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Research paper

Pediatric drug formulations of sodium benzoate: II. Coated granules with a lipophilic binder

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Abstract

Sodium benzoate is used as a therapeutic agent in the treatment of some rare disorders that predominantly affect children. In preliminary investigations, liquid and semi-solid formulations of sodium benzoate failed because children refuse the oral uptake due to the bad taste of the drug. Recently developed microcapsules with macrogol as a hydrophilic binder raise concern in high-dose treatment regimens because acceptable daily intake limits are exceeded. A novel microcapsule formulation was developed consisting of a lipophilic core with high sodium benzoate load and a saliva-resistant coating. A new powder quality of saturated triglycerides from plant origin was introduced which complies with the Ph. Eur. monograph 'Hard fat'. Sodium benzoate and the triglyceride were mixed and directly extruded at room temperature. The extrudates were spheronized and coated in a fluidized-bed process. The resulting coated granules are small-sized microcapsules and taste neutrally. They can be mixed with food before administration. As the amount of released sodium benzoate is negligible within the first minutes, children do not recognize the bad taste and accept the medication. Recently, sodium benzoate in this novel formulation has been designated by the European Community as an orphan drug in the treatment of non-ketotic hyperglycinemia.

Keywords: Pediatric formulations; Orphan drugs; Microencapsulation; Solvent-free granulation; Cold extrusion; Triglycerides; Sodium benzoate; Polymethacrylate

1. Introduction

Sodium benzoate is therapeutically used at high doses in the treatment of some rare diseases such as hyperammonemia and non-ketotic hyperglycinemia [1,2]. In most cases children are affected by these inherited metabolic disorders. Often they refuse the oral uptake of liquid sodium benzoate preparations due to the bad taste of the drug. Large volumes of diluted solutions cannot be used for children. Solid single-unit formulations like capsules or tablets cannot be swallowed by the majority of pediatric patients [3]. Most recently, microcapsules have been developed in our working group containing 69% sodium benzoate together with hydrophilic macrogol (polyethylene glycol) binders in the core and Eudragit E coatings [4]. These formulations completely release sodium benzoate in less than 15 min at all pH levels, but in phosphate buffer pH 6.8 *R* Ph. Eur. the release is significantly diminished in the first minutes compared to various acidic media. Hence, the microcapsules appear taste-free in the buccal space and are well accepted by the pediatric patients. However, the content of some excipients in the formulations, especially Macrogol, raised concern in high-dose therapy at least for some children. Another disadvantage of the recently developed microcapsules is the low stability when mixed up with some type of food before administration. In acidic media like applesauce or orange juice they rapidly release the sodium benzoate. Therefore, the aim of the present investigation was to develop novel microcapsules with less toxic excipients and with a slower drug release.

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2. Materials and methods

2.1. Materials

Sodium benzoate was purchased from Pontepharm (Schriesheim, Germany), ethanol 96% from Bundesmonopolverwaltung für Branntwein (Offenbach, Germany), and colloidal silicium dioxide hydrate (Syloid® 244 FP) from Grace (Worms, Germany). Stearic acid, type 50 Ph. Eur., from plant origin was obtained from Merck (Darmstadt, Germany) and glycerol distearate, Precirol® Ato 5, from Gattefossé (Gennevilliers, France). All were of Ph. Eur. grades. Powdered hard fat (Witocan® 42/44 mikrofein) was a gift from Sasol (Witten, Germany). Witocan 42/44 is registered as a food ingredient and has been characterized as Ph. Eur. quality for the first time in the present study. Eudragit® E 100 which complies with the German Pharmacopoeia (DAB 2001) monograph Butylmethacrylate-(2-dimethylaminoethyl)methacrylate–methylmethacrylate–copolymer (1:2:1) was purchased from Röhm (Darmstadt, Germany). Benzoic acid USP reference standard was purchased from LQS (Eschborn, 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

Sodium benzoate powder was mixed together with 10–25% lipophilic binder (stearic acid, glycerol distearate or hard fat) and homogenized for 5 min in a Bosch mixer (Stuttgart, Germany). The dry powder blends were fed to the rotary ring die press PP 85 (Schlüter, Neustadt, Germany) at room temperature. The bulk was extruded through a 90° entry die of 1-mm diameter and 2.0–5.0 mm length. The piston was running at up to 400 rpm. Cylindrical extrudates with a length of 1–3 cm and a diameter of 1 mm were obtained and collected in a beaker. The extrudates were rounded at 900 rpm for up to 5 min using a Spheronizer RM 300 (Schlüter, Neustadt, Germany).

