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Extrusion–spheronization of pH-sensitive polymeric matrix pellets for possible colonic drug delivery

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Abstract

The aim of this study was to investigate extrusion–spheronization pelletization for preparing pH-sensitive matrix pellets for colon-specific drug delivery. The effects of three independent variables (amounts of Eudragit™ S, citric acid and spheronizing time) on pellet size, shape (roundness and aspect ratio), and drug release were studied with central composite design. The pellets contained ibuprofen as a model drug, citric acid as a pH-adjusting agent, Eudragit™ S as a pH-sensitive binder and microcrystalline cellulose (MCC). The pellets were prepared with Nica extrusion–spheronizing equipment and subsequently enteric-coated using an air-suspension technique. Eudragit™ S as a pH-sensitive matrix former in pellets increased the pellet size and influenced pellet roundness. In small amounts Eudragit™ S increased pellet roundness but in larger amounts pellet roundness was reduced. Citric acid promoted the pelletization process resulting in a narrower area distribution. The pH-sensitive matrix pellet failed to delay the drug release. The combination of citric acid and enteric coating, however, delayed the drug release for 15 min in a pH 7.4 phosphate buffer.

Keywords: Colon targeting/Site-specific drug delivery/lag-time; Eudragit™ S 100; Hydroxypropyl methylcellulose acetate succinate; Pellets; Shape

1. Introduction

In recent years, oral site-specific drug delivery systems, such as colon targeting systems, have been the focus of intense research. A wide range of different approaches for targeting the drug to the colon has been studied. One of the most tested approaches and the first commercial system is the use of a pH-sensitive polymer as a coating material (Dew et al., 1982). The use of a pH-sensitive polymer for colon targeting is based on the assumption that the pH value increases from the

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small intestine to the large intestine. Studies of healthy volunteers, however, have shown that the pH value at the end of the small intestine is about 7.5 and this falls in the ascending colon to pH 6.5, after which it rises again to values of 7 (Sasaki et al., 1997).

In our laboratories multiple-unit systems have been developed where drug release is controlled by first using enteric polymer as binder in matrix granules and thereafter coating the matrices with an enteric coat (Marvola et al., 1999). In our first paper it was concluded that with an enteric matrix and an enteric coating it is possible to target drug release to the distal part of the small intestine and partially also to the colon (Marvola et al., 1999). In the next step organic acids (citric acid, tartaric acid or succinic acid) were included in the matrices to investigate whether the pH granule micro-environment could be reduced and thus further delay the drug release (Nykänen et al., 1999). The conclusion was that although inclusion of an organic acid in the formulation retarded in vitro release of the model drug, no corresponding effect was evident in in vivo studies. One reason for the lack of in vivo retardation could be mechanical weakness of the manually prepared granules.

The first aim of the study reported here was to investigate whether it is possible to manufacture stronger and more uniform granules (pellets) by using an extrusion–spheronization technique. Replacing the manual technique for preparing the granules with a pilot-plant method is also a prerequisite if the aim is to produce the developed product as a commercial preparation. On the basis of the previous results Eudragit™ S was selected as the binder material, Aqoat™ AS-HF as the coating material and citric acid as the pH regulating agent. The effects of two material variables (i.e. the amount of the binder and the amount of the pH-regulating agent) and one process variable (spheronizing time) on in vitro drug release, friability, as well as on the size and shape characteristics of the pellets, were studied.

2. Materials and methods

2.1. Experimental design

A three-factor central composite design was used as the experimental design. The independent variables studied were the amount of Eudragit™ S (X_1), the amount of citric acid (X_2), and

Table 1
Matrix of the central composite design

No.	Coded values of variables			Actual values of variables		
	X_1	X_2	X_3	Eudragit™ S 100 (X_1) (%)	Citric acid (X_2) (%)	Spheronization time (X_3) (min s)
1	−1	−1	−1	0.8	4.1	1.22
2	−1	−1	1	0.8	4.1	4.38
3	−1	1	−1	0.8	15.9	1.22
4	−1	1	1	0.8	15.9	4.38
5	1	−1	−1	3.3	4.1	1.22
6	1	−1	1	3.3	4.1	4.38
7	1	1	−1	3.3	15.9	1.22
8	1	1	1	3.3	15.9	4.38
9	−1.682	0	0	0	10.0	3.0
10	1.682	0	0	4.2	10.0	3.0
11	0	−1.682	0	2.1	0	3.0
12	0	1.682	0	2.1	20.0	3.0
13	0	0	−1.682	2.1	10.0	0.15
14	0	0	1.682	2.1	10.0	5.45
15–24	0	0	0	2.1	10.0	3.0

spheronizing time (X_3). The total number of experiments was 24 (Table 1).

