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COATED CAPSULES FOR DRUG TARGETING TO PROXIMAL AND DISTAL PART OF HUMAN INTESTINE

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Abstract: Coated hard capsules are becoming increasingly important for a number of reasons such as administration of new active ingredients, oral vaccination, colon drug delivery or their use in preclinical and clinical trials. The independency of coating composition on capsules filling is the major advantage of this dosage form. In our study, two types of hard capsules (gelatin and hypromellose) were coated by non-aqueous solutions of Eudragit® L and S 12.5, respectively, to achieve intestinal and distal ileic drug delivery. Gelatin hard capsules were coated with Eudragit® film either directly or using hydroxypropyl cellulose sub-coating prior to the final coating. Hypromellose capsules were coated directly. Coated capsules were evaluated for coating thickness by optical microscope and for dissolution in different pH media. Gelatin capsules do not seem to be suitable for direct coating with Eudragit® due to insufficient film adhesion to the smooth capsule surface and a brittleness of formed films. These problems can be solved by hydroxypropyl celullose interlayer application. Hypromellose hard capsules could be directly easily coated with both Eudragit® solutions. Dissolution of caffeine from coated capsules showed the potency for enteric delivery in gelatin capsules with interlayer and Eudragit® L film in 7.5 and 10.0% concentrations and in hypromellose capsules coated with Eudragit® L in 5-17.5% coating levels. Gelatine capsules with interlayer and 10% Eudragit® S film and hypromellose capsules only with high coating level (20%) provided potential distal ileum targeting of incorporated drug. Eudragit® S film sprayed onto hypromellose capsules surface was brittle especially in the junction zone between capsule cap and body. Better plasticity of Eudragit® S coating could be probably achieved using a different plasticizer.

Key words: capsules, Eudragit®, enteric coating, ileic delivery, oral vaccination

Nowadays, gelatin is the most commonly used material for capsules manufacturing. Gelatin capsules were first patented by Mr. Mothes in Paris in 1834 as the edible container to mask the taste and odor of medicines (1). Coating process of gelatin capsules is very sensitive, especially when aqueous dispersions are used resulting in shell softening and capsule sticking due to interaction of water and gelatin (2). To solve these problems the non-aqueous coating solutions can be used (3).

Hypromellose (HPMC) capsules are the choice for pharmaceutical applications when a non-animal capsule is required as the vegetarian alternative to gelatin (2). The Japanese company, Shionogi Qualicaps, was the first one to patent a system using hypromellose solutions with carrageenan as a network former and potassium chloride as a gelation promoter (1). Good mechanical properties are one of advantages of HPMC capsules. Hypromellose is a well-characterized and stable material with pH-independent solubility *in vitro*. Low moisture content (4-6%) ensures stability with hygroscopic fills. Excipients such as lactose, maize starch, sorbitol, magnesium stearate, pre-gelatinized starch, microcrystalline cellulose and carboxymethyl cellulose are all compatible with HPMC capsules.

The disintegration times of uncoated gelatin or HPMC capsules evaluated *in vivo* showed no significant differences (1). Important difference between these two types of capsules was found especially in the surface structure. The gelatin capsules surface is smooth, whereas the rough surface can be observed on the HMPC capsules. Due to this fact, the better adhesion of coating materials to HPMC shells surface is assumed (2).

Copolymers of methacrylic acid and either methyl methacrylate or ethyl acrylate, well known under the brand name Eudragit®, are commonly used

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as the pH-sensitive coating materials. Eudragit® L 12.5 and Eudragit® S 12.5 are 12.5% (w/w) isopropyl alcohol solutions containing 3% (w/w) of deionized water. Eudragit® L 100 and Eudragit® S 100 are anionic copolymers based on methacrylic acid and methyl methacrylate. The ratio of the free carboxyl groups to the ester groups is approx. 1 : 1 in Eudragit® L 100 and approx. 1 : 2 in Eudragit® S 100. Eudragit® L 12.5 is soluble in dissolution medium above pH 6.0, thus enabling an enteric coating to protect drugs against degradation in the stomach or to prevent irritation of gastric mucosa. Eudragit® S 12.5 is soluble in medium with higher pH value, approx. above 7.0 (4). Thus, it can be a good candidate for ileic or colonic drug delivery in local treatment of a variety of intestinal diseases or improving the oral bioavailability of some drugs such as peptides and proteins (5). pH-dependent coated hard capsules are able to achieve site specific drug delivery and present a perspective possibility for application of oral vaccines delivering the capsule content near to the Peyer's patches – the aggregations of lymphoid tissue located in the lamina propria layer of the mucosa and extending into the submucosa of the ileum. The number of Peyer's patches increases further down the intestine. Terminal ileum contains the most Peyer's patches. They play important roles in the immune surveillance of the intestinal lumen and in facilitating the generation of the immune response within the mucosa. In oral vaccination, the uptake by Peyer's patches is an essential step (6). Potencially, microsized or nanosized delivery particles could be transported in coated hard capsules. These particles were designed for crossing the mucosal barriers and releasing the antigen into lymphoid tissue (7).