2.3. Microencapsulation

The granules were screened by sieve analysis; 2000 g of the fraction between 400 and 1000 μm was subjected to the HKC-5 Quattro Kugelcoater (Hüttlin, Steinen, Germany). The temperature of the inlet air was 25 °C, outlet air 15 °C and air volume 300 m^3/h. Product temperature was 21.0 °C at the beginning and 25.9 °C at the end of the coating process. The polymeric coating dispersion, consisting of 200 g Eudragit E 100, 20 g silicium dioxide hydrate, and 1600 g ethanol 96%, was applied to the nozzle by 10–15 g/min; 12 g/min was identified as the best spray rate. After 150 min the coating process was stopped. The microcapsules were dried for 10 min in the apparatus.

2.4. Sodium benzoate assay

A fully validated high-performance liquid chromatography (HPLC) method, earlier described in detail [4], was used to determine the content of sodium benzoate in microcapsules with different composition. The USP reference standard for benzoic acid was used for method validation. The method was linear with a correlation coefficient of 0.999. The sodium benzoate concentrations were determined in five samples per batch.

2.5. Dissolution studies

Samples of 100.0 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, phosphate buffer 6.8 *R* Ph.Eur. or purified water. The 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 (0.2 cm) 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 registered over 120 min. Absorption was measured at 232 nm. The dissolution test was performed five times per batch at the specified conditions.

2.6. 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).

3. Results and discussion

3.1. Cold extrusion experiments

In preliminary studies with macrogol as a hydrophilic binder [4], cold extrusion was successfully employed for processing robust and regular granules of the irregular, small-sized sodium benzoate crystals. Solvent-free cold extrusion appears as an advantageous method for the development of sodium benzoate granules because the residual solvent burden of the children is reduced to zero, the process is suitable for the hygroscopic and evaporating drug, simple to scale up and further, it can be conducted with extruders without temperature gradient control. In the studies with different polyethylene glycols, Macrogol 1500 perls with a melting point of 46.5 °C was the most suitable grade

Table 1
Daily doses of the ingredients in the formulations for a patient with non-ketotic hyperglycinemia Typ I (male, 1.5 years, 10 kg body weight, 11.5 g sodium benzoate per day)

Ingredient	Macrogol formulation		Triglyceride formulation		ADI
	(%)	(mg/kg b.w. per day)	(%)	(mg/kg b.w. per day)	(mg/kg b.w. per day)
Sodium benzoate	68.7	1150.0	75.0	1150.0	5.0
Macrogol 1500	23.3	390.0	–	–	10.0
Triglyceride	–	–	18.8	288.3	Not limited
Eudragit E	6.7	112.2	5.7	87.4	Not established[a]
Triethyl citrate	0.7	11.7	–	–	20.0
Silicium dioxide hydrate	0.7	11.7	0.6	9.2	Not limited

b.w., body weight.
[a] An ADI limit has not been established by the JECFA/WHO yet. Internal report with an estimation for the no observed effect limit (NOEL) is available at the supplier.