2.2. Preparation of pellets

Pellets contained 30% ibuprofen (Knoll Pharma Chemicals, UK) and 48–49% microcrystalline cellulose (Avicel™ PH-101, FMC International, Ireland). The combined amount of mannitol (Roquette Freres, France) and citric acid monohydrate (J.T. Baker, Holland) was 20%. Mannitol replaced the reduced citric acid amount.

The dry substances (3 kg) were blended in a high shear mixer (Fielder PMA 25, J.K. Fielder Ltd., UK) for 1 min. Poly (methacrylic acid, methylmethacrylate) i.e. Eudragit™ S 100 in ethanol (60%) solution was used as a binder solution. The final fraction of Eudragit S in the cores can be seen in Table 1. The binder solution added was 66% of the dry substances at a rate of 170 g/min.

The mass was extruded immediately after the granulation (NicaE 140, Nica System Ab, Sweden). The length of the dies was 1.25 mm and the diameter 1 mm. The speed of the feeder was 45 rpm and that of the agitator was 35 rpm. The extrudate was spheronized in loads of 300 g using a speed of 900 rpm in a Nica spheroniser (Nica S320, Nica System Ab, Sweden). The pellets were dried on trays as a monolayer at room temperature (21 ± 2°C).

2.3. Coating procedure

The 200 g pellet batches representing the axial points (Nos. 9–14) and the central point (Nos. 15–17) were enteric film-coated. The film coating was performed in an air-suspension coater (Aeromatic Strea-1, Aeromatic AG, Switzerland). The pellets were enteric-coated with a 10% aqueous dispersion of hydroxypropyl methylcellulose acetate succinate (HPMCAS; Aqoat™ AS-HF, Shin-Etsu Chemical Co., Japan). A total of 3.5% of triethyl citrate (Henkel, Germany) was used as a plasticizer. To ensure dissolution of triethyl citrate, the dispersion was blended by a magnetic blender for 30 min. 3% magnesium stearate (Henkel, Germany) was used as an anti-adhesive agent.

The HPMCAS solution was kept on an ice bath during the film coating to prevent nozzle blockage. The granules were heated to 40°C before the coating was started. The pneumatic spraying pressure used was 1.2 ± 0.1 bar, the air flow 130 ± 5 m^3/h and the inlet temperature 40 ± 5°C. The coating solution was added at a rate of 5 g/min and the coating was continued until a 20% theoretical weight increase was achieved. The granules were dried for 5 min at 40°C in the coating chamber.

2.4. Microscopic image analysis

The shape and the area of 300 uncoated pellets/batch were investigated by optical microscopic image analysis. The image analyser consists of a computer system linked to a videocamera and a microscope (magnification $6.3\times$) (Leica MZ6, Leica Microskopie et Systeme GmbH, Germany). The digitized images were analysed by Leica image analysing software (Leica Qwin 1.0, Leica Imaging Systems, Germany). The area was measured and two shape factors were calculated:

$$\text{Aspect ratio} = \frac{d_{\max}}{d_{\min}} \quad (1)$$

$$\text{Roundness} = \frac{\text{area}}{\pi^* \ (d_{\max})^2} \quad (2)$$

$d_{\max}$ and $d_{\min}$ was the longest and shortest Feret diameters measured (64 measurements for each pellet).

2.5. Friability

The friability of the uncoated pellets was tested with a 100 ml glass jar with 20 g of pellets and 40 g of glass spheres in a Turbula mixer for 30 min.

2.6. Dissolution tests

The dissolution tests were carried out in automated dissolution testing equipment (Sotax AT7, Sotax AG, Switzerland). The dissolution medium was 900 ml of phosphate buffer solution, pH 7.4 (USP XXIII), at 37°C. Six parallel samples in baskets were tested for 6–9 h. The absorbances were measured at 221 nm.

