MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 29, No. 4, pp. 429–440, 2003

RESEARCH PAPER

Studies on Modifying the Tackiness and Drug Release of Kollicoat® EMM 30 D Coatings

H. Erdmann,[1] S. Gebert,[2] K. Kolter,[2,*] and G. Schepky[1]

[1]Fachhochschule Abt. Pharmatechnik, Sigmaringen, Germany
[2]BASF Aktiengesellschaft, Product Development Pharma Ingredients, Ludwigshafen, Germany

ABSTRACT

In the search for antitack additives for Kollicoat EMM 30 D (ethyl acrylate-methyl methacrylate 30% dispersion, Ph. Eur.) film coatings, various possibilities were investigated. The best results were obtained using a combination of simethicone and talc. This mixture was tested on propranolol, theophylline, and verapamil HCl blank pellets in a previously developed Kollicoat EMM 30 D basic formulation. Almost any desired drug release rate can be obtained with all three pellet formulations by varying the two pore formers hypromellose 3mPas and microcrystalline cellulose type 105. A thin application of colloidal silica onto the coated pellets additionally prevents them from sticking together during storage.

1. INTRODUCTION

Kollicoat EMM 30 D is a recently marketed polyacrylate dispersion 30%, Ph. Eur. Like the other branded article, Eudragit NE 30 D, it has a pronounced tendency to tackiness,[1] which cannot always be satisfactorily remedied by adding existing antitack agents. Currently used antisticking agents include talc,[1,2] glyceryl monostearate,[3] and a mixture of talc, hypromellose 3mPas, and microcrystalline cellulose type 105.[4]

The purpose of this study was to find further and possibly better antitack agents for Kollicoat EMM 30 D, the most suitable of which would be incorporated into an existing basic formulation[4] by means of a further procedure. With this formulation, sustained-release pellets with the widest possible release profile were then to be produced from blank

*Correspondence: K. Kolter, BASF Aktiengesellschaft, Product Development Pharma Ingredients, D-67056 Ludwigshafen, Germany; E-mail: karl.kolter@basf-ag.de.

DOI: 10.1081/DDC-120018378
0363-9045 (Print); 1520-5762 (Online)

www.dekker.com

pellets using three different active ingredients, by varying the two pore formers hypromellose 3 mPas and microcrystalline cellulose type 105.

2. EXPERIMENTAL PROCEDURE

2.1. Materials

Barium sulfate (Fluka Chemie AG, Buchs, Switzerland); caffeine, fine powder, anhydrous (Knoll AG, Ludwigshafen, Germany); calcium silicate (Micro-Cel®, BASF Corporation, MI 48192, USA); calcium stearate (Riedel de Haen AG, Seelze, Germany); citric acid monohydrate (Riedel de Haen AG, Seelze, Germany); colloidal silica (Aerosil® 200, Degussa-Hüls AG, Frankfurt am Main, Germany); colloidal silica (Aerosil® R 972 Degussa-Hüls AG, Frankfurt am Main, Germany); ethyl acrylate-methyl methacrylate-copolymer (Kollicoat® EMM 30 D, BASF AG, Ludwigshafen, Germany); glyceryl monostearate (Tokyo Kasei Kogyo Co. Ltd., Tokyo 103, Japan); hydroxypropyl methylcellulose, hypromellose (Pharmacoat® 603, Shin-Etsu, Tokyo, Japan); iron oxide (Sicovit® Red 30, BASF AG, Ludwigshafen, Germany); lactose (Granulac® 230, Meggle GmbH, Wasserburg, Germany); magnesium stearate (Bärlocher GmbH, Munich, Germany); magnesium aluminium silicate (Veegum® F, C. H. Erbslöh KG, Krefeld, Germany); maize starch C-PHARM® (Cerestar, Krefeld, Germany); microcrystalline cellulose (Avicel® PH 101, Lehmann & Voss & Co., Hamburg, Germany); PEG-hydrogenated castor oil (Cremophor® RH 40, BASF AG, Ludwigshafen, Germany); povidone (Kollidon® 30, BASF AG, Ludwigshafen, Germany); precipitated silica (Sipernat 22 S (Degussa, Frankfurt, Germany); propranolol HCl 80 (Knoll AG, Ludwigshafen, Germany); simethicone (Pharsil® 21046 VP, Wacker-Chemie GmbH, Burghausen, Germany); sodium stearyl fumarate (Knoll AG, Ludwigshafen, Germany); stearic acid (Fluka Chemie AG, Buchs, Switzerland); stearyl alcohol (Lorol® C 18, Henkel, Düsseldorf, Germany); sucrose stearate (Ryoto sugar ester S 1670, Mitsubishi-Kagaku Foods Corporation, Tokyo, Japan); talc (Lucenac® 20 MO, Lucenac Val Chisone, Pinerolo, Italy); talc (Riedel de Haen AG, Seelze, Germany); talc (Pharma S, Lucenac Val Chisone, Pinerolo, Italy); theophylline anhydrous powder 200 (Knoll AG, Ludwigshafen, Germany); titanium dioxide, micronized (Sachtleben, Duisburg, Germany, or Kronos, Leverkusen, Germany); tribehenin (Compritol® 888 ATO, Gattefossé S. A., Saint Priest, France); verapamil HCl (Knoll AG, Ludwigshafen, Germany); vinyl acetate-vinylpyrrolidone-copolymer, copolyvidone (Kollidon VA 64, BASF AG, Ludwigshafen, Germany).

2.2. Apparatus

Diosna mixer V 50 (Dierks & Söhne Maschinenfabrik, Osnabrück, Germany); electronic stirrer RZR 2051 (Heidolph-Elektro GmbH & Co. KG, Kelheim, Germany); dissolution tester PTW S (Pharmatest Apparatebau GmbH, Hainburg, Germany); dosing pump gamma/4 (ProMinent Dosiertechnik, Heidelberg, Germany); corundum disc mill 0112 MS (Fryma Maschinenbau GmbH, Rheinfelden, Switzerland); test sieve JEL 200 (J. Engelmann AG, Ludwigshafen, Germany); tubing pump ismatec MV-MS3 (Ismatec Laboratoriumstechnik GmbH, Wertheim-Mondfeld, Germany); spectrophotometer 8452 A (Hewlett Packard GmbH, Böblingen, Germany); spheronizer RUMA 30/4 (M. Heller Labortechnik, Mutterstadt, Germany); Coating Aeromatic Fluid Bed Dryer Strea-1 (Aeromatic-Fielder AG, Bubendorf, Switzerland); Aeromatic MP-1 Fluid Bed Dryer (Aeromatic Fielder AG, Bubendorf, Switzerland).

