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Research paper

Pediatric drug formulations of sodium benzoate: I. Coated granules with a hydrophilic binder

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Abstract

High doses of sodium benzoate are applied in the treatment of some rare metabolic disorders. In most cases children are affected who often refuse the oral uptake of sodium benzoate as a powder or in solution due to its bad taste. Therefore, small-sized, saliva-resistant microcapsules have been developed containing high doses of the drug substance. Granules were produced by roller compacting of sodium benzoate powder without any additives, by solvent-free cold extrusion and hot-melt extrusion adding poly(ethylene glycol)s of different grades. The granules with a diameter of less than 1 mm were film-coated by an ethanolic solution of Eudragit® E 100. The microcapsules from hot-melt extrusion containing 25% Macrogol 4000 were most stable during the coating process and showed the highest yields. Sodium benzoate is completely released from the microcapsules within 9 min into 0.1 N HCl and 0.01 N HCl whereas dissolution into buffer pH 6.8 is different in the initial phase and completed after 14 min. The bad taste of sodium benzoate is not recognized in the buccal space for at least 5 min. The microcapsules are stable during storage for at least 6 months.

Keywords: Pediatric formulations; Orphan drugs; Inherited metabolic disorders; Urea cycle disorders; Microencapsulation; Solvent-free granulation; Roller compacting; Extrusion; Sodium benzoate; Polymethacrylate

1. Introduction

Sodium benzoate is usually added to pharmaceutical preparations as a preservative agent. Furthermore, sodium benzoate has been successfully applied at high doses in the symptomatic treatment of rare, inherited metabolic disorders such as non-ketotic hyperglycinemia [1,2], hyperammonemia [3], and hyperargininemia [4]. In the liver benzoate conjugates with glycine forming hippurate, which is efficiently excreted in the urine. High doses of sodium benzoate (250–700 mg/day per kg body wt.) are necessary for the treatment, e.g. six times 1 g for a 2-year-old infant per day. Due to the bad taste of sodium benzoate, most children refuse the oral uptake of drug solutions or suspensions in any composition. In general, the development of oral dosage forms that are well accepted by children at different development stages is often neglected [5]. The objective of the present study was to develop solid, multiparticulate formulations of sodium benzoate, which are easy to swallow and suitable for pediatric patients. The new formulations should release only negligible amounts of sodium benzoate into the buccal space, but should dissolve in the acidic gastric fluid releasing sodium benzoate rapidly and completely.

Sodium benzoate is commercially available as a fine powder. The crystals are too small for film-coating by pan or air-suspension techniques [6,7]. Sodium benzoate is hygroscopic, highly soluble in water at neutral or basic pH and partly undergoes sublimation. Classical wet granulation techniques are crucial in this matter because humidity, solvent evaporation, curing or drying may decrease the drug load of the granules significantly [8]. Roller compacting [9], hot-melt extrusion [10], extrusion at moderate temperatures [11], and cold extrusion [12] are relatively new techniques

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in the pharmaceutical field, which yield homogeneous and stable granules without any solvent residuals. In the present study, various techniques were applied for preparing robust granules with high sodium benzoate content.

2. Materials and methods

2.1. Materials

Sodium benzoate, Macrogol 4000 powder, Macrogol 2000 powder, and Macrogol 1500 perls were obtained from Synopharm (Barsbüttel, Germany). Macrogol 4000 fine powder was a gift from BASF (Ludwigshafen, Germany). Triethylcitrate was obtained from Boehringer (Ingelheim, Germany), ethanol from Merck (Darmstadt, Germany), and colloidal silicium dioxide hydrate (Syloid® 244 FP) from Grace (Worms, Germany). All were of Ph. Eur. grades. Eudragit® E 100 which complies with the German Pharmacopoeia (DAB 2001) monograph Butylmethacrylate-(2-dimethylaminoethyl)methacrylate–methylmethacrylate–copolymer (1:2:1) was a gift from Röhm (Darmstadt, Germany). Hydrochloric acid, acetic acid, dibasic sodium phosphate, ammonium acetate and citric acid were of analytical grades and obtained from Merck (Darmstadt, Germany). All materials were used as received.