In this paper, two types of hard capsules (gelatin and HPMC) were coated by non-aqueous solutions of Eudragit® L and S 12.5, respectively. In the case of gelatin hard capsules, Eudragit® film was applied directly on the capsule surface or hydroxypropyl cellulose pre-coating was used. In HPMC capsules, Eudragit® solution was applied without any subcoating. The aim of this study was to investigate the suitability of different origin capsules for Eudragit® L and S 12.5 coating. The coated capsules were evaluated for coating thickness by optical microscopy and dissolution tests in different pH media.

EXPERIMENTAL

Materials

Caffeine (Jilin Province Shulan Synthetic Pharmaceutical Co., Ltd., Shulan city, China) as the model substance together with soluble filler α-lactose monohydrate (Cerapharm, Vienna, Austria) were filled into hard gelatin capsules of size 4 (Capsugel, Borneum, Belgium) or HPMC capsules of size 4 – Vcaps® (Capsugel, Colmar, France). Declared surface area value of capsule size 4 is 235 mm^2. Eudragit® L 12.5 or Eudragit® S 12.5 (Evonik Röhm GmbH, Darmstadt, Germany) and hydroxypropyl celulose (HPC) – Klucel EF® (Aqualon, Wilmington, USA) were used as coating materials. Polyethylene glycol (PEG) 6000 (Sigma-Aldrich, Prague, Czech Republic) was added into Eudragit® solutions as a plasticizer. All materials were of Ph. Eur. quality.

Methods

Hard capsules filling and evaluation of uncoated capsules

Hard capsules (gelatin and HPMC) were filled in manual filling machine with caffeine and lactose monohydrate mixture which was prepared by homogenization of 10.0 g of caffeine and 2.3 g of lactose monohydrate to fill 100 pieces of hard capsules. Weight uniformity and drug content were evaluated according to Ph. Eur. 5. for each capsules batch used for coating. Characterization of hard capsules batches is presented in Table 1 and 2.

Table 1. Characterization of hard capsules batches.

Batch	Film coating material	Hard capsules material	Intermediate layer	Theoretical content of caffeine (mg)	Practical content of caffeine (mg)
1	Eudragit® L 12.5	gelatin	-	100	105.25 ± 5.65
2	Eudragit® L 12.5	gelatin	HPC	100	98.52 ± 2.59
3	Eudragit® L 12.5	HPMC	-	100	101.85 ± 3.85
4	Eudragit® S 12.5	gelatin	-	100	96.71 ± 3.89
5	Eudragit® S 12.5	gelatin	HPC	100	98.89 ± 0.56
6	Eudragit® S 12.5	HPMC	-	100	95.78 ± 4.81

Table 2. Obtained samples with different amount of Eudragit® film coating.

Batch	Average uncoated capsules weight ± SD (g)	Theoretical film coat weight (%)							
		2.5	5.0	7.5	10.0	12.5	15.0	17.5	20.0
		Labelling of successfully obtained film coated hard capsules samples and average coated capsules weight ± SD (g)							
1	0.1575 ± 0.0040	**1** *2.5%* 0.1621 ± 0.0045	**1** *5.0%* 0.1663 ± 0.0039	**1** *7.5%* 0.1692 ± 0.0029	-	-	-	-	-
2	0.1581 ± 0.0035	**2** *2.5%* 0.1623 ± 0.0037	**2** *5.0%* 0.1675 ± 0.0045	**2** *7.5%* 0.1699 ± 0.0044	**2** *10.0%* 0.1742 ± 0.0037	-	-	-	-
3	0.1557 ± 0.0025	**3** *2.5%* 0.1597 ± 0.0026	**3** *5.0%* 0.1640 ± 0.0029	**3** *7.5%* 0.1695 ± 0.0048	**3** *10.0%* 0.1715 ± 0.0028	**3** *12.5%* 0.1766 ± 0.0012	**3** *15.0%* 0.1797 ± 0.0016	**3** *17.5%* 0.1840 ± 0.0035	-
4	0.1631 ± 0,0043	**4** *2.5%* 0.1673 ± 0.0041	**4** *5.0%* 0.1694 ± 0.0035	**4** *7.5%* 0.1721 ± 0.0026	-	-	-	-	-
5	0.1615 ± 0.0028	**5** *2.5%* 0.1656 ± 0.0058	**5** *5.0%* 0.1674 ± 0.0013	**5***7.5%* 0.1707 ± 0.0016	**5** *10.0%* 0.1753 ± 0.0027	-	-	-	-
6	0.1571 ± 0.0056	**6** *2.5%* 0.1615 ± 0.0031	**6** *5.0%* 0.1637 ± 0.0054	**6** *7.5%* 0.1679 ± 0.0032	**6** *10.0%* 0.1719 ± 0.0038	**6** *12.5%* 0.1758 ± 0.0026	**6** *15.0%* 0.1795 ± 0.0019	**6** *17.5%* 0.1834 ± 0.0027	**6** *20.0%* 0.1874 ± 0.0061