2.3. Composition and Preparation of the Blank Pellets

Thirty-kilogram batches of raw materials (see Table 1) were preblended in the Diosna for 10 min at setting 2, wetted with demineralized water, and subsequently kneaded for 8 min at setting 1 (see Table 1). After passing through a sieve of mesh size 1.5 mm, the pellets were rounded in a spheronizer (see Table 2). Sieve fractions between 0.71 and 1.41 mm, and for verapamil HCl blank pellets 0.71–2.5 mm, were used for coating.

2.4. Composition and Preparation of the Spray Suspensions

2.4.1. Test for Antitack Effect

The following additives were then investigated: colloidal silica, Aerosil R 972, barium sulfate, calcium stearate, tribehenin (Compritol 888 ATO), tribehenin (7.5% Compritol 888 ATO) + 5.0% talc,

Table 1. Composition of the different pellets (parts by weight).

	Caffeine pellets	Propranolol HCl pellets	Theophylline pellets	Verapamil HCl pellets
Active ingredient	10.00	30.00	60.00	48.00
Avicel pH 101	43.75	46.66	37.50	30.00
Granulac 230	43.75	20.84	—	—
Kollidon VA 64	2.50	2.50	2.50	2.00
Aerosil 200	—	—	—	2.50
Talc	—	—	—	17.50
Total	100.00	100.00	100.00	100.00
Water demineralized	58.00	54.00	86.00	40.00

Table 2. Equipment parameter settings of the spheronizer.

	Caffeine pellets	Propranolol HCl pellets	Theophylline pellets	Verapamil HCl pellets
Extrudate (kg)	1.7	1.2–1.7	1.2	0.5
Revolutions (rpm)	380–420	200–400	300–400	300–400
Time (min)	10	3–10	3–5	3–5

Table 3. Investigation of spray-coating suspensions (parts by weight) with different antitack additives.

Kollicoat EMM 30 D	41.67	41.67	41.67	41.67	41.67
Antitack additives	2.50	5.00	7.50	10.00	12.50
Simethicone	0.025	0.025	0.025	0.025	0.025
Water demineralized	55.805	53.305	50.805	48.305	45.805
Total	100.00	100.00	100.00	100.00	100.00

stearyl alcohol, talc (Lucenac 20 MO), magnesium stearate, maize starch, calcium silicate (Micro-Cel), monostearin, sodium stearyl fumarate, simethicone, 7.5% simethicone + 5.0% talc, sucrose stearate (Ryoto sugar ester S 1670), precipitated silica (Sipernat 22 S), stearic acid, talc (Pharma S), titanium dioxide micronized, magnesium aluminium silicate (Veegum F).

In order to enable incorporation in a spray suspension, the test additives were combined with the mixture of water and simethicone (see Table 3), if necessary, with addition of up to 5% PEG-hydrogenated castor oil (Cremophor RH 40) (with reference to the antitack additive). Subsequently, Kollicoat EMM 30 D was admixed.

2.4.2. Variation of Dissolution Rates

Composition of the spray suspensions (see Tables 4, 5, and 6):

The polymer and pigment suspensions were prepared separately and then mixed together.

Polymer suspension: Hypromellose and/or microcrystalline were initially added to the water, followed by Kollicoat EMM 30 D.

Pigment suspension: Povidone (Kollidon 30) was dissolved in water, iron oxide (Sicovit Red 30) and talc were then suspended, and the resulting mixture was processed in the corundum mill at gap width 0. Finally, simethicone was incorporated.

2.5. Coating of Blank Pellets

The studies on the various antitack agents were performed using caffeine blank pellets with a film thickness of 2 mg/cm^2. Dissolution rates were varied using the best antitack additive according to the above studies.

Coating was performed to the film thickness:

- propranolol HCl blank pellets to 3.3 mg/cm^2
- theophylline blank pellets to 2.6 mg/cm^2
- verapamil blank pellets to 2.4 mg/cm^2.

Table 4. Coating dispersions (parts by weight) applied on propranolol HCl pellets.

	I	II	III	IIIWP	IV	IVWS
			Polymer suspension			
Kollicoat EMM 30 D	39.30	39.30	39.30	39.30	39.30	39.30
Avicel PH 105	—	—	—	—	1.40	1.40
Pharmacoat 603	—	0.70	1.40	1.40	0.70	0.70
Water demineralized	22.13	22.91	23.69	23.69	24.47	24.47
			Pigment suspension			
Kollidon 30	0.50	0.50	0.50	0.50	0.50	0.50
Sicovit Red 30	0.50	0.50	0.50	0.50	0.50	
Simethicone	7.095	7.095	7.095	—	7.095	7.095
Talc	4.72	4.72	4.72	4.72	4.72	4.72
Water demineralized	25.755	24.275	22.795	29.89	21.315	21.815
Total	100.00	100.00	100.00	100.00	100.00	100.00
Solid matter content	19.82	20.52	21.22	18.91	21.92	21.42

Table 5. Coating dispersions (parts by weight) applied on theophylline pellets.

	A	B	C	D	E	F
			Polymer suspension			
Kollicoat EMM 30 D	32.50	32.50	32.50	32.50	32.50	32.50
Avicel PH 105	—	2.25	4.50	4.50	4.50	4.50
Pharmacoat 603	—	—	—	0.50	1.00	1.40
Water demineralized	18.50	28.87	27.23	31.25	31.98	32.56
			Pigment suspension			
Kollidon 30	0.50	0.50	0.50	0.50	0.50	0.50
Sicovit Red 30	0.50	0.50	0.50	0.50	0.50	0.50
Simethicone	5.875	5.875	5.875	5.875	5.875	5.875
Talc	3.90	3.90	3.90	3.90	3.90	3.90
Water demineralized	38.225	25.605	24.995	20.475	19.245	18.265
Total	100.00	100.00	100.00	100.00	100.00	100.00
Solid matter content	16.56	18.81	21.06	21.56	22.06	22.46

Table 6. Coating dispersions (parts by weight) applied on verapamil HCl pellets.

