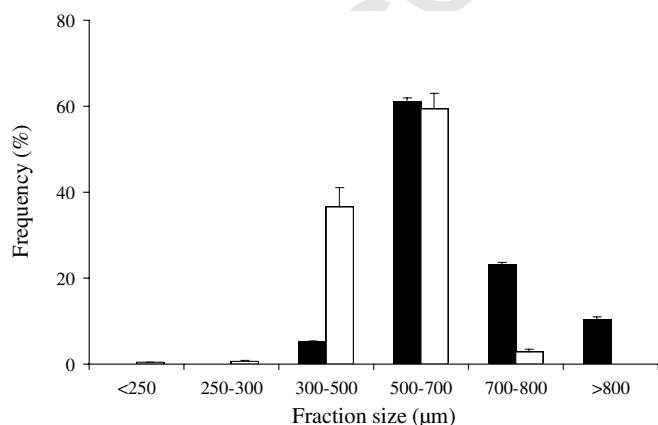


Fig. 2. Size distribution of the pellets containing 20% quinine sulphate and produced via extrusion/spheronisation using extrusion screens having 400  $\mu\text{m}$  ( $\square$ ) and 600  $\mu\text{m}$  ( $\blacksquare$ ) perforations, diameter.

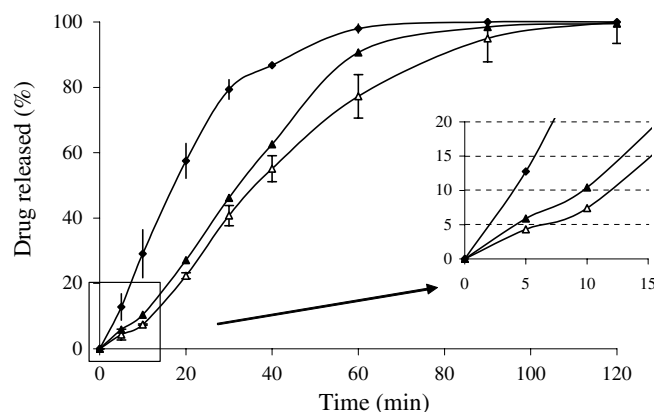


Fig. 3. Release (%) of quinine sulphate in water ( $n = 3$ ), from pellets coated with 20% (w/w) Eudragit<sup>®</sup> E PO using 15% ( $\Delta$ ) dibutyl sebacate, 10% ( $\blacklozenge$ ) dibutyl sebacate and 15% stearic acid ( $\blacktriangle$ ) as plasticizer.

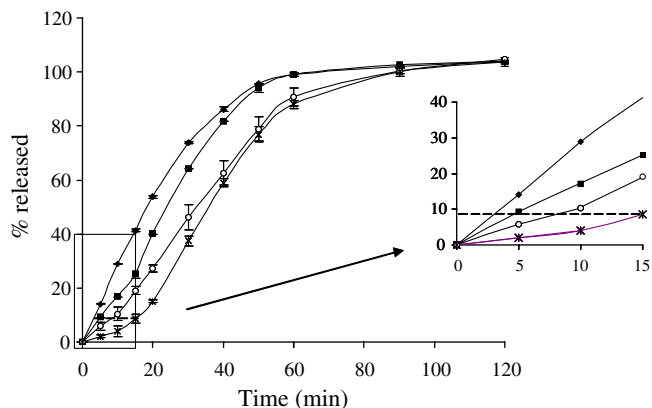


Fig. 4. Release of quinine sulphate in water ( $n = 3$ ), from uncoated pellets (◆) and coated pellets with 10 (■), 20 (○) and 30% (×) (w/w) Eudragit® E PO. Dashed line ( $\sim 9.4$  mg/l quinine sulphate) indicating the upper limit concentrations without bitter taste mouth feel according to Suzuki et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

299 into the pellet and dissolve the drug. This correlated well  
 300 with the loss of the taste-masking properties of the formula-  
 301 tion. Substituting DBS as a plasticizer by StA (15% based  
 302 on polymer weight) yielded pellets which were less sensitive  
 303 to sticking. This might be due to the higher glass transition  
 304 temperature ( $T_g$ ) when Eudragit® EPO is plasticized by  
 305 StA (26 °C) [14]. Adding stearic acid to the coating disper-  
 306 sion had no effect on the taste-masking potential as confir-  
 307 med by the dissolution profiles (Fig. 3). As a delay in  
 308 the onset of drug release was essential to obtain a taste-  
 309 masking effect, the dissolution profiles of the coated pellets  
 310 in water (Fig. 4) confirmed the ability of a Eudragit® E PO-  
 311 based coating to delay quinine sulphate release from pel-  
 312 lets. These release data in water (pH  $\sim 7$ ) suggested that  
 313 Eudragit® E PO can sufficiently delay the release of quinine  
 314 sulphate in saliva whose pH is between 6.8 and 7.4 [17].  
 315 Whereas about 14% of quinine sulphate was released from  
 316 uncoated pellets within the first 5 min, the initial release  
 317 was reduced depending on the amount of coating: 9.2%,  
 318 5.9% and 2.1% drug released from pellets coated with

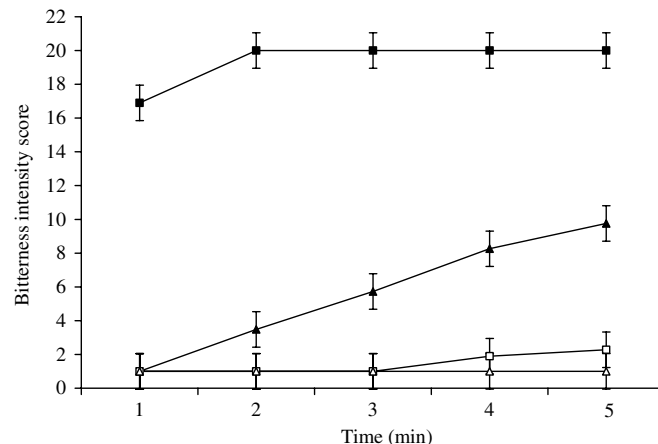


Fig. 5. Bitterness score ( $\pm$ SD,  $n = 6$ ) of quinine sulphate pellets in function of time. Bitterness of quinine sulphate pellets (uncoated (■) and coated with 10 (▲), 20 (□) and 30% (△) (w/w) Eudragit® E PO) was measured using the Astree electronic tongue and its Bitterness Prediction Module.