Film solutions preparation and capsules coating

Two hundred of hard capsules of each batch were coated using Wurster-M 100 coater (Medipo ZT, s.r.o., Brno, Czech Republic). Eudragit® L 12.5 (batches 1, 2, 3) and Eudragit® S 12.5 (batches 4, 5, 6) were used as the coating materials. The final composition of coating material was prepared by addition of PEG 6000, purified water and isopropyl alcohol according to the producer recommendation. The both final coating solutions (100 g) contained 66.67 g Eudragit® 12.5 (S or L), 5.05 g of 33% water solution of PGE 6000 and 28.28 g of isopropyl alcohol (solid content of the polymer was 8.3%). The HPC intermediate layer was applied on batches 2 and 5. Its solution was prepared by agitation of 9.9 g of HPC together with 100.0 g of deionized water for 30 min. Approximately, 2% coating level of HPC interlayer was formed.

For the coating process, 1 mm nozzle port was used, the inlet air temperature was kept on 30°C, the air pressure was 100 kPa, coating solution was sprayed onto the capsules surface at a flow rate of 0.8 mL/s.

Within the coating process, the samples of 20 hard capsules with increasing coating concentration were withdrawn for subsequent evaluation (coating layer thickness measurement and dissolution tests).

Determination of coating thickness

The thickness of the film was determined by an optical analysis using the optical microscope (DN 45, Lambda, Prague, Czech Republic) connected to the CCD camera (Alphaphot, Nikon, Tokyo, Japan) and operated by Ia32 software. Ten different positions were measured for each tested capsule to obtain a mean thickness and a standard deviation of measurement.

Determination of dissolution profiles

To evaluate the applied coating quality, the dissolution profiles of prepared capsules were determined (SOTAX AT 7 On-Line System – Donau Lab, Zurich, Switzerland) using paddle method at 50 rpm in 1000 mL of different buffers (pH 1.2, 5.5, 6.5 for batch 1, 2 and 3 coated with Eudragit® L and 1.2, 6.8; and pH 7.5 for batch 4, 5 and 6 coated with Eudragit® S) at 37°C. Samples were analyzed for the released drug amount in a UV spectrophotometer (Lambda 25, Perkin Elmer, Wellesley, USA) at 273 nm for caffeine. The mean value and a standard deviation (SD) of three samples of each capsule batch were calculated. The appearance of capsule shell was observed under the microscope.

RESULTS AND DISCUSSION

In this study, six batches of hard gelatin or HPMC capsules 200 pieces each were coated with Eudragit® L (batches 1, 2, 3) and Eudragit® S (batches 4, 5, 6) to obtain 3 – 8 different samples with increasing film coating thickness (from 2.5 to 20%

Table 3. Thickness of Eudragit® coating layer.

Batch	Thickness of Eudragit® layer (μm)							
	2.5 %	5.0 %	7.5 %	10.0 %	12.5 %	15.0 %	17.5 %	20.0 %
1	43.85 ± 5.12	72.15 ± 6.02	87.56 ± 6.52	-	-	-	-	-
2	46.05 ± 6.56	74.22 ± 5.23	90.98 ± 7.96	117.60 ± 7 .25	-	-	-	-
3	45.54 ± 3.29	75.82 ± 8.61	90.17 ± 12.19	122.28 ± 11.25	154.95 ± 9.08	196.65 ± 13.82	211.35 ± 11.54	-
4	42.18 ± 4.36	71.82 ± 5.56	88.63 ± 7.01	-	-	-	-	-
5	37.56 ± 4.90	77.47 ± 5.44	92.72 ± 4.22	115.25 ± 6.33	-	-	-	-
6	34.88 ± 6.85	59.07 ± 5.97	79.7 ± 5.66	100.85 ± 12.74	119.83 ± 12.75	156.95 ± 5.24	196.67 ± 14.71	224.85 ± 27.23

of the uncoated and filled capsule weight). Characterization of hard capsules batches is shown in Table 1 and 2. Drug content was found 95.78-105.25% of the theoretical amount (Table 1), weight uniformity laid between 157.1 to 163.1 mg (Table 2). Obtained values are in accordance within Pharmacopoeia limits.