	1	2	3	4	5
		Polymer suspension			
Kollicoat EMM 30 D	32.50	32.50	32.50	32.50	32.50
Avicel PH 105	—	2.25	4.50	4.50	4.50
Pharmacoat 603	—	—	—	0.35	0.70
Water demineralized	20.81	30.18	35.87	28.05	28.51
		Pigment suspension			
Kollidon 30	0.50	0.50	0.50	0.50	0.50
Sicovit Red 30	0.50	0.50	0.50	0.50	0.50
Simethicone	5.875	5.875	5.875	5.875	5.875
Talc	3.90	3.90	3.90	3.90	3.90
Water demineralized	35.915	24.295	16.355	23.825	23.015
Total	100.00	100.00	100.00	100.00	100.00
Solid matter content	16.56	18.81	21.06	21.41	21.76

Table 7. Equipment parameter settings of the aeromatic, STREA 1, and MP 1.

	Type STREA-1	Type MP-1
Batch size (kg)	0.5	1.0
Equipment	Wurster	Wurster
Nozzle (mm)	0.8	0.8
Atomizing pressure (bar)	1.0	1.0
Inlet air (m^3/h)	80–100	100–120
Inlet air volume temperature (°C)	35	40–45
Product temperature (°C)	29–31	29–31
Outlet air temperature (°C)	27–29	28–30
Prewarming time (min)	3	3
Drying time (min)	5	5
Spray rate (g/min)	4–6	7–11

The spray suspensions were stirred throughout the entire spraying process. On conclusion of the coating process and a drying period of 3 min in the coater, 0.1% colloidal silica (with reference to pellets) dispersed in water was sprayed onto the pellets. Tackiness which occurred during the spraying process was determined according to the extent of agglomeration of pellets and adhesion to the equipment walls (see Table 7).

2.6. Investigation of Blank Pellets and Coated Pellets

2.6.1. Dissolution Rate (Table 8)

2.6.2. Tack Behavior and Flowability After Storage

Sealed 50-mL glass containers filled up to two-thirds of capacity were stored under vibration-proof conditions and then slowly rotated through 180° to evaluate tack behavior and flowability. It was investigated as to whether the pellets were free flowing and whether they could be separated only by impact such as jolting or rolling the container.

3. RESULTS AND DISCUSSION

3.1. Effect on Tackiness

Kollicoat EMM 30 D is a very soft neutral copolymer. The low glass transition temperature of 6°C results in a significant plastic behavior associated with a certain degree of tackiness. According to their mode of action, antitack agents can be divided into three different classes:

1. Water-soluble or water-swellable, nonhygroscopic agents with a high glass transition temperature or melting point. The application of these materials, e.g., HPMC, is limited to pore formation, which accelerates the dissolution rate and diminishes the sustained release effect.
2. Water-insoluble inorganic agents. Finely dispersed particles, e.g., talc or pigments, reduce the interaction at the film's surface mainly due to an increase in stiffness.
3. Lipophilic organic agents. These materials can be either dissolved in the film-forming

Table 8. Determination of the dissolution rate of coated and uncoated pellets according to USP, apparatus 1.

	Caffeine pellets	Propranolol HCl pellets	Theophylline pellets	Verapamil HCl pellets
Dissolution method	pH change after 2 h Basket	Full change after 1.5 h Basket	pH change after 2h basket	pH change after 2 h Basket
Medium (mL)	890	900	890	900
pH 1.2	0.08 M HCl	0.08 M HCl	0.08 M HCl	0.08M HCl
pH 6.8	+20 mL K_3PO_4-buffer[a]	Buffer according USP	+20 mL K_3PO_4-buffer[a]	+20 mL K_3PO_4-buffer[a]
Revolutions (rpm)	50	100	50	50
Wavelength (nm)	273	289	272	278
Sampling after (h)	1, 2, 4, 8, 12, 16, 20, 24	1, 2, 4, 8, 12, 16, 20, 24	1, 2, 4, 8, 12, 16, 20, 24	1, 2, 4, 8, 12, 16, 20, 24

[a]659 g $K_3PO_4 \times 3\,H_2O$, demineralized water 1000 mL.

polymer, probably increasing the glass transition temperature, or dispersed and thus replace the tacky polymer at the surface.

A large proportion of the test additives studied to assess their potential for reducing tackiness of Kollicoat EMM 30 D films listed in Section 2.4.1 were already discarded during the spray dispersion preparation trials due to processing problems. The most common problems were coagulation, excess viscosity, deficient wettability (even after addition of 5% Cremophor RH 40), or excessive sedimentation.

Those antitack agents, that can be processed into spray dispersions under simulated practical conditions are listed in Table 9.

They were subjected to further trials in the form of spray experiments with caffeine blank pellets, which led to still more elimination, firstly due to blockage of the spray nozzle and secondly due to inadequate antitack effect. The remaining additives are listed in Table 10.

Spray dispersions containing tribehenin (Compritol 888 ATO) form a light film on the wall of the storage vessel, reduction of which can be achieved by adding talc. In the case of simethicone, the addition of 5% talc causes a further decrease in the tack tendency of the coated pellets. Since talc, as a representative of water-insoluble inorganic materials, increases the stiffness of the film and simethicone, and as a representative of lipophilic organic materials, partly replaces the film-forming polymer, a combination of both exhibits a more pronounced effect. Generally, to reduce the tack of a coating, materials from different classes should be used.

3.2. Variation of Active Ingredient, Dissolution of Pellets with Three Different Active Ingredients, and Reduced Tack Tendency

Pilot trials with Kollicoat EMM coatings containing tribehenin (Compritol 888 ATO) revealed excessively rapid dissolution rates even without addition of pore formers. Thus only simethicone can be considered as a suitable antitack additive from all possibilities shown in Table 10. Simethicone 7.5% with 5% talc was selected.

The basic formulation for the film coatings of the three blank pellet types was adopted from a previous study[4] and includes hypromellose 3mPas and microcrystalline cellulose type 105 as pore formers to control the dissolution rate. The former agent is frequently described in the relevant literature.[5–8]

A further component of the basic formulation is colored pigment Sicovit Red 30. This is used to enhance the optical assessment of the pellet surface during and after the spraying process. In Fig. 1, propranolol HCl pellets are used to demonstrate that this additive, which is unusual in production formulations, has no significant impact on the dissolution rate.

Table 9. Antitack additives incorporated into Kollicoat EMM 30 D (Table 3).