2.2. Granulation by roller compacting

Sodium benzoate powder was homogenized for 5 min in a Bohle LM 20 mixer (Ennigerloh, Germany). Roller compaction and dry granulation was carried out by a Gerteis Minipaktor® (Jona, Switzerland) at 20 kN/cm using plain rolls with mounted side rim sealing system. Gap width and roll speed were set to 1.5 mm and 3 rpm, respectively. These parameters were kept constant by using the fully automatic production mode [13]. Subsequently, the ribbon was dry granulated using a screen of 1.0-mm mesh width.

2.3. Granulation by cold extrusion

Sodium benzoate powder was mixed together with up to 25% (w/w) Macrogol and homogenized for 5 min in a Bosch mixer (Stuttgart, Germany). The dry powder blends were fed at room temperature to the rotary ring die press PP 85 (Schlüter, Neustadt, Germany) [14]. The bulk was extruded through a 90° entry die of 1-mm diameter and 5-mm length. The piston was constantly running. Cylindrical extrudates with a length of 3–5 cm and a diameter of 1 mm were collected in a beaker. The extrudates were then passed through a 1.0-mm mesh sieve crushing to granules.

2.4. Granulation by hot-melt extrusion

Sodium benzoate powder was passed through a 1-mm sieve and mixed together with up to 25% (w/w) Macrogol 4000 in a Bohle LM 20 mixer for 5 min. The dry powder blend was fed to a twin-screw extruder Micro 27 GL (Leistritz, Nürnberg, Germany). A temperature gradient was chosen with five segments from the feeding area at 70 °C, then one segment at 40 °C, and 20 °C just before the die. Cylindrical extrudates with a diameter of 1 mm were obtained. The extrudates were dry granulated by a Minipaktor® Granulator (Gerteis, Jona, Switzerland) using a screen of 1.0-mm mesh width.

2.5. Microencapsulation

The granules obtained by roller compaction, hot-melt or cold extrusion were screened by sieve analysis; 250 g of the fraction between 400 and 1000 μm was subjected to a fluid-bed coater Strea-1 (Aeromatic-Fielder, Bubendorf, Switzerland). The coating system was used in the Wurster configuration using a bottom-spray nozzle, a draft tube and a large expansion chamber [15]. A perforated stainless steel plate used as an air distributor was located at the lower end of the product container. The temperature of the inlet air was 40 °C, outlet air 31 °C and the air volume was 30 m^3/h. For granules with Macrogol 1500, the temperature of the inlet air was reduced to 30 °C. The polymeric coating dispersion, consisting of 25 g Eudragit® E 100, 2.5 g triethyl citrate, 2.5 g silicium dioxide hydrate, and 200 g ethanol 96%, was continuously applied to the nozzle via a peristaltic pump IPC-S (Ismatec, Wertheim, Germany) using flow rates between 0.8 and 1.2 g/min. Curing was carried out for 30 min in the apparatus under the aforementioned conditions.

2.6. Sodium benzoate assay

A high-performance liquid chromatography (HPLC) method, modified from Pylypiw[16], was used to determine the content of sodium benzoate in microcapsules of different composition. A 50.0 mg sample was completely dissolved in 100 ml ethanol in a volumetric flask; 5.0 ml of the solution was diluted to 100 ml by the degassed HPLC eluent, a mixture of 30% acetonitrile and 70% 0.01 M aqueous ammonium acetate solution which was adjusted to pH 4.5 by acetic acid. Fifty microliters of the solution was injected into the HPLC apparatus 655A-11 (Merck, Darmstadt, Germany) equipped with a LaChrom® L-7360 column oven (Merck) adjusted to 30 ± 0.1 °C, a reversed-phase prepacked column LiChrospher® 100 RP-18 (dimensions: 125 × 4 mm, size of packing material: 5 μm; Merck), a 655A UV/Vis spectrometer station (Merck), and an analysis computer terminal. Flow rate was 1.0 ml/min. Absorption was measured at 225 nm. The sodium benzoate contents of the microcapsules were calculated by the area under the curve of clearly resoluted absorption peaks at a retention time from 1.96 to 2.01 min compared to external calibration standards of the pure drug treated in the same manner. The method was linear over the range 0–50 mg sample weight

with a correlation coefficient of 0.999. The sodium benzoate concentrations were determined in five samples per batch.