Preparation of Eudragit-coated capsules

Different amount of applied film coating is presented in Table 2 and expressed as percent of capsule weight. Using direct coating of gelatin capsules with Eudragit® L (batch 1) and S (batch 4) only three different concentrations of film coat – 2.5, 5.0 and 7.5%, respectively, were obtained. In higher amount, coat shelling occurred as it can be observed in Figure 1. Higher Eudragit® amount, i. e. 10.0%, could be layered on capsule surface after previous coating of 2% HPC intermediate layer (batches 2, 5) which changed the smooth surface of gelatin capsules, allowed to prepare 10% Eudragit® coat and led to shortening of the coating time. When HPMC capsules were coated (batches 3, 6), coating levels from 2.5 to 17.5% of Eudragit® L and from 2.5 to 20.0% of Eudragit® S 12.5, respectively, were prepared without any shelling problems. From these results it can be concluded that HPMC capsules are more suitable for Eudragit® L and S solutions film coating than gelatin capsules with or without HPC interlayer. This fact corresponded with the published literature data (8).

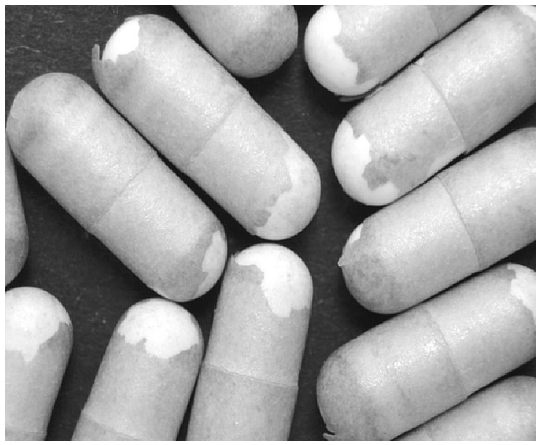

Figure 2. Rupture of Eudragit® S film of samples **1** $_{2.5\%}$ (A) and **1** $_{7.5\%}$ (B) after dissolution test in pH 1.2 (i. e. gelatin capsules without HPC subcoating)

Determination of coating thickness

Average thickness of Eudragit® L or S films and standard deviation of 10 measurements for evaluated samples are summarized in Table 3. In gelatin capsules, the coating thickness varied in range 43.85-87.56 μm for Eudragit® L (batch 1) and 42.18-88.63 μm for Eudragit® S (batch 4); (coating amount 2.5-7.5%). In gelatin capsules with HPC, sublayer the thickness of Eudragit® L film (batch 2) was in the range 46.05-117.60 μm and of Eudragit® S film (batch 5) from 37.56 to 115.25 μm (coating amount 2.5 – 10.0%). The thickness of Eudragit® L film applied onto HPMC capsules (batch 3) was in the range 45.54 – 211.35 μm (coating amount 2.5 – 17.5%) and Eudragit® S onto the same type of capsules (batch 6) 34.88 – 224.85 μm (coating amount 2.5 – 20.0%).

In vitro dissolution studies

To evaluate the quality of layered coating, the released amounts of a model substance from coated capsules in dissolution media of different pH values were monitored. The results related to dissolution profiles of the studied formulations are presented in Table 4 for Eudragit® L and in Table 5 for Eudragit® S.

The necessary presumption for both enteric coating and ileic delivery is successful capsule passage through stomach (pH 1.0-2.0) (9, 10). In fasting state, the mean gastric residence time for single solid dosage forms is considered to be 0.25-2 h (11, 12). Therefore, artificial gastric juice (AGJ) of pH 1.2 was selected as the basic dissolution medium for dissolution tests. Samples liberating more caffeine than 0.1% within 2 h lasting dissolution test in pH 1.2 were removed from other dissolution testing (13, 14). Consequently, for coating quality evaluation, samples exhibiting sufficient gastro-resistance were tested in dissolution medium of slightly lower and/or higher pH value than declared coating solubility, i. e., for Eudragit® L pH 5.5 and 6.5, for Eudragit® S pH 6.8 and 7.5, respectively. Contemporaneously, in the case of Eudragit® S, for potential distal ileic delivery it is necessary to ensure, in fasting state, 4 h intestinal resistance at pH 6.8 (4). With respect to previous gastric passage (120 min), the caffeine amount released between 120 and 360 min of performed dissolution test at pH 6.8 was a crucial parameter for coating effectivity evaluation. Within this interval, only 10% of drug could be released at the maximum. Used buffer solutions of pH 6.5, 6.8 a 7.5 simulated proximal, lower and terminal parts of the small intestine, respectively (4, 12, 15).

Eudragit-coated gelatin capsules

All directly coated Eudragit® capsules (batch 1 and 4) released 49 – 68.5% (Eudragit® L; Table 4) or 51.4 – 72.0% (Eudragit® S; Table 5) of caffeine within 120 min in AGJ depending on the coating

Table 4. Dissolution profiles of samples coated by Eudragit® L 12.5 in different dissolution media.