forming stable sodium benzoate granules at a concentration of 25%. However, this results in daily doses of macrogol in some pediatric patients, which dramatically exceed the acceptable daily intake (ADI) of 10 mg/kg body weight per day recommended for polyethylene glycol as food additive (Table 1). As the prescribed doses of sodium benzoate are extremely high—200 to 1200 mg/kg body wt./day depending on the disorder type—only those substances can be used as excipients which are recognized as safe in almost all doses. International harmonization on the acceptability of formulation excipients, as recently demanded in a guideline for pediatric clinical trials by the International Conference of Harmonization ICH and the European Agency EMEA [5] will probably not be in reach for years. The database of food additives [6] evaluated by the Joint Expert Committee of Food Additives (JECFA) at the World Health Organization (WHO) contain only few substances without any limit for the acceptable daily intake. From these substances, stearic acid, glycerol distearate and hard fat were selected for cold extrusion experiments. The binder for sodium benzoate must melt or at least soften under the extrusion conditions to form robust cylindrical extrudates. Furthermore, the excipient must be available in a powder quality or micronization must be possible in order to achieve homogeneous mixtures together with the fine sodium benzoate crystals. Stearic acid and glycerol distearate fulfill these criteria, but the pharmaceutical qualities of triglycerides available on the market did not. Either they were not available as a powder but as beads or pellets or they showed melting points outside the determined range for the cold extrusion process. In the food industry, a triglyceride quality is known under the trademark 'Witocan 42/44 mikrofein' from the supplier Sasol in Witten, Germany. This product is a fine triglyceride powder with a mean particle size of about 200 μm and a relatively rough surface (Fig. 1). The melting range is specified from 42 to 44 °C, the applied batch has a melting point of 42.6 °C. The batch was retested by the supplier according to the Ph. Eur. monograph 'Hard fat' before implementation into the present study. The criteria of the pharmacopoeia were completely fulfilled.

In cold extrusion experiments, Witocan 42/44 appeared to be superior to stearic acid and glycerol distearate (Precirol ato 5). The amount of unbounded powder material was higher for glycerol distearate even at a concentration of 25% where extrudates with a length of 1 cm were formed. Stearic acid, which has been successfully used in melt pelletization in high shear mixers [7], did not even show any binding at the same concentration. Therefore, the resulting masses were again subjected to the extruder. Binding and length of the extrudates were increased in all cases. After 10 min of extrusion the stearic acid formulation blocked the die. Using Witocan 42/44 at concentrations between 15 and

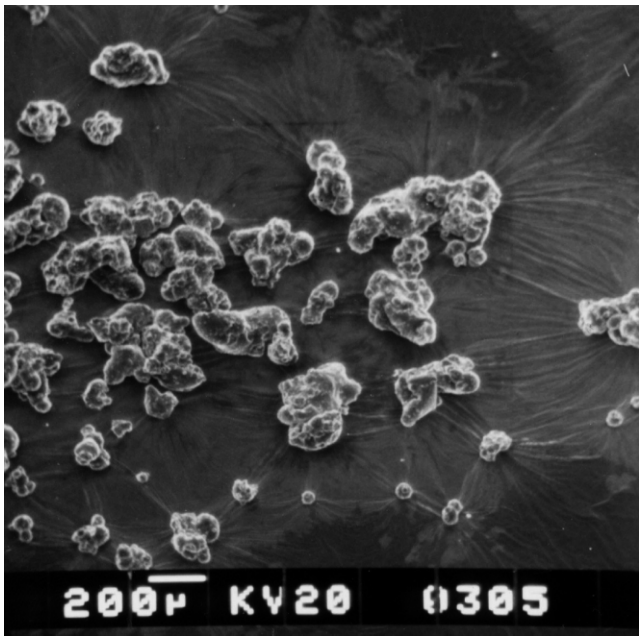

Fig. 1. Scanning electron micrograph of Witocan 42/44, the applied powdered triglyceride quality. Scale bar represents 200 μm.

Fig. 2. Scanning electron micrograph of an extruded mixture of 20% triglyceride and 80% sodium benzoate. Scale bar represents 200 μm.

25%, almost complete binding was achieved in the first extrusion step (Fig. 2). Higher concentrations of the binders were not tested because the sodium benzoate dose in the granules should be as high as possible to reduce the required intake.

In the subsequent spheronization process of the triglyceride pellets it became obvious that ideal spherical pellets consisting of sodium benzoate and hard fat cannot be produced because the extrudates warm up in the spheronizer due to mechanical friction. If the mass warms up, it plasticizes and forms large agglomerates at a critical temperature. Different process times and rotating speeds were evaluated showing best results for 4-min spheronization at 900 rpm. At this time point the temperature of the extruded mass is about 39 °C if started at room temperature. Therefore, in the subsequent scale-up process the temperature of 39 °C was claimed as the end point of the spheronization process. The resulting granules have a cylindric geometry with rounded edges. The maximum diameter of the granules is 1 mm and the length varies between 1 and 2.5 mm.