Antitack additives	Parts in weight (related to dispersion)
Colloidal silica (Aerosil 200)	2.5
Tribehenin (Compritol 888 ATO)	12.5[a]
Tribehenin (Compritol 888 ATO)	7.5[a]
Tribehenin (Compritol 888 ATO)	7.5[a] + 5% Talc
Stearyl alcohol	2.5[a]
Talc (Lucenac 20 MO)	7.5
Magnesium stearate	2.5[a]
Sodium stearyl fumarate	2.5
Simethicone	7.5
Simethicone	10.0
Simethicone	12.5
Simethicone	7.5 + 5% Talc
Sucrose stearate (Ryoto Sugar Ester S 1670)	7.5
Titanium dioxide	7.5

[a]+5% Cremophor RH 40.

Table 10. Positively rated antitack additives incorporated into Kollicoat EMM 30 D (Table 3) and sprayed onto caffeine pellets.

Antitack additives	Parts in weight (related to dispersion)
Tribehenin (Compritol 888 ATO)	12.5[a]
Tribehenin (Compritol 888 ATO)	7.5[a]
Tribehenin (Compritol 888 ATO)	7.5[a] + 5% Talc
Simethicone	12.5
Simethicone	7.5 + 5% Talc

[a]+5% Cremophor RH 40.

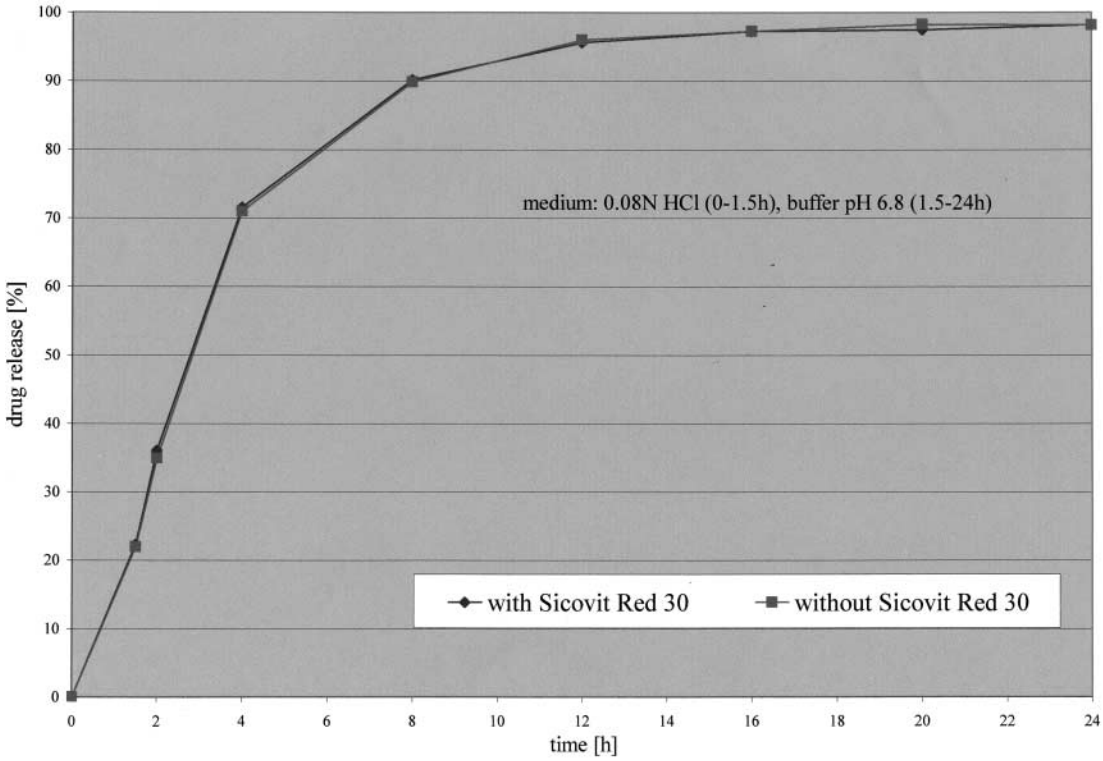

Figure 1. Propranolol HCl pellets with and without Sicovit Red 30 (Table 4, form. IV + IVWS).

It was also shown in the above study[4] that admixture of 0.1% colloidal silica to the finished coated and dried pellets reduces their tack tendency. This protection was also used in the subsequent trials, however, by spraying on an aqueous colloidal silica dispersion rather than injecting Aerosil 200 dry powder. In Fig. 2, verapamil pellets are used to show that this additive also does not alter the active ingredient dissolution.

Finally, it was interesting to establish the impact of the new antitack agent simethicone on the dissolution rate of the basic formulation. A comparison between a simethicone-containing and simethicone-free coating on propranolol HCl pellets revealed no significant difference (Fig. 3).

3.2.1. Propranolol Pellets

While the blank pellets show rapid release in both media (see Figs. 4 and 5), variation of