2.7. Dissolution studies

The samples (100 mg) were subjected to the dissolution test, which was performed according to the basket method specified in Ph.Eur. using 1000 ml of different dissolution media: 0.1 N hydrochloric acid, 0.01 N hydrochloric acid, or phosphate buffer 6.8 Ph.Eur. Temperature was fixed at 37 ± 0.5 °C, the basket was rotated at 150 rpm. The dissolution medium was continuously pumped (Ismatec IPC-S, Weinheim, Germany) at a rate of 15 ml/min in a circuit reaching a flow-through cell in a Hitachi 100-40 (Tokyo, Japan) UV/Vis spectrophotometer with a time lag of 10 s. Hence, the absorption of the liquid was continuously registrated over 120 min. Absorption was measured at 226 nm in hydrochloric acid and at 232 nm in phosphate buffer 6.8 *R*. The dissolution test was performed five times per batch at the specified conditions.

2.8. Scanning electron microscopy

The samples were fixed on an aluminum holder G 301 (Plano, Marburg, Germany) using photo-splits. The objects were gold sputter coated for 180 s at 25 mA under an argon atmosphere in a SCD 040 (Balzers Union, Lichtenstein). The obtained gold surfaces were observed at 20 kV using the scanning electron microscope Stereoscan S4 (Cambridge Instruments, Cambridge, UK).

2.9. Particle size analysis

Laser diffraction measurements were performed using a laser-beam droplet and particle size analyzer Series 6200 (Malvern Instruments, Herrenberg, Germany) in the long-bed option equipped with a helium–neon laser (wavelength 633 nm, 18-mm beam size), a 1000-mm Fourier transform mount range lens, and a 31-element solid state, concentric detector array. The raw data were transformed to particle size distributions by the modeling software from the same company.

3. Results and discussion

3.1. Granules

The commercially available grades of sodium benzoate contain irregular agglomerates of small crystals with a mean particle size of about 10 μm (Fig. 1). These microparticles could not be film-coated by pan or air-suspension techniques. Granulation is an appropriate method to form larger and more regular particles with high robustness. As sodium benzoate is highly soluble in water and volatile during drying processes, wet granulation techniques were not

Fig. 1. Scanning electron micrograph of sodium benzoate crystals. Scale bar represents 10 μm.

applied. Three solvent-free granulation techniques have been investigated: roller compacting, cold extrusion, and hot-melt extrusion. The concentration of sodium benzoate in the granules was chosen as high as possible because of the large amount of required therapeutic doses.

Sodium benzoate was roller compacted without any additives at 20 kN/cm. At lower compaction forces the quality of the ribbon was not appropriate for further processing. A significant increase of the temperature at the drive aggregates was recorded indicating high friction forces. The compacted ribbons were crushed in the granulator yielding a homogeneous granulate with a narrow size distribution and a mean particle size of about 800 μm (Fig. 2).

Granules made by extrusion techniques require additives because sodium benzoate does not melt or soften under the conditions of the process. Polyethylene glycol (Macrogol) is one of the excipients most often used in extrusion experiments [17] and is compatible with Eudragit E [18] selected as the coating material. Various powder grades of macrogol were mixed together with sodium benzoate at different concentrations. For hot-melt extrusion Macrogol 4000 was added which melts between 53 and 59 °C. The used Micro 27GL twin-screw extruder allows an individual temperature control of seven separate segments. The first five segments after the feeding area were heated to 70 °C in order to melt the macrogol fraction of the mixture. Hence, a fine suspension of sodium benzoate in macrogol was obtained in situ. The regular motion of the extruder maintains the homogeneity of the mixture until reaching the die. The next segment was kept at 40 °C and the last one just before the die at 20 °C. Hence, the mixture cools down, becomes semi-solid