Time (min)	Released amount of caffeine (%) in dissolution medium with different pH value											
	pH 1.2			pH 5.5							pH 6.5	
	30	60	120	30	60	120	180	240	300	360	30	60
1 $_{2.5\%}$	38.76 ± 6.33	60.39 ± 24.21	68.55 ± 16.24	-	-	-	-	-	-	-	-	-
1 $_{5.0\%}$	21.48 ± 6.47	38.76 ± 8.08	57.58 ± 6.29	-	-	-	-	-	-	-	-	-
1 $_{7.5\%}$	0.37 ± 0.53	9.74 ± 7.43	49.02 ± 6.78	-	-	-	-	-	-	-	-	-
2$_{2.5\%}$	39.15 ± 23.86	55.03 ± 15.50	77.97 ± 4.04	-	-	-	-	-	-	-	-	-
2 $_{5.0\%}$	0,72 ± 1.26	1.53 ± 1.78	2.34 ± 2.07	-	-	-	-	-	-	-	-	-
2 $_{7.5\%}$	0.02 ± 0.03	0.07 ± 0.10	0.00 ± 0.00	0.44 ± 0.04	0.50 ± 0.01	0.64 ± 0.16	0.79± 0.13	1.18 ± 0.25	1.51 ± 0.31	1.92 ± 0.54	103.25 ± 7.34	103.62 ± 7.71
2 $_{10.0\%}$	0.00 0.00	± 0.00 ± 0.00	0.00 ± 0.00	0.94 ± 1.00	0.97 ± 0.90	1.06± 1.00	1.26± 1.12	1.61 ± 1.40	1.89 ± 1.68	2.24 ± 2.03	97.10 ± 1.67	97.76 ± 0.25
3 $_{2.5\%}$	2,72 ± 1.66	5.52 ± 1.98	10.06 ± 3.07	-	-	-	-	-	-	-	-	-
3 $_{5.0\%}$	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.17 ± 0.13	1.25 ± 0.20	2.57± 0.16	4.47± 0.49	5.73 ± 0.44	7.05 ± 0.450.49	8.19 ± 2.75	102.32 ± 3.85	103.52 ±
3 $_{7.5\%}$	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.77 ± 0.33	1.35 ± 0.23	2.32± 0.98	5.02± 1.25	5.99 ± 1.65	6.98 ± 2.01	8.06 ± 1.55	101.77 ± 4.21	102.57 ± 2.55
3 $_{10.0\%}$	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.47 ± 0.01	1.69 ± 0.04	2.65± 0.09	4.63± 0.18	5.91 ± 0.25	6.93 ± 0.33	7.91 ± 0.35	60.11 ± 3.65	98.34 ± 1.94
3 $_{12.5\%}$	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.23 ± 0.16	1.36 ± 0.62	2.49± 0.45	4.28± 0.66	5.87 ± 1.23	6.94 ± 1.31	7.89 ± 1.52	58.66 ± 2.75	100.77 ± 1.21
3 $_{15.0\%}$	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.17 ± 0.02	1.40 ± 0.04	2.30± 0.19	4.42± 0.14	5.71 ± 0.21	6.7 3± 0.38	7.84 ± 0.55	53.68 ± 7.05	108.68 ± 5.98
3 $_{17.5\%}$	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	1.29± 2.30	2.72± 2.21	2.98 ± 1.19	4.11 ± 1.55	5.15 ± 1.89	51.36 ± 6.35	91.23 ± 2.63

Table 5. Dissolution profiles of samples coated by Eudragit® S 12.5 in different dissolution media.