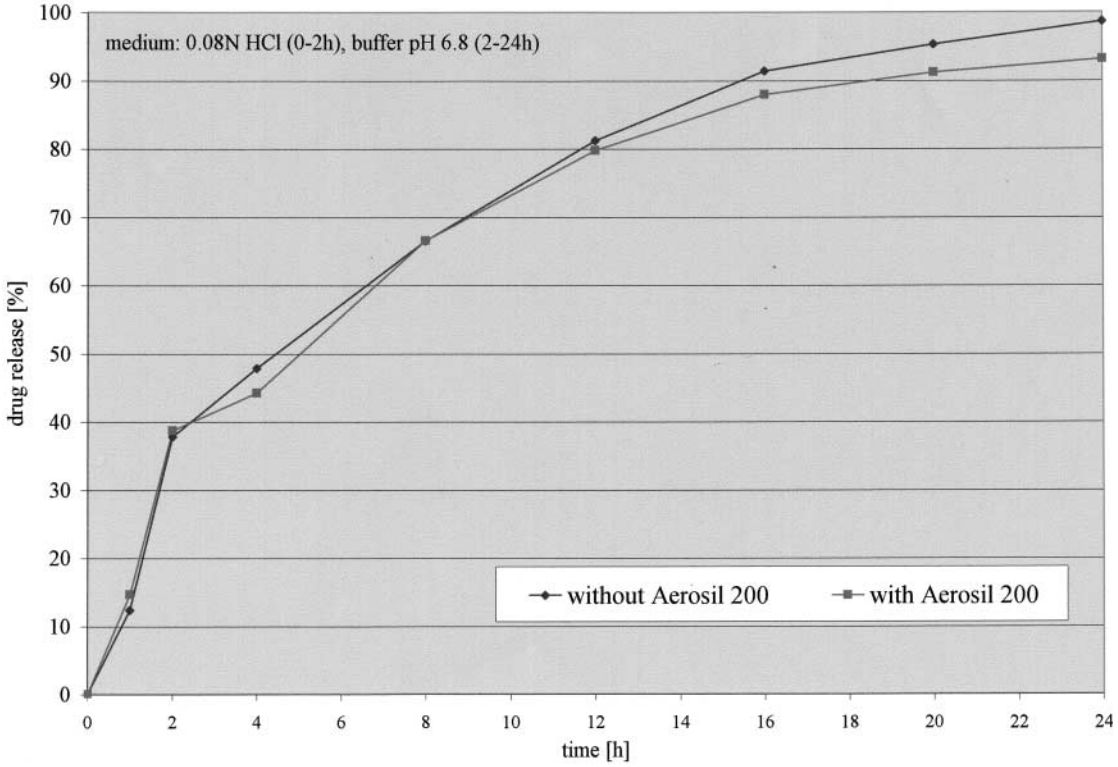

Figure 2. Verapamil HCl pellets with and without Aerosil coating (Table 6, form. 4).

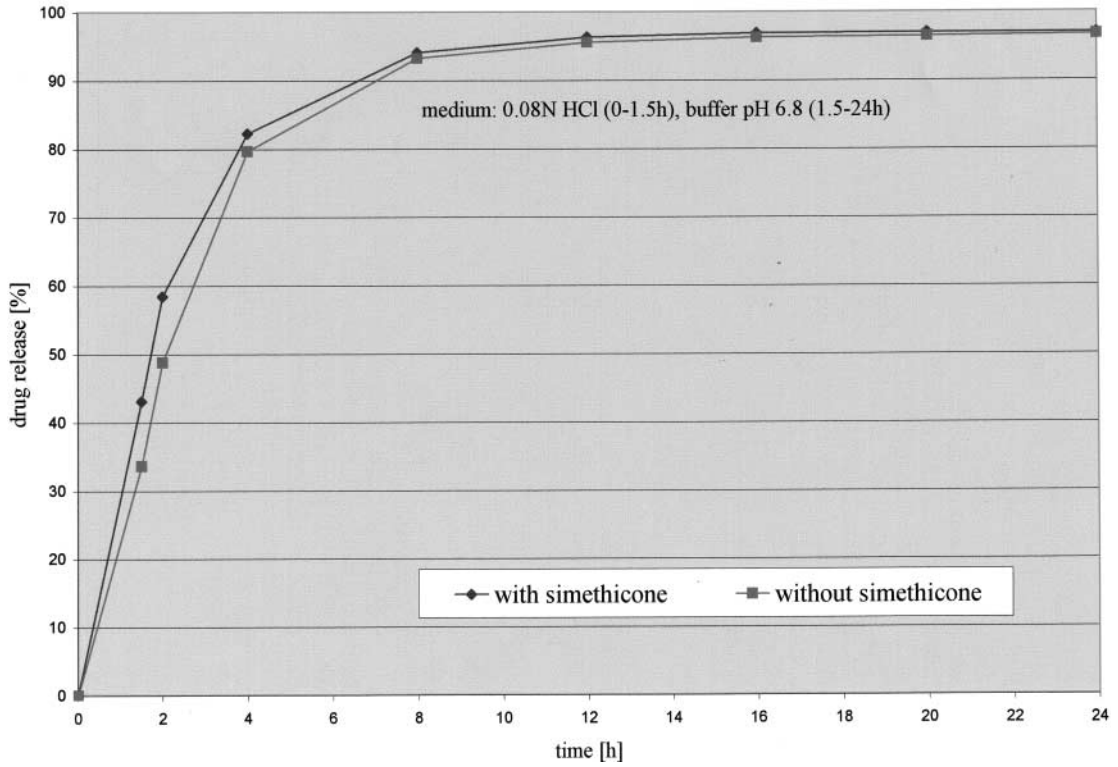

Figure 3. Propranolol HCl pellets with and without simethicone (Table 4, form. III + IIIWP).

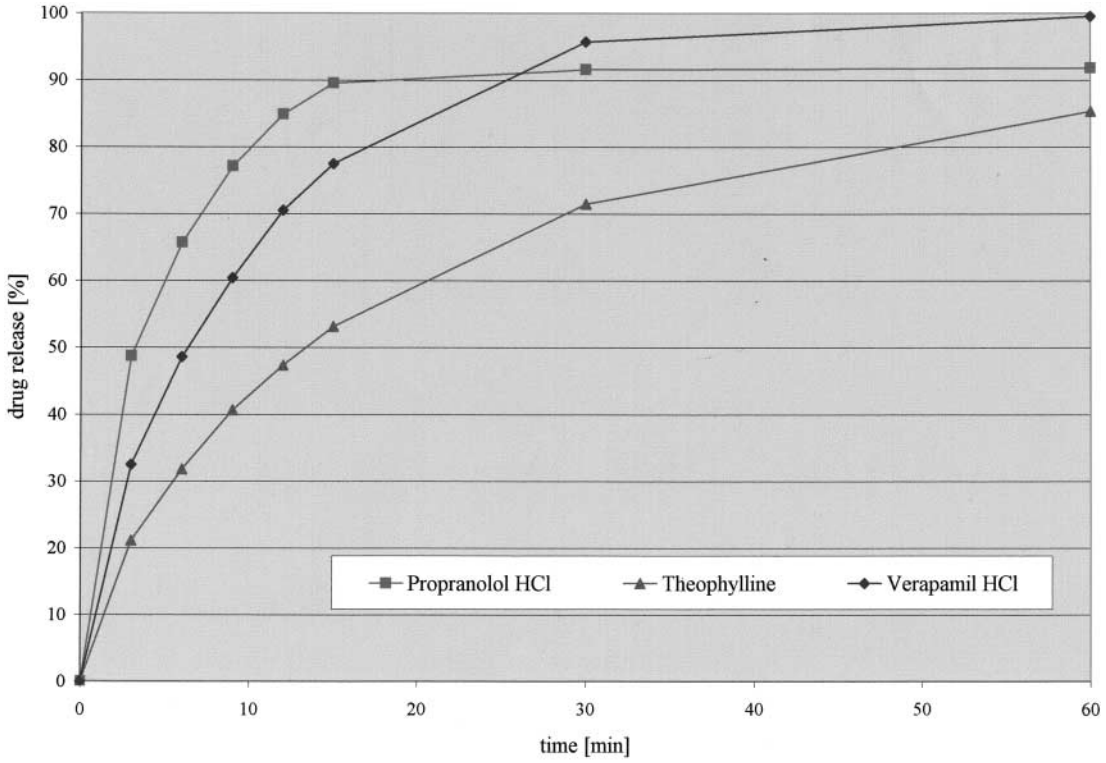

Figure 4. Release characteristics of blank pellets in simulated gastric fluid (Tables 1, 2, and 8).