3.2. Coating of the granules

The granules were coated in a lab-scale Hüttlin Kugelcoater HKC 5 quattro. Eudragit E 100 was used in ethanolic solution as the saliva-resistant polymer and colloidal silicium dioxide hydrate as an anticaking agent. In deviation to the coating of macrogol containing granules, a plasticizer was not used. Eudragit E does not need a plasticizer for forming films. In the macrogol formulations, triethyl citrate was added to reduce the tackiness of the granules, which was much more pronounced in the macrogol than in the triglyceride formulations. Macrogol is sometimes added to Eudragit E polymer solutions as a plasticizer to increase the elasticity of the films. Ethanol was chosen as the solvent because its residuals were supposed to be more acceptable in pediatrics than isopropanol or acetone, which are the suggested solvents in the supplier's product information. Aqueous coating solutions are hard to control in the coating process because of the high water solubility of sodium benzoate. The product temperature was kept between 20 and 22 °C controlled by adjusting the temperature of the inlet air. When drying at the end of the coating process, inlet air temperature was increased to 29 °C. Spraying rate started with 10 g/min increasing to 14 g/min, when tackiness was observed. Therefore, the spraying rate was adjusted to 12 g/min until the end of the process. At 5% theoretical polymer mass, the process was stopped and the coated granules were evaluated by taste sensation. The bad taste of sodium benzoate was almost completely masked but the saliva resistance lasted only for a minute. Therefore, the coating process was continued up to 8% theoretical polymer mass. The granules have been completely coated (Fig. 3). They are taste-masked releasing only negligible amounts of sodium benzoate into the buccal space for at least 5 min.

3.3. Properties of the coated granules

HPLC analysis revealed a sodium benzoate content of 81.30 ± 1.63% in the rounded extrudates and 75.50 ± 0.91% in the coated granules. The triglyceride content can be calculated as 18.7% in the rounded extrudates and can

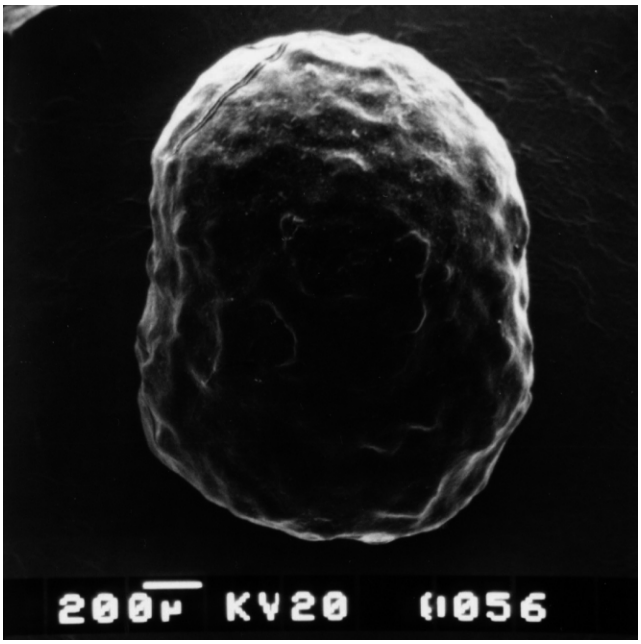

Fig. 3. Scanning electron micrograph of a saliva-resistant microcapsule containing 75% sodium benzoate. Scale bar represents 200 μm.