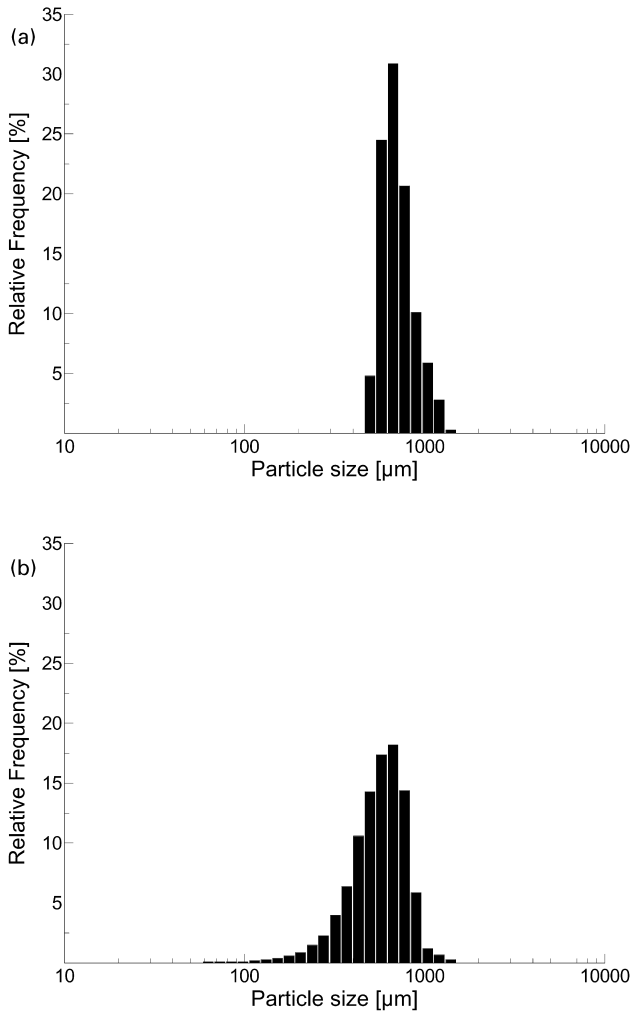

Fig. 2. Size distribution of granules obtained by roller compacting (a) before and (b) after coating. Particle sizes have been calculated from laser diffraction data.

and solidifies afterwards without loosing its plasticity. Ribbon–shaped extrudates with a length of 3–5 cm and a diameter of 1 mm were obtained. The best extrudates resulted from mixtures with 25% Macrogol 4000. The determination of the sodium benzoate content of the prepared granules revealed 77.5 ± 1.5% sodium benzoate. Plasticity was not sufficient at concentrations of less than 10% macrogol indicated by powdered products and blocking of the extruder.

In cold extrusion experiments, addition of Macrogol 4000 did not yield any suitable extrudates. Perisutti et al. [19] have recently found that the best extrudates of Macrogol 4000 together with the drug carbamazepine processed in a ram extruder were obtained at 50 °C. The occurring friction forces in our experiments at room temperature were too small for melting or at least weakening the polymer. Therefore, other macrogol qualities with lower melting points were investigated. Most macrogol types are commonly available as beads but not as a powder, which is necessary for the cold extrusion process. A granulated grade of Macrogol 1500, so called perls, with a melting point between 42 and 48 °C revealed the best results in the cold extrusion experiments. Ribbon–shaped extrudates with a length of 2–4 cm and a diameter of 1 mm were obtained which had higher plasticity but lower robustness than the extrudates from hot-melt extrusion containing Macrogol 4000. Granulation was finished by passing the extrudates through sieves with a mesh size of 1.0 mm.

3.2. Microcapsules

The granules obtained by roller compaction, hot-melt or cold extrusion were coated in a fluid-bed apparatus using the Wurster configuration. Eudragit E 100 was used in an ethanolic solution as the functional polymer. It is soluble at low pH values and swellable at higher pH conditions. Sodium benzoate is poorly soluble in ethanol. Triethyl citrate was used as a plasticizer and colloidal silicium dioxide hydrate as an anticaking agent.