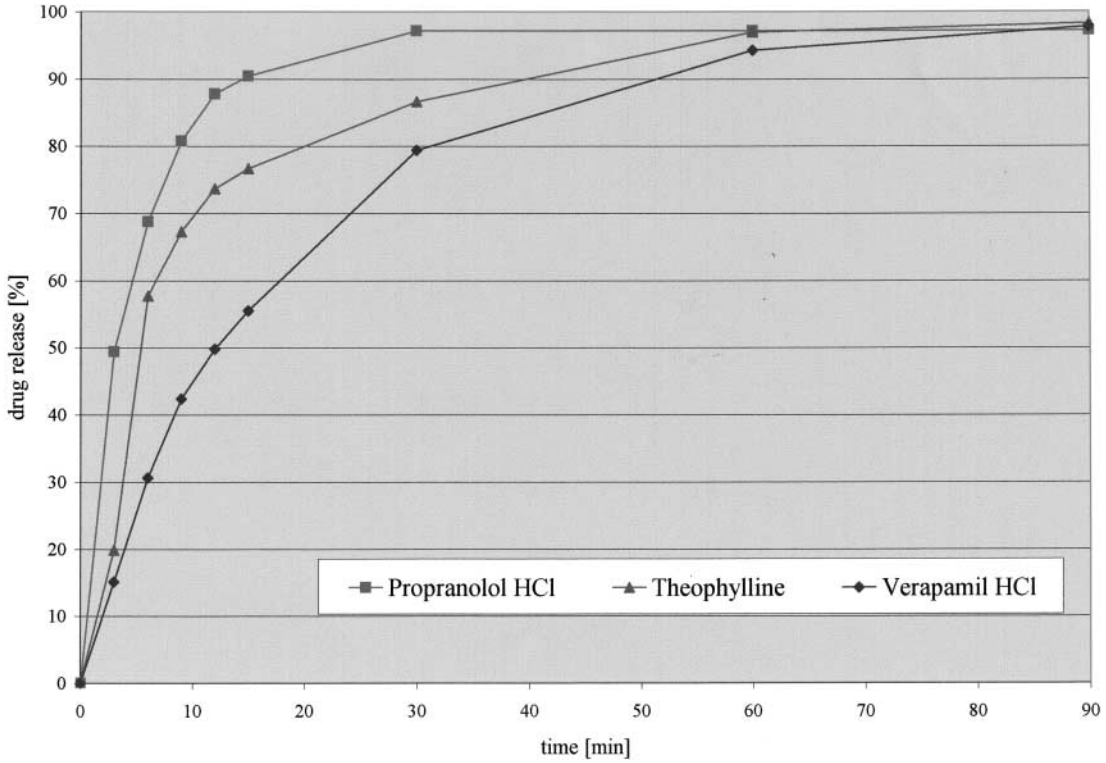

Figure 5. Release characteristics of blank pellets in simulated intestinal fluid (Tables 1, 2, and 8).

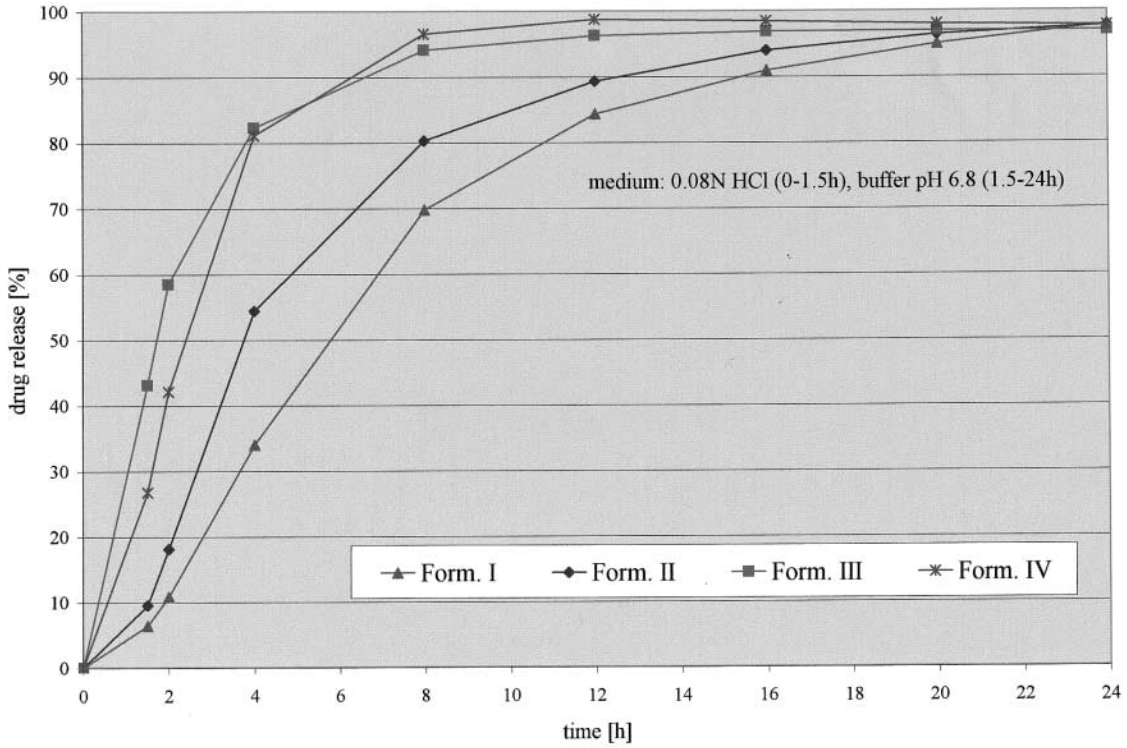

Figure 6. Release characteristics of propranolol HCl pellets coated with formulation I–IV (Table 4).

the pore former additives microcrystalline cellulose and hypromellose in Kollicoat EMM 30 D films produces an adequate range of dissolution rates (Fig. 6).