Time (min)	Released amount of caffeine (%) in dissolution medium with different pH value											
	pH 1.2			pH 6.8							pH 7.5	
	30	60	120	30	60	120	180	240	300	360	30	60
4 $_{2.5\%}$	21.03 ± 7.02	54.90 ± 10.66	71.99 ± 4.36	-	-	-	-	-	-	-	-	-
4 $_{5.0\%}$	8.73 ± 11.53	38.75 ± 12.54	65.65 ± 4.28	-	-	-	-	-	-	-	-	-
4 $_{7.5\%}$	11.45 ± 4.13	30.73 ± 4.21	51.40 ± 0.65	-	-	-	-	-	-	-	-	-
5 $_{2.5\%}$	55.61 ± 0.78	67.06 ± 1.30	75.13 ± 4.74	-	-	-	-	-	-	-	-	-
5 $_{5.0\%}$	0.01 ± 0.01	0,07 ± 0.09	0.10 ± 0.13	0.07 ± 0.11	0.63 ± 0.43	28.58 ± 3.60	100.2 ± 4.55	100.37 ± 4.45	100.42 ± 4.38	100.52 ± 4.38	-	-
5 $_{7.5\%}$	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.21 ± 0.02	0.11 ± 0.02	0.33 ± 0.11	1.36 ± 1.10	7.01 ± 5.43	25.57 ± 11.38	49.05 ± 23,33	-	-
5 $_{10.0\%}$	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.10 ± 0.14	1.17 ± 1.39	4.31 ± 3.42	9.01 ± 1.12	97.10 ± 1.67	97.76 ± 0.25
6 $_{2.5\%}$	0.0 ± 0.00	16.52 ± 6.58	32.56 ± 6.05	-	-	-	-	-	-	-	-	-
6 $_{5.0\%}$	0.0 ± 0.00	0.0 ± 0.00	13.79 ± 1.56	-	-	-	-	-	-	-	-	-
6 $_{7.5\%}$	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.02	0.87 ± 0.22	31.32 ± 30.20	85.40 ± 11.08	94.82 ± 4.06	94,95 ± 4.12	95.11 ± 4.04	-	-
6 $_{10.0\%}$	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.01	7.07 ± 9.96	12.88 ± 16.28	31.48 ± 28.31	72.80 ± 22.56	91.99 ± 3.97	98.97 ± 5.19	-	-
6 $_{12.5\%}$	0.03 ± 0.04	0.03 ± 0.03	0.03 ± 0.03	0.00 ± 0.00	0.00 ± 0.00	6.99 ± 9.89	15.79 ± 21.52	26.71 ± 31.34	51.64 ± 35.07	79.28 ± 6.29	-	-
6 $_{15.0\%}$	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	9.42 ± 13.32	30.42 ± 42.99	34.50 ± 46.03	47.42 ± 36.02	70.33 ± 11.37	-	-
6 $_{17.5\%}$	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.16 ± 0.22	0.52 ± 0.47	14.61 ± 14.23	66.16 ± 22.95	87.78 ± 12.10	-	-
6 $_{20.0\%}$	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00± 0.00	0.00 ± 0.00	0.11 ± 0.15	0.23 ± 0.33	0.52± 0.35	1.48 ± 0.08	2.96 ± 0.09	90.07 ± 4.13	90.17 ± 4.62

thickness. These samples were found to be unsatisfactory for following testing. Figure 2 shows the microscopic photographs of Eudragit® S coated samples 1 $_{2.5\%}$ and 1 $_{7.5\%}$ after dissolution test. The occurrence of polymer coating ruptures allowed the penetration of dissolution medium into the gelatin capsule and caused fast drug release. This coating behavior in dissolution medium is probably related to brittleness of Eudragit® film combined with insufficient adhesion of polymer coating to the gelatin capsules surface. To summarize, it was impossible to apply isopropyl alcoholic Eudragit® L and S solutions with PEG 6000 successfully onto the surface of gelatin hard capsules and to obtain a dosage form for enteric or distal ileic drug delivery this way. This problem might be partly solved by the change of capsule surface properties.

Eudragit-coated gelatin capsules with HPC intermediate layer

Application of HPC intermediate layer brought improvement in the quality of Eudragit® film layering and function. The lower Eudragit® coating amount, i.e., Eudragit® L 2.5 and 5.0% (43.85, 72.15 μm); batch 2, Table 4 and Eudragit® S 2.5% (46.05 μm); batch 5, Table 5, did not ensure necessary protection of capsules filling, as 78%, 2.3% and 75.1%, respectively, of the drug were released within 2 h. Higher coating amounts led to an achievement of required lag time of capsules in AGJ. Eudragit® film brittleness was suppressed by better adhesion onto the HPC interlayer. Samples ($2_{7.5\%}$, $2_{10.0\%}$, $5_{5.0\%}$, $5_{7.5\%}$, $5_{10.0\%}$) released no amount of caffeine within 120 minutes test in AGJ (Table 4 and 5).

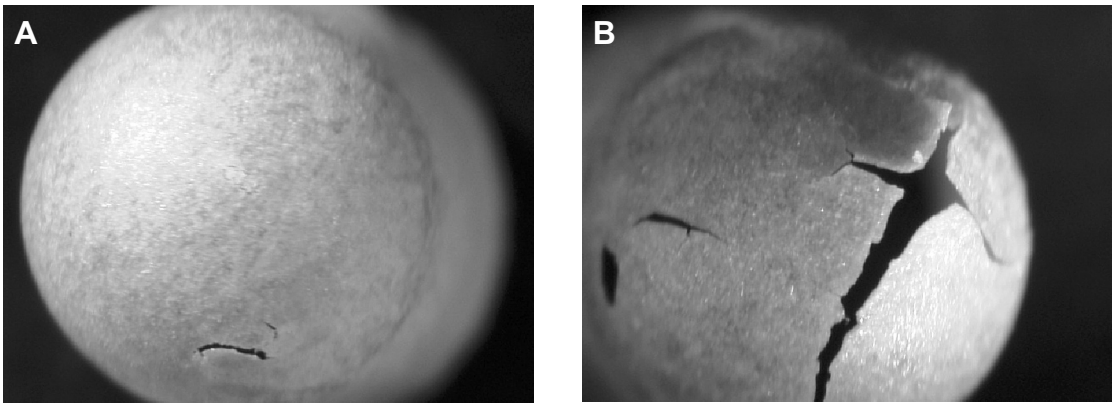

Figure 2. Rupture of Eudragit® S film of samples $\mathbf{1}_{2.5\%}$ (A) and $\mathbf{1}_{7.5\%}$ (B) after dissolution test at pH 1.2 (i. e. gelatin capsules without HPC subcoating)