The granules obtained by different granulation methods showed varying behavior during the coating process. The mechanical forces occurring in the process partly destroyed the roller compacted granules. The resulting microcapsules showed a smaller mean particle size and a broader size distribution than the uncoated granules (Fig. 2). Large amounts of fine powder were found in the outlet filters. Although the roller compacted granules seemed to be homogeneous and physically stable, they do not have the appropriate robustness for the coating process.

The granules obtained by hot-melt extrusion showed the best properties in the coating process. The particle sizes were only slightly modified during the coating process (Fig. 3). Smaller amounts of powder were found in the outlet filters compared to the granules prepared by roller compaction. Scanning electron micrographs of the microcapsules show intact and regular coatings on the particle surfaces (Fig. 4). Coating thickness is less than 10 µm. Determination of the sodium benzoate content of the microcapsules revealed 68.7 ± 2.9% sodium benzoate. Subtracting the determined sodium benzoate content of the granules, the amount of coating material on the microcapsules can be estimated as 8.1%. The microcapsules are stable during storage. The determination of the sodium benzoate content showed a decrease of 0.02% within 6 months stored in a glass container at 25 °C and 60% relative humidity which is less than the determined precision of the analytical method. Further stability testing is ongoing.

3.3. Drug release from microcapsules

Benzoate release from the different microcapsule formulations was determined in 0.1 N hydrochloric acid, 0.01 N hydrochloric acid, and phosphate buffer pH 6.8 dissolution media over 120 min. The basket method Ph. Eur. was applied because of its superior suitability for small-sized and floating microcapsules. The microcapsules

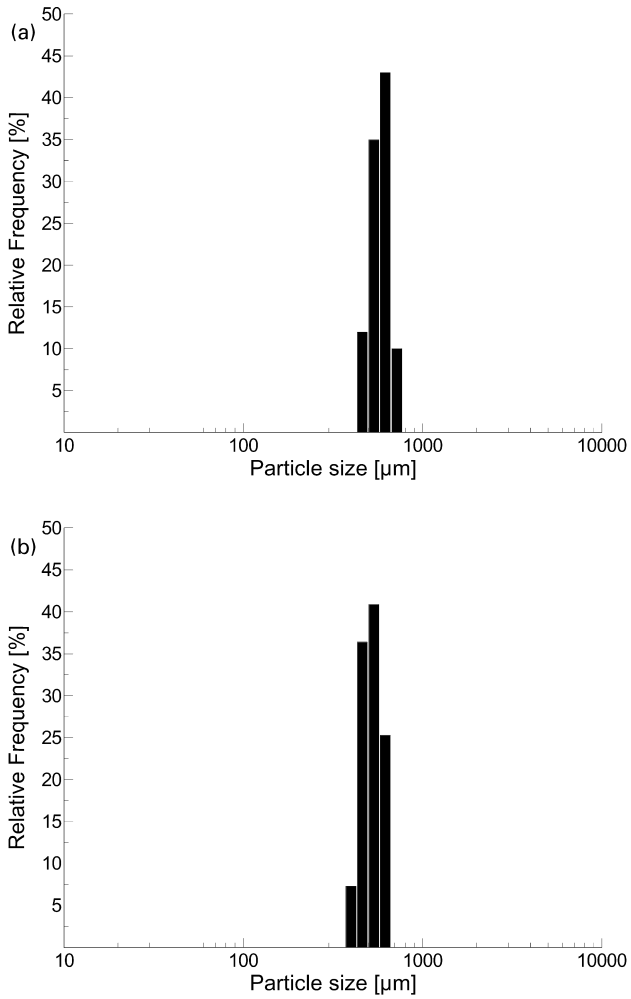

Fig. 3. Size distribution of granules obtained by hot-melt extrusion (a) before and (b) after coating. Particle sizes have been calculated from laser diffraction data.