Table 2
Summary of fitted models, r^2 values and RMS%

Fitted model	r^2 value	RMS %
Roundness $= -9.88 \cdot 10^{-3} \cdot X_1$ $- 6.64 \cdot 10^{-3} \cdot X_2$ $+ 3.09 \cdot 10^{-} \cdot X_3$ $- 1.30 \cdot 10^{-2}\ X_3^2$ $+ 8.85 \cdot 10^{-1}$	0.90	1.10
Aspect ratio $= -0.03 \cdot X_3 + 1.12$	0.41	2.29

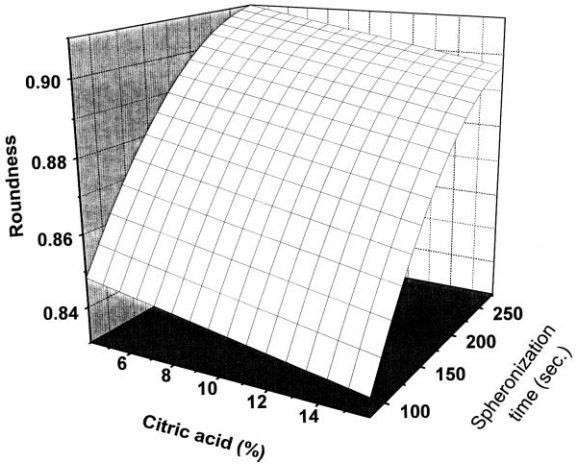

Fig. 1. Effect of citric acid and spheronizing time on the roundness of uncoated pellets (amount of Eudragit™ S 2.1%).

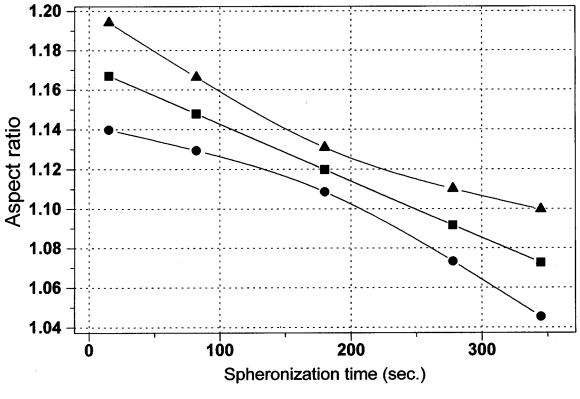

Fig. 2. A prediction of the influence of spheronizing time on the aspect ratio values for uncoated pellets (citric acid amount 10% and Eudragit™ S 2.1%). The 95% confidence interval is shown.

2.7. Statistic analysis

The effects of process variables were modelled using a second-order polynomial equation. The model was simplified with a multi-linear backward, stepwise regression technique. The validity of every term was tested by t-test. Only significant terms ($P < 0.05$) were chosen for the final model. The modelling was performed using Modde for Windows (Version 4.0, Umetri AB, Sweden). The fitted models for coded values, root mean square (RMS%) and r^2 values are shown in Table 2.

3. Results and discussion

3.1. Roundness and aspect ratio

Pellets are generally regarded as flexible preparations for further processing including application of film coatings and packaging. The prerequisite for successful processing is that the shape of the pellets is of high quality. The two shape factors calculated, roundness and aspect ratio, are sensitive parameters for evaluating pellet shape (Hellén and Yliruusi 1993a). All independent variables, i.e. spheronizing time, the amount of citric acid and the amount of Eudragit™ S, had a statistically significant effect on pellet roundness. As the residence time in the spheronizer was prolonged the pellets became more spherical and rounder (Fig. 1). The results obtained with the roundness and aspect ratio parameters, however, were somewhat contradictory: according to the values for roundness, the pellets do not become rounder after 4 min of spheronizing (0-level pellets) (Fig. 1), whereas aspect ratio values suggest that the pellets become slightly rounder even after a 4-min residence time in a spheronizer (Fig. 2). Only the spheronizing time showed statistical significant effect for the aspect ratio factor, whereas all variables gave statistically significant effects for roundness. This in accordance with the results of Podczeck and Newton (1994), who pointed out the limitations of aspect ratio for describing a sphere. The r^2-value is also clearly better for the roundness parameter than for the aspect ratio (Table 2). The

results can not be fully explained by the roundness and the aspect ratio models. There are factors in the pelletization process that can not be controlled-these influence the results. Furthermore, the image analysis system transforms the pellets to a binary image which also decreases the predictability of the models.