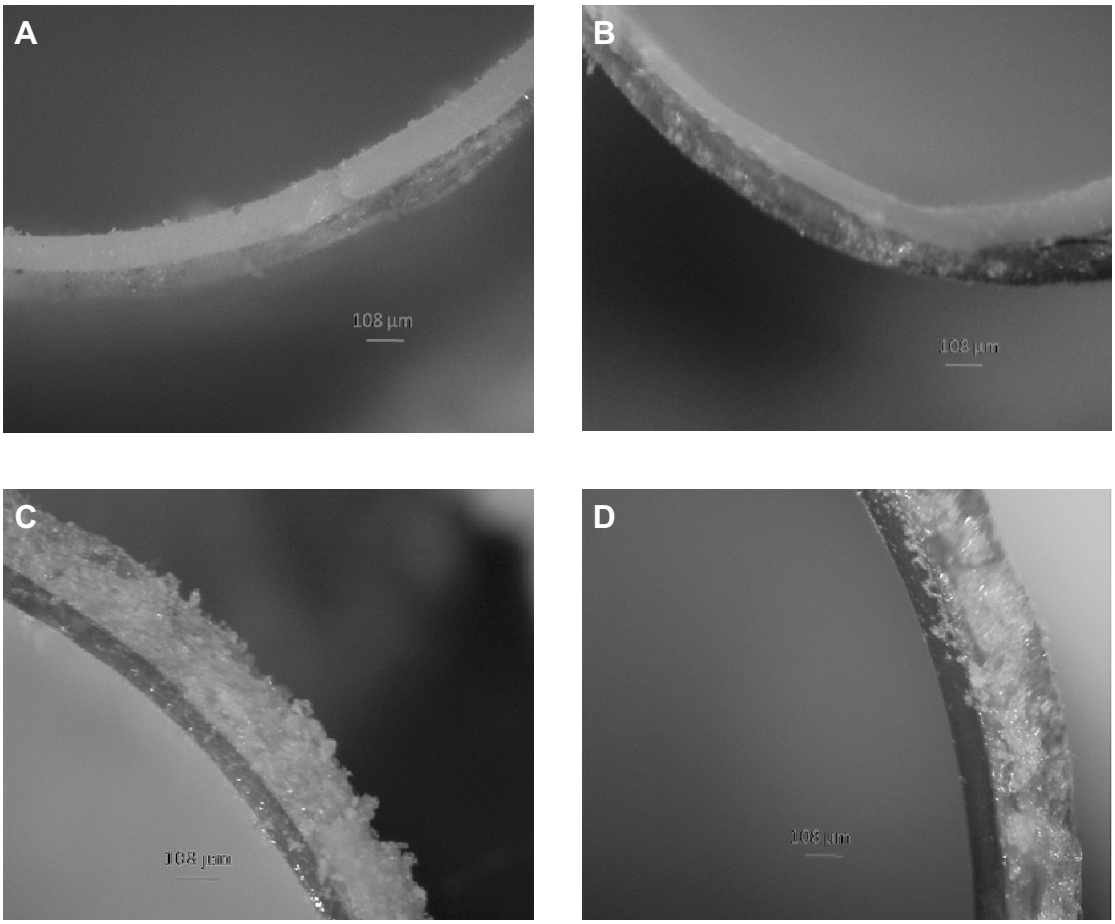

Figure 3. Selected examples of efficiently coated samples: A - 7.5% Eudragit® L coating on gelatin hard capsules with HPC interlayer, B - 10.0% Eudragit® S coating on gelatin hard capsules with HPC interlayer, C - 17.5% Eudragit® L coating on HPMC hard capsules, D - 20.0% Eudragit® S coating on HPMC hard capsules

From the results obtained (Table 4), it is obvious that samples $2_{7.5\%}$ (Fig. 3 A) and $2_{10.0\%}$ can be used for delayed drug release in small intestine. The coating quality was confirmed in dissolution medium of pH 5.5 when less than 2.3% of caffeine was released from coated capsules. Subsequently, the entire amount of incorporated drug was released in dissolution medium of pH 6.5 corresponding to proximal small intestine pH. The average coating thickness of samples $2_{7.5\%}$ and $2_{10.0\%}$ was 90.98 μm (5.02 mg/cm^2) and 117.60 μm (6.58 mg/cm^2), respectively (Table 4).