released the complete amount of drug into all dissolution media in less than 20 min. Differences were only observed in the initial dissolution phase (Fig. 5). In 0.1 N hydrochloric acid (pH 1) about 40% of the loaded drug and in 0.01 N hydrochloric acid (pH 2) 25% were released within the first minute. After 2 min, 60% (pH 1) and 70% (pH 2) benzoate, respectively, were released. In both acidic media, drug release was completed after 9 min. The differences in the initial phase are related to two overlaying effects: Eudragit E is better soluble at lower pH values. Therefore, leaking of the film is higher and faster at pH 1 than at pH 2. At both pH values sodium benzoate undergoes protonization forming benzoic acid at the surface of the microcapsules, which is less soluble in aqueous media, but at pH 1 protonization is 10 times higher. Hence, the dissolution profiles cross each other revealing a faster release at pH 2 after 1 min. In buffer solution at pH 6.8, the dissolution profile is different showing less than 10 % drug release after 1 min and less than 20% after 2 min. Dissolution was completed after 14 min. The reduced level of released sodium benzoate in the initial phase at neutral pH conditions is the principle of saliva resistance. Furthermore, it is important to note that the physicochemical properties of Eudragit E allow complete dissolution of the highly soluble drug even at neutral pH within 20 min. Hence, complete drug release can be assumed even if gastric passage should be unusually fast after swallowing the microcapsules.

From the dissolution studies it could be assumed that sodium benzoate cannot be tasted for about 2 min in the buccal space after application but that it is completely released into the gastrointestinal tract. Preliminary trials in humans revealed that sodium benzoate in the novel

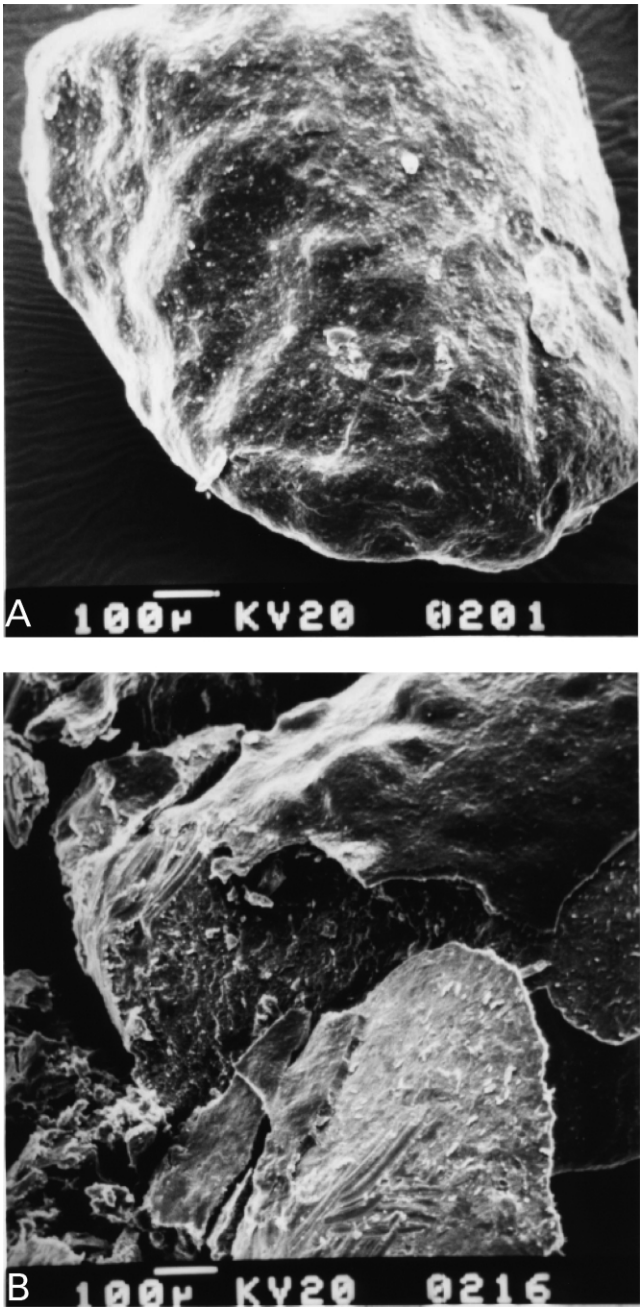

Fig. 4. Scanning electron micrographs of (a) intact and (b) broken microcapsules prepared from melt-extruded granules. Scale bars represent 100 µm.