The amount of citric acid had a negative effect on the roundness of pellets (Fig. 1). In small amounts, Eudragit™ S improved pellet roundness values. However, the response surface plot of roundness (0-level) showed that when the Eudragit™ S amount in the pellets exceeds 2% pellet roundness is reduced (Fig. 3). Eudragit™ S can, thus, be used as a binder, but in larger amounts Eudragit™ S makes the granulated mass viscous and more difficult to form.

3.2. Projected area

For uniform film coating and packaging, the size and size distribution of pellets are expected to be controlled. Increasing the amount of Eudragit™ S resulted in a increase of the projected area values of the pellets (Fig. 4). This was probably due to a more viscous and sticky mass, which promoted pellet agglomeration. Eudragit™ S also made the pellet area distribution slightly wider (Fig. 4). When the amount of citric acid was increased, the projected area of the pellets was slightly decreased (Fig. 4). When comparing the batches with and without citric acid, the largest difference was that the pellets with citric acid had a much narrower area distribution (Fig. 4). Thus, organic acid actually stabilises the pH-sensitive polymer and thereby promotes successful pelletization.

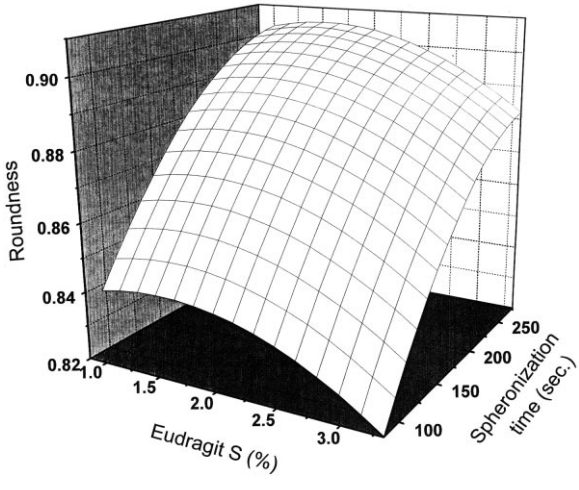

Fig. 3. Effect of Eudragit™ S and spheronizing time on the roundness of uncoated pellets (amount of citric acid 10%).

The spheronizing time did not statistically influence the pellet size (Fig. 4). This result is supported by the study on sustained release methacrylic resin polymers, where the residence time did not affect the yield of a certain pellet mesh size (Goskonda et al., 1994). The size of pellets containing methacrylate polymers as a binder seems not to be influenced by the spheronizing time, while the size of pellets containing no binder tend to be more influenced by the residence time, although the direction of the influence has been the subject of contradictory reports. The residence time has been reported to reduce the size of pellets (Hellén et al., 1993b), increase the mean diameter of pellets (Hasznos et al., 1992) or increase the size of the pellets for up to 10 min, while a further increase in residence time decreased the pellet size (Wan et al., 1993).

3.3. Friability

The friability was studied in order to determine the mechanical properties of the pellets, as the lack of in vivo retardation in our previous study was speculated to be due to the mechanical weakness of the manually prepared granules (Nykänen et al., 1999). Pellets require also a certain resistance to friability to withstand further processing including film coating. The friability of the pellets tested with glass spheres was below 0.1%, and thus the pellets were hard and of good quality with respect to friability. The preliminary aim to produce mechanically strong pellets was thereby achieved.

3.4. Drug release in vitro

According to our previous study, an Eudragit™ S granule matrix is disintegrated at pH 6.8 (Marvola et al., 1999). The solubility of ibuprofen is