Due to its water solubility, hypromellose appears to accelerate dissolution to a greater degree than microcrystalline cellulose.

Two further batches of formulation 1 demonstrate the good reproducibility of the dissolution rate of this formulation (Fig. 7).

3.2.2. Theophylline Pellets

Compared to propranolol pellets, the dissolution of theophylline pellets can be varied over a much greater range with the basic film formulation (see Fig. 8). The different drug solubility and the resulting different dissolution rates of the two blank pellets may play a major role in this respect (see Figs. 4 and 5). Generally a lower solubility results in a slower dissolution rate.

Again, the content of hydroxypropyl methylcellulose has a greater impact on the dissolution rate than that of microcrystalline cellulose.

3.2.3. Verapamil HCl Pellets

As with the theophylline blank pellets, the dissolution rate of the verapamil HCl blank pellets was also seen to be highly dependent on the pH of the medium—although in the opposite direction (Figs. 4 and 5). While the dissolution of theophylline improves with increasing pH, the less readily soluble base forms from verapamil HCl. This effect probably explains the increasingly pronounced inflection point on the dissolution curve after the 2-hr value (i.e., the point at which simulated gastric fluid is replaced by simulated intestinal fluid) also observed with the coated verapamil pellets. Furthermore, the basic film formulation also allows a wide drug dissolution range to be achieved with verapamil pellets (see Fig. 9). And once again, hypromellose makes a more effective contribution in this respect than microcrystalline cellulose.

4. CONCLUSION

The dissolution curves can be adjusted within wide limits by varying the two pore formers

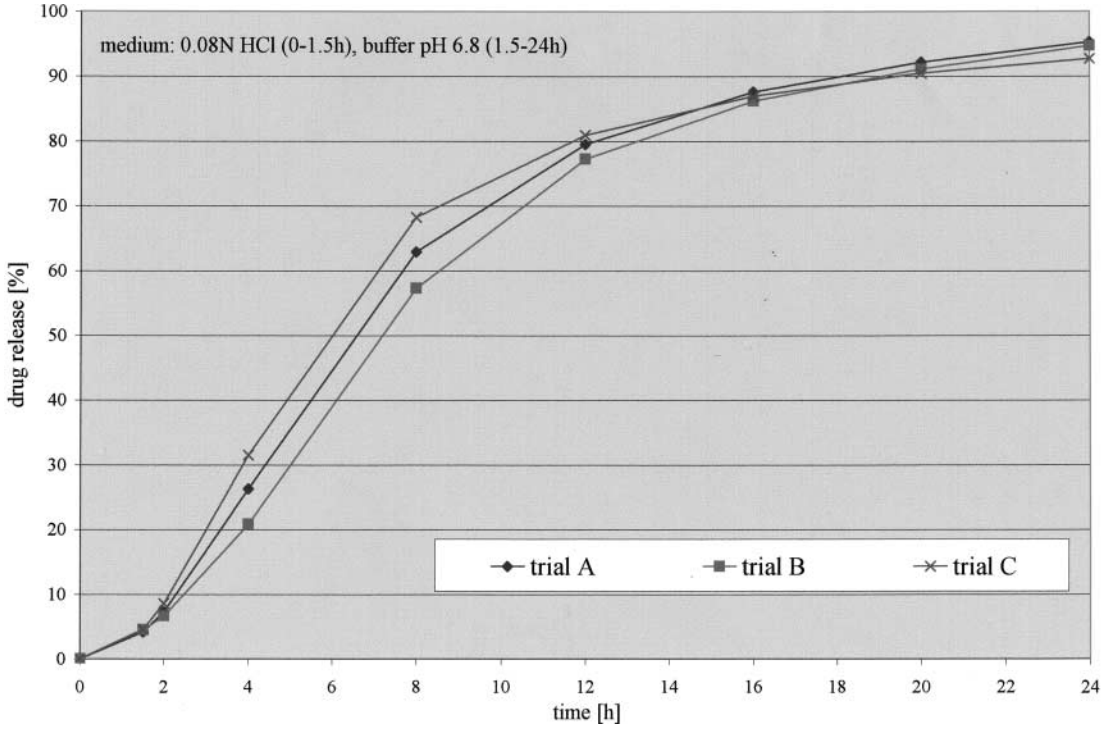

Figure 7. Reproducibility of the release characteristics of propranolol HCl pellets coated with formulation I (Table 4).