10%, 20% and 30% (w/w) Eudragit® E PO, respectively. 319  
 Based on papers of Suzuki et al. [8] and Katsuragi et al. 320  
 [9] a drug release below 9% resulted in a solution with an 321  
 acceptable bitter taste (i.e. quinine sulphate solutions hav- 322  
 ing a concentration below 10 mg/l). However, based on the 323  
 dissolution profiles it was impossible to assess which pellet 324  
 formulations will have an acceptable taste perception for 325  
 the patient during in vivo application (due to the different 326  
 experimental conditions, e.g. volume and mixing hydrody- 327  
 namics). Therefore, pellets were evaluated under conditions 328  
 which are a better representation of the conditions during 329  
 administration of these formulations: immersion in 330  
 100 ml water (pellets are mixing with food or fluids before 331  
 administration) during 5 min. The bitterness score of the 332  
 resulting quinine sulphate solutions was evaluated in func- 333  
 tion of time using the bitterness prediction module of the 334  
 electronic tongue (providing a direct correlation with the 335  
 in vivo bitterness perception via a model established with 336  
 a taste panel) (Fig. 5). Without coating the bitterness 337

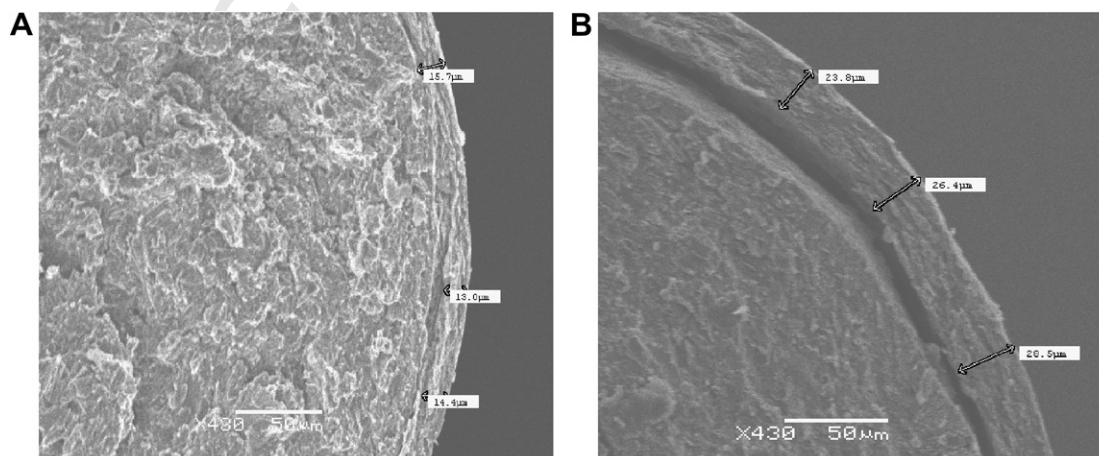


Fig. 6. SEM picture of a cross-section of a pellet coated with (A) 10 and (B) 20% (w/w) Eudragit® E PO.

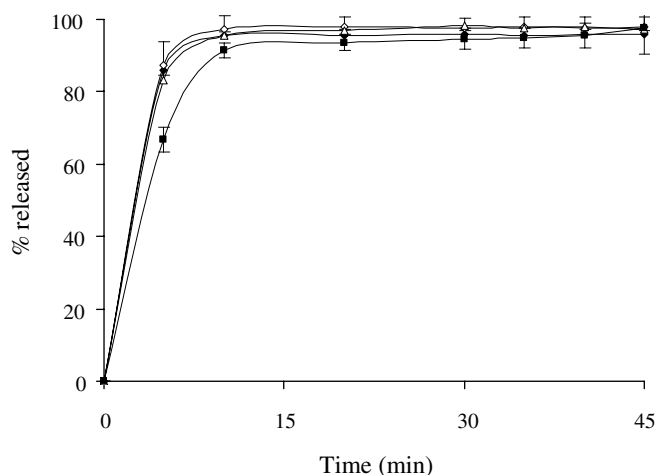


Fig. 7. Release of quinine sulphate in 0.1 N hydrochloric acid ( $n = 3$ ), from uncoated pellets ( $\diamond$ ) and coated pellets with 10 ( $\blacklozenge$ ), 20 ( $\triangle$ ) and 30% ( $\blacksquare$ ) (w/w) Eudragit<sup>®</sup> E PO.

reached an unacceptable level (intensity score  $\geq 16.5$ ) within the first minute. Using a 10% (w/w) Eudragit<sup>®</sup> 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  $\geq 20\%$  (w/w) Eudragit<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> E PO-formulation for taste-masking purposes since the film (coating thickness:  $26.1 \pm 1.5 \mu\text{m}$ ) appeared smooth and continuous, constituting a barrier between the formulation and dissolution medium. In contrast, at a coating level of 10% (w/w) Eudragit<sup>®</sup> E PO the film appeared thin and discontinuous, suggesting that taste-masking might not be sufficient. The Eudragit<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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.

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