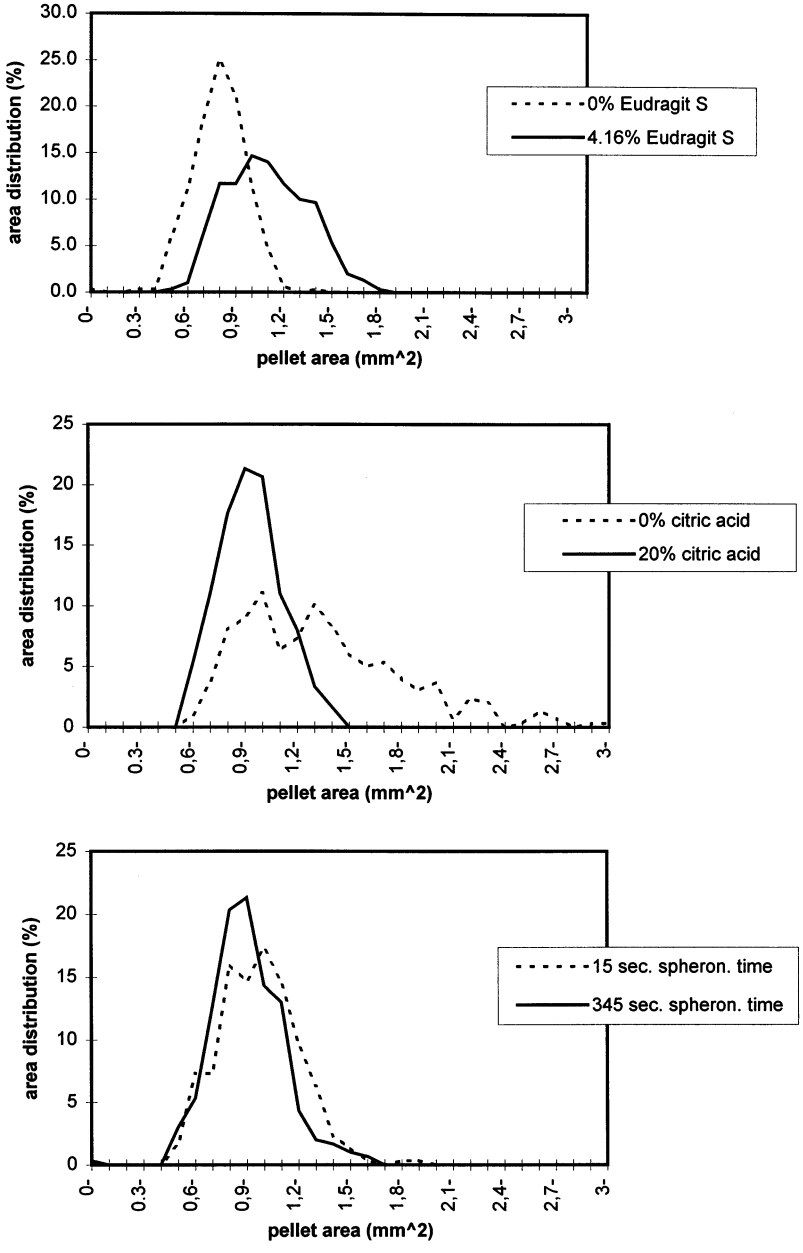

Fig. 4. A comparison of the projected area distributions for uncoated pellets, batches 9–14 ($n = 300$).

pH dependent, the solubility increases rapidly at pH values higher than the pK_a-value of the drug (pH 5.3), and the dissolution rate of ibuprofen is very high at pH 7.5 (Herzfeldt and Kümmel, 1983). Because of the above-mentioned facts, the dissolution tests were conducted at a pH of 7.4, also mimicking the pH in the end of the small intestine. Figs. 5 and 6 show that citric acid affected the drug release by delaying it, whereas the influence of Eudragit™ S was negligible. The effects of Eudragit™ S could not be statistically shown. A study by Varshosaz et al. (1997) showed

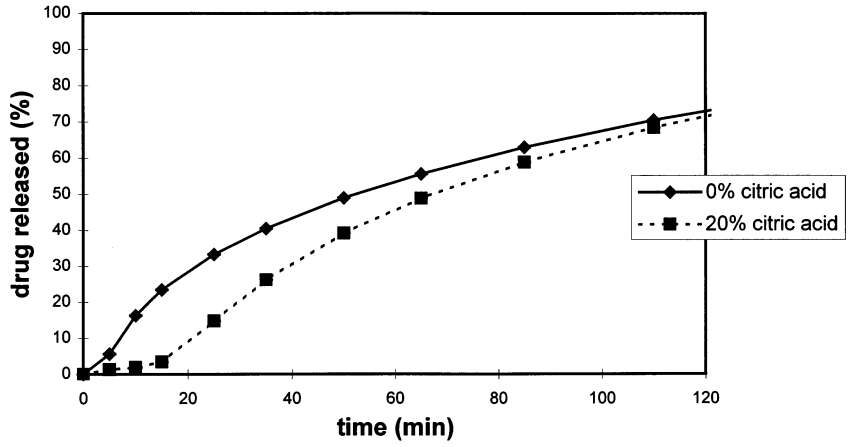

Fig. 5. Effect of citric acid on drug release from coated ibuprofen pellets in pH 7.4 buffer solution (batches 11 and 12) (mean ± SD, $n = 6$).