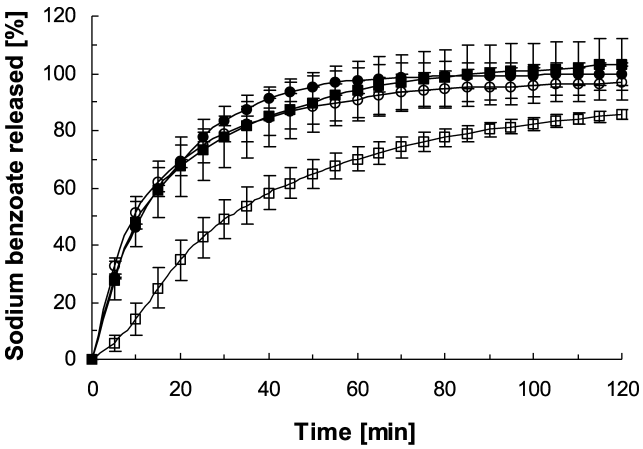

Fig. 4. Sodium benzoate release from prepared microcapsules containing triglyceride as lipophilic binder into different dissolution media $n = 5$; mean ± S.D.). ●, 0.1 N hydrochloric acid (pH 1); ○, 0.01 N hydrochloric acid (pH 2); ■, phosphate buffer 6.8 *R* Ph. Eur.; □, purified water.

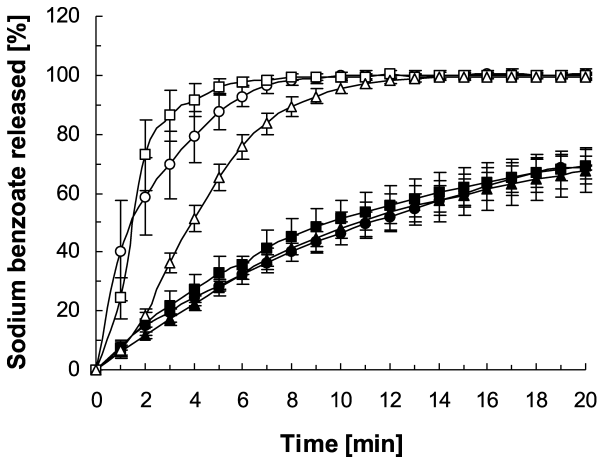

Fig. 6. Sodium benzoate release from prepared microcapsules containing triglycerides or macrogol into different dissolution media ($n = 5$; mean ± S.D.). ●, 0.1 N hydrochloric acid (pH 1), triglyceride formulation; ○, 0.1 N hydrochloric acid (pH 1), macrogol formulation; ■, 0.01 N hydrochloric acid (pH 2), triglyceride formulation; □, 0.1 N hydrochloric acid (pH 2), macrogol formulation; ▲, phosphate buffer 6.8 *R* Ph. Eur, triglyceride formulation; △, phosphate buffer 6.8 *R* Ph. Eur, macrogol formulation.

be estimated as 17.4% in the final product. Hence, the calculated Eudragit E mass ratio is 6.4% and silicium dioxide 0.7%, respectively.

Benzoate release from the different microcapsule formulations was determined in 0.1 N hydrochloric acid, 0.01 N hydrochloric acid, phosphate buffer pH 6.8 *R* Ph. Eur. and purified water media over 120 min. The coated granules released the complete amount of drug within 120 min into 0.1 N and 0.01 N hydrochloric acid and into phosphate buffer pH 6.8 but not into purified water (Fig. 4). Eudragit E is soluble below pH 5. At higher pH it is poorly soluble but undergoes swelling and allows the permeation of water. As sodium benzoate is highly soluble in water, it is almost completely released in the dissolution media even if an matrix of triglyceride and polymer (at higher pH) remains intact until the end of the test (Fig. 5). Phosphate buffer pH 6.8 and purified water have similar pH values. Obviously, the ionic strength additionally influences the diffusion of sodium benzoate through the polymer membrane at neutral pH and accelerates benzoate dissolution. The influence of the ionic strength and ion species on drug dissolution has been demonstrated for a number of polymethacrylates but not for Eudragit E [8–10].