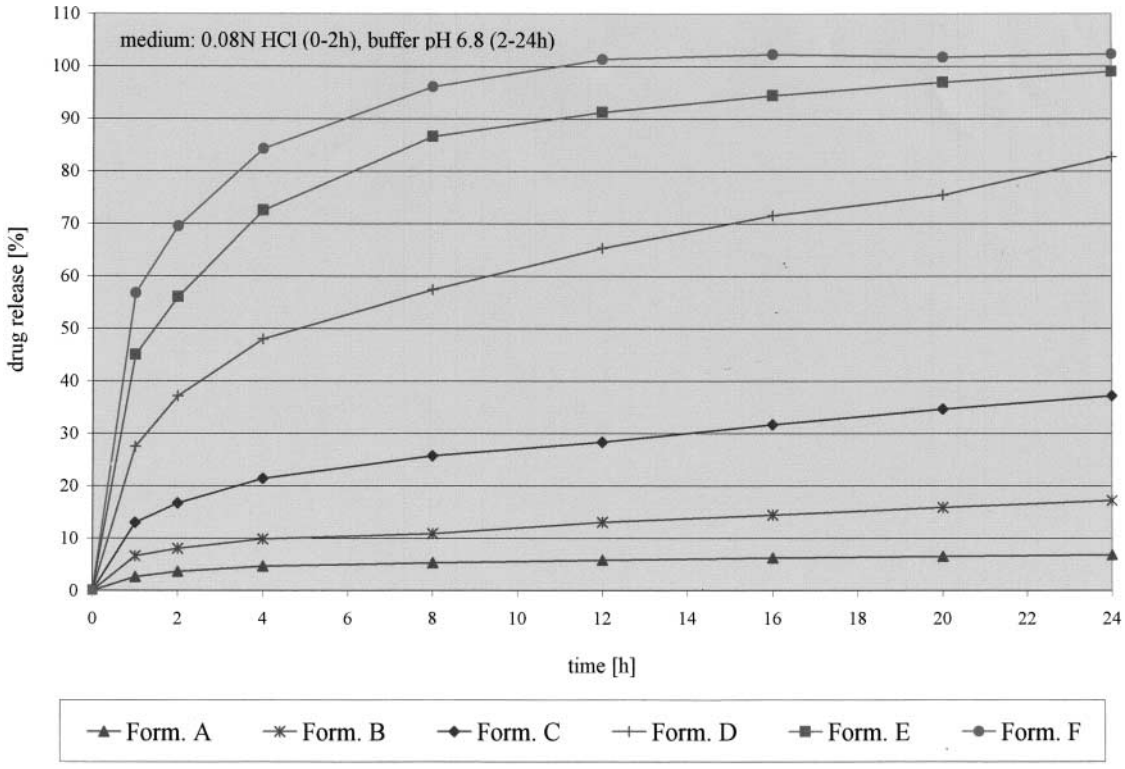

Figure 8. Release characteristics of theophylline HCl pellets coated with formulation A–F (Table 5).

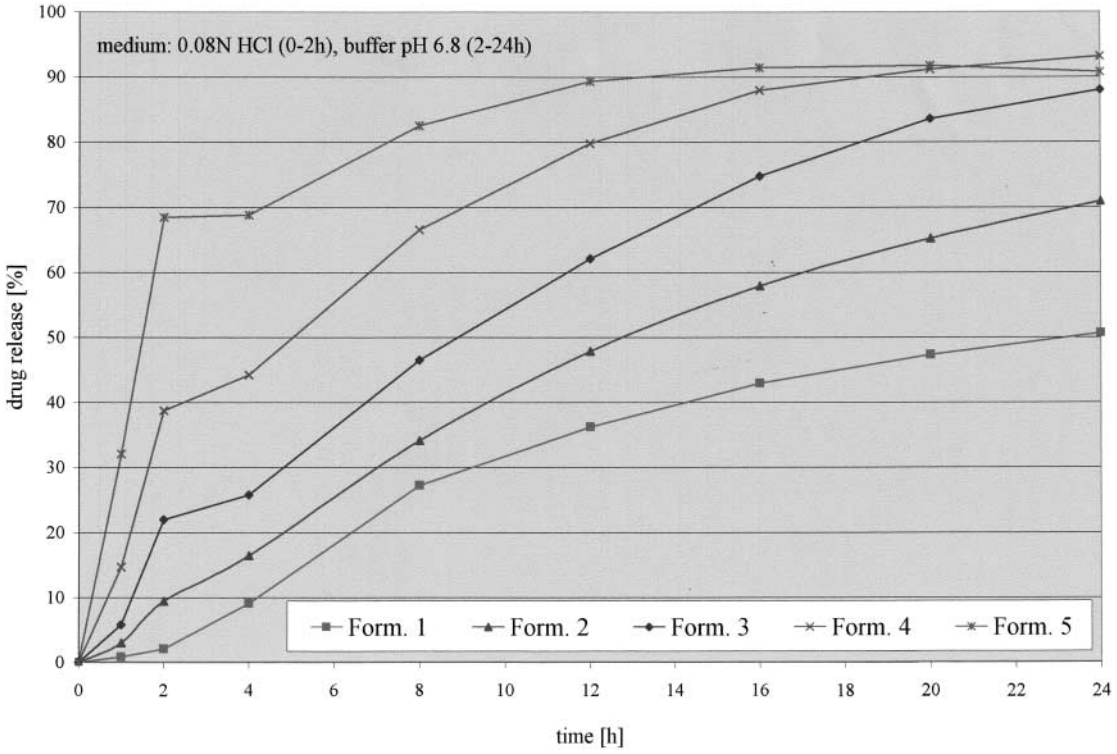

Figure 9. Release characteristics of verapamil HCl pellets (Table 6).

hypromellose 3mPas and microcrystalline cellulose type 105 with the studied basic film formulation on pellets containing different active ingredients. The use of simethicone and talc, if necessary, combined with a colloidal silica coating, prevents agglomeration of the pellets during the coating process and during storage.

REFERENCES

1. Wesseling, M.; Kuppler, F.; Bodmeier, R. Tackiness of acrylic and cellulosic polymer films used in the coating of solid dosage forms. Eur. J. Pharm. and Biopharm. **1999**, *47* (1), 73–78.
2. Deshpande, A.A.; Shah, N.H.; Rhodes, Chr.T.; Malick, W. Evaluation of films used in development of a novel controlled-release system for gastric retention. Int. J. Pharm. **1997**, *159*, 255–258.
3. Petereit, H.-U.; Aßmus, M.; Lehmann, K. Gylceryl monostearate as a glidant in aqueous film-coating formulations. Eur. J. Pharm. and Biopharm. **1995**, *47* (4), 219–228.
4. Kovacevic, D.; Schepky, G.; Kolter, K. Sustained-release polyacrylate dispersion coatings comparative studies of pellets containing various active ingredients. *Pharmaceutical Technology Tableting & Granulation Yearbook*; October, 2000; 2–7.
5. Steward, P.A.; Hearn, J.; Wilkinson, M.C. Studies on permeation through polymer latex films, iii. modification using soluble polymeric additives. Polymer International **1995**, *38*, 23–32.
6. Steward, P.A.; Hearn, J.; Wilkinson, M.C.; Wilson, A.J.; Roulstone, B.J. *Permeation and Morphology in Polymer Latex Films Containing Leachable Additives*; Symposium series, American Chemical Society: Washington, D.C., 1996; *648* (23), 359–402.
7. Amighi, K.; Moes, A.J. Influence of curing conditions on the drug release rate from Eudragit NE 30 D film coated sustained-release theophylline pellets. S.T.P. Pharma Sciences **1997**, 7 (2), 141–147.
8. Vecchio, C.; Fabiani, F.; Lombardi, C.; Gazzaniga, A. Tangential spray coating of indobufen pellets prepared by direct pelletization using rotary fluidized bed. Proceedings of the 23rd International Symposium on Controlled Release of Bioactive Materials, 1996; Controlled Release Society: Kyoto, Japan, 533–534.