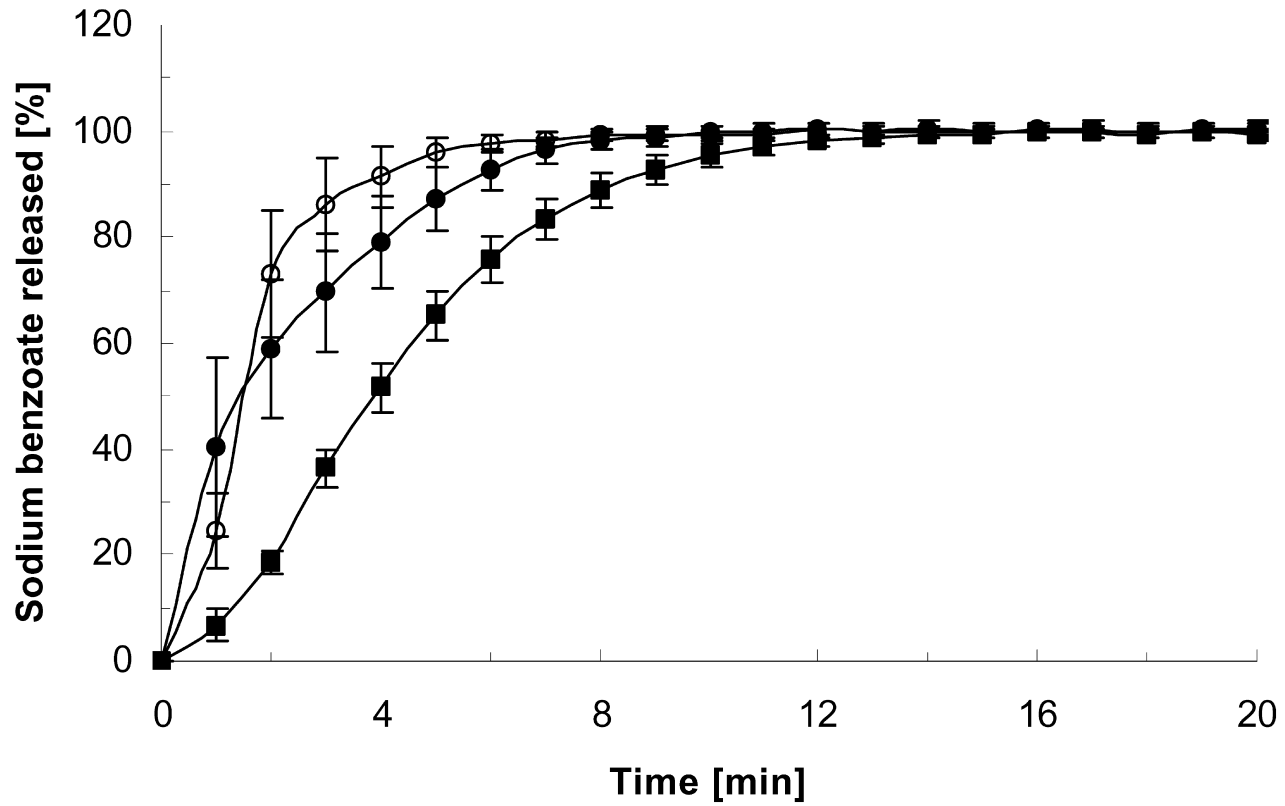

Fig. 5. Sodium benzoate release from microcapsules prepared by hot-melt extrusion and subsequent coating into different dissolution media ($n = 5$; mean ± S.D.). ●, 0.1 N hydrochloric acid (pH 1); ○, 0.01 N hydrochloric acid (pH 2); ■, phosphate buffer 6.8 *R* Ph. Eur.

formulations is taste-masked for at least 5 min when circulating in the buccal space. Mixing the coated granules together with milk, jelly, or blancmange directly on a spoon facilitates the swallowing. However, in dissolution testing about 70% sodium benzoate have been released after 5 min. Obviously, the conditions of the dissolution test do not adequately reflect the in vivo conditions for saliva-resistance or taste-masking. The developed microcapsules are the first taste-masked dosage forms of sodium benzoate and could be a substantial progress in the treatment of pediatric patients.

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