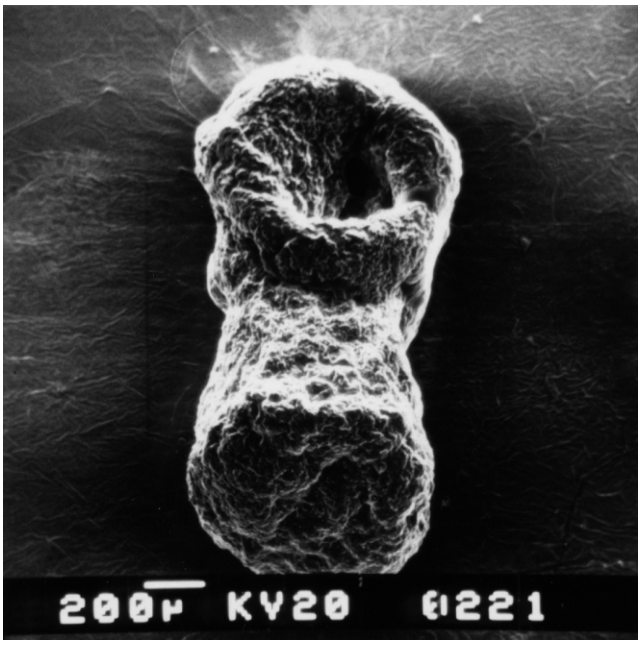

Fig. 5. Scanning electron micrograph of a saliva-resistant microcapsule with sodium benzoate after 60 min in the dissolution test with purified water as dissolution medium. Scale bar represents 200 μm.

In the triglyceride formulation, the sodium benzoate release is predominantly influenced by diffusion from the lipophilic matrix. The Eudragit E coating does not control the drug dissolution as much as in the case of the macrogol formulations. While in the macrogol formulations 7% (pH 6.8), 25% (pH 2) or 40% (pH 1) of the sodium benzoate load is released within the first minute, the release from the triglyceride formulations is about 7% at all pH values. The initial release is similar to the release from the macrogol formulations at neutral pH (Fig. 6). But still, the Eudragit E coating is required because the bad taste of sodium benzoate from the uncoated granules with lipophilic binders can be immediately recognized in the buccal space. The thickness of the Eudragit E coating layer can be reduced to a minimum of 6% mass ratio in order to increase the drug load and to decrease the total dose and the excipient burden.

The novel lipophilic formulation of sodium benzoate presented in this paper has been subjected to a scale-up procedure and has recently received the orphan drug status of the European Community for the treatment of non-ketotic hyperglycinemia.

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References

[1] J.L.K. Van Hove, P. Kishnani, J. Muenzer, R.J. Wenstrup, M.L. Summar, M.R. Brummond, A.M. Lachiewicz, D.S. Millington, S.G. Kahler, Benzoate therapy and carnithine deficiency in non-ketotic hyperglycinemia, Am. J. Med. Gen. 59 (1995) 444–453.

[2] T.P. Green, R.P. Marchessault, D.K. Freese, Disposition of sodium benzoate in newborn infants with hyperammonemia, J. Pediatr. 102 (1983) 785–790.

[3] J. Breitkreutz, T. Wessel, J. Boos, Dosage forms for peroral drug administration to children, Paediatr. Perin. Drug Ther. 3 (1999) 25–33.

[4] J. Breitkreutz, M. Bornhöft, F. Wöll, P. Kleinebudde, Pediatric drug formulations of sodium benzoate: I. Coated granules with a hydrophilic binder, Eur. J. Pharm. Biopharm. 56 (2003) d.o.i. 10.1016/S0939-6411(03)00091-2.

[5] European Agency for the Evaluation of Medicinal Products (EMEA), Clinical investigation of medicinal products in the paediatric population (CPMP/ICH/211/99)

[6] Joint Expert Committee for Food Additives (JECFA), www.inchem.org/pages/jecfa.html

[7] D. Voinovich, M. Moneghini, B. Perissutti, E. Franceschinis, Melt pelletization in high shear mixer using a hydrophobic melt binder: influence of some apparatus and process variables, Eur. J. Pharm. Biopharm. 52 (2001) 305–313.

[8] K. Knop, Influence of buffer solution composition on drug release from pellets coated with neutral and quarternary acrylic polymers and on swelling of free polymer films, Eur. J. Pharm. Sci. 4 (1996) 293–300.

[9] R. Bodmeier, X. Guo, E.E. Sarabia, P.F. Skultety, The influence of buffer species and strength on diltiazem HCl release from beads coated with the aqueous cationic polymer dispersions, Eudragit RS, RL 30 D, Pharm. Res. 13 (1996) 52–56.

[10] K.G. Wagner, Mechanisms of ionic interactions between dissolution medium an a cationic PMMA film, Arch. Pharm. Pharm. Med. 334 (Suppl.2) (2001) 23.