that the effect of an enteric material in a pellet core could be shown at lower pH, but not in a buffer solution with a pH as high as 7.4. The amount of citric acid had a clear retarding effect on the early-stage drug release. As the citric acid amount in the pellets was increased the drug release during the first 15 min was decreased (Fig. 7). The equation for the curve for uncoded values presented in Fig. 7 is $f = 23.4 * \exp(-0.09 * X_2)$ where X_2 is the amount of citric acid ($P = 0.0001$, $r^2 = 0.93$). In the pH 7.4 buffer solution, citric acid (20%) induced a clear lag time (Fig. 6). This means that citric acid in combination with Aqoat™ AS-HF coating buys the pellet system time to travel further down the gastrointestinal tract before drug release.

4. Conclusions

By using extrusion–spheronization pelletization mechanically strong pH-sensitive polymer matrix pellets with citric acid can be produced with a pilot-plant method. Eudragit™ S as a binder in

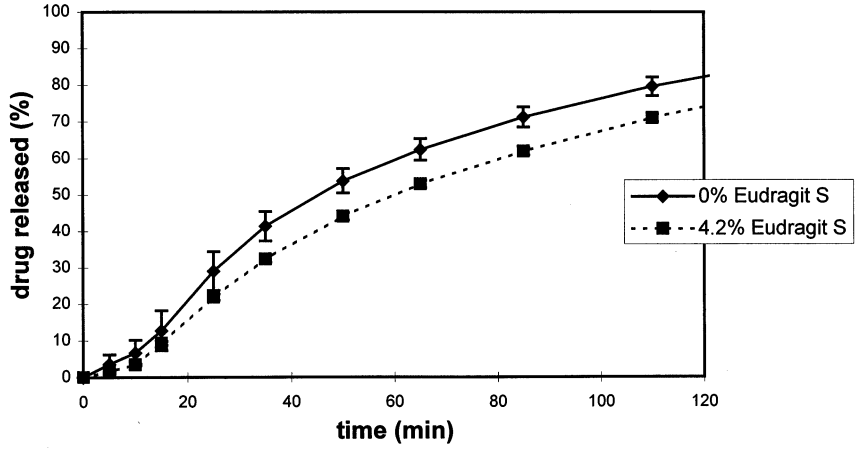

Fig. 6. Effect of Eudragit™ S on drug release from coated ibuprofen pellets in pH 7.4 buffer solution (batches 9 and 10) (mean ± SD, $n = 6$).

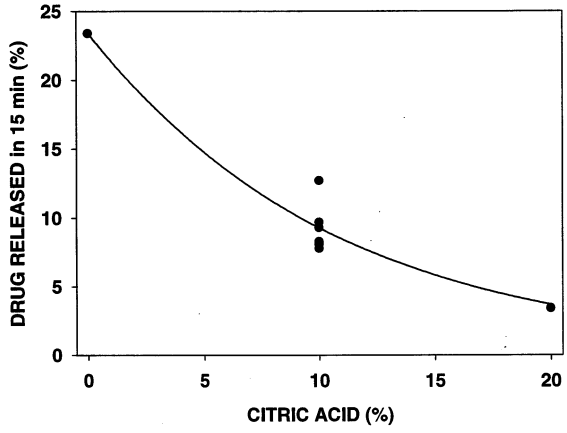

Fig. 7. Effect of citric acid on in vitro (pH 7.4) drug release in 15 min for coated pellets (spheronizing time 3 min, Eudragit S 3.3%).

pellets increases the matrix pellet size, influences pellet roundness positively in small amounts and negatively in larger amounts. Citric acid stabilised Eudragit™ S and thereby promoted the pelletization process. It can be concluded that although Eudragit S was expected to delay the drug release, it could not be shown statistically, whereas the combination of organic acid and pH-sensitive coating was sufficient to produce a delay in drug release.

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