Among samples coated by Eudragit® S intended for drug delivery to distal ileum, only sample $5_{10.0\%}$ fulfilled the demanded criteria and released less than 10.0 % within 360 min in dissolution medium of pH 6.8 (Table 5). Rapid release of caffeine was determined at 30 min in dissolution medium of pH value simulating terminal ileum (pH 7.5). The average coating thickness of this sample was 115.25 μm (5.87 mg/cm^2) (Fig. 3 B).

Thus, HPC interlayer applied on hard gelatin capsules surface allowed to achieve the required lag time for enteric drug delivery in a relatively low amount of Eudragit® L film (7.5 and 10.0 %) and for drug delivery to distal ileum at a coating level of 10% of Eudragit® S. The application of HPC interlayer seems to be necessary for practical utilization of Eudragit® L and S coatings containing PEG 6000 as a plasticizer onto gelatin capsules.

Eudragit-coated HPMC capsules

The samples of wide film thickness range (2.5 to 17,5%) were obtained when HPMC capsules were coated with Eudragit® L. All samples (batch 3, Table 4) were able to protect the capsule filling in dissolution medium of pH 1.2 (i. e., no drug was released) with the exception of sample $3_{2.5\%}$ which liberated 10.06 % of caffeine within 2 h. In this sample, the coating amount was not sufficient to cover the junction zone between capsule body and cap and they separated within dissolution test. The microscopic observation of undissolved film did not confirm any coating ruptures. Coating thickness of this sample was 45.54 μm (1.70 mg/cm^2).

The quality of prepared film coatings of samples $3_{5.0\%}$ – $3_{17.5\%}$ was confirmed by dissolution test at pH 5.5. The maximum drug amount released was 8.19% (sample $3_{5.0\%}$) and minimum amount 5.15% (sample $3_{17.5\%}$). An amount released below 10% complied with demanded requirements. In proximal small intestine conditions (pH 6.5) more than 91.23% of caffeine was released within 1 h from tested samples $3_{5.0\%}$ – $3_{17.5\%}$. The caffeine released amount in 30 min decreased as the coating level increased: sample $3_{17.5\%}$ liberated 51.26 % of caffeine in 30 min and sample $3_{5.0\%}$ released 102.32 % of the drug during the same time interval. The coating thickness of these samples varied in the range from 75.82 μm (3.53 mg/cm^2) in sample $3_{5.0\%}$ to 211.35 μm (12.04 mg/cm^2) in sample $3_{17.5\%}$ (Table 4, Fig. 3 C). Thus, these samples can be used for enteric delivery of incorporated substance and ensure a complete disintegration of the coating in the proximal small intestine.

Similarly, also the samples of wide film thickness from 2.5 to 20.0% were obtained when HPMC capsules were coated with Eudragit® S. The declared solubility of this pH sensitive coating material is at pH ≤ 7, and therefore, the applied coating should completely dissolve in distal parts of the small intestine. Samples $6_{2.5\%}$ and $6_{5.0\%}$ did not protect capsules fillings in acidic medium and released 32.56% and 13.79%, respectively, within 2 h. Thus, these samples were excluded from following testing. Consequently, the other samples ($6_{7.5\%}$ – $6_{20.0\%}$) releasing almost none caffeine in AGJ were tested in dissolution medium of pH 6.8. However, only samples with the highest coating level ($6_{20.0\%}$) showed a required lag time and liberated only 2.96% of the drug at pH 6.8 (Fig. 3 D). The other samples ($6_{7.5\%}$ – $6_{17.5\%}$) released higher drug amount than required 10%. In dissolution medium of pH 6.8, Eudragit® S film did not dissolve, but capsules cup and body were separated. Early drug release was probably caused by dissolution medium penetration through the brittle film ruptures formed especially in junction zone of capsules cap and body. Water penetration became more difficult with increasing coating level, thus caffeine liberation decreased. The Eudragit® S film thickness of sample $6_{20.0\%}$ was 224.85 μm (12.89 mg/cm^2). This sample released 90.07% of caffeine in 30 min at pH 7.5 and thus good drug availability from HPMC capsules under conditions corresponded to terminal ileum was confirmed.

The problem with Eudragit® S film brittleness could be probably solved by the addition of different plasticizer.

CONCLUSION

Two types of hard capsules, gelatin and hypromellose, were coated by pH sensitive coating material – Eudragit® L and S 12,5 – with PEG 6000 as the plasticizer for enteric and distal ileic drug delivery. Hard gelatin capsules coated with 2% HPC interlayer and Eudragit® L layer (7.5 and 10.0%) and

hard hypromellose capsules coated with Eudragit® L layer (5.0 to 17.5%) were suitable for drug release in the small intestine. For drug delivery into distal ileum, hard gelatin capsules with HPC interlayer and 10.0% Eudragit® S layer and hard hypromellose capsules with 20% Eudragit® S coating showed *in vitro* capability to withstand dissolution media of pH 1.2 and 6.8 and to release the capsule content at pH 7.5 within 30 min.

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