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A Study to Assess the Gastro-Resistance and Dissolution Rate of Enteric Coated Not-Banded Gelatin and HPMC Capsules

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PURPOSE

Oral enteric dosage forms represent an approach to overcome the severe acidic environment of the stomach to release low pH sensitive drugs. Additionally, it can be used for targeted drug delivery to a specific tract of the digestive system. This aim can be achieved using coated hard-shell capsules that, at early stages of a pharmaceutical development program, are more time (and cost) efficient than enteric tablets or pellets.

Understanding the main factors and process parameters that impact the capsule's gastro-resistance and dissolution rate is key to develop a suitable coating process. In a previous work, it was achieved gastro-resistance in banded and non-banded HPMC capsules (Piccinni, 2022).

In this context, the present study aimed to assess the acid-resistance and dissolution rate of not-banded gelatin and HPMC capsules filled at two different filling weights and coated with an enteric polymer at four coating levels.

The purpose was to evaluate the minimum enteric polymer needed to achieve gastro-resistance. Assess the performance of gelatin shells versus HPMC shells in the coating process. Evaluate the impact of the capsule filling level and the curing step on the dissolution profile of the dosage form as the coating process parameters were fixed.

METHODS

Niacin was used as a highly water-soluble drug model to manufacture a blend for capsule filling at 10% (w/w) drug loading. Capsule filling machines (Zanasi E6 and Zanasi E12) were used to fill size 0 gelatin and HPMC capsules and manufacture 10 mg (low-fill weight: 100 mg) and 30 mg (high-fill weight: 300 mg) niacin capsules. The coating step was conducted with a Vector LDSC machine equipped with a 6.0 L pan (batch size ca. 2900 capsules). An aqueous Eudragit® L30 D-55 based coating suspension was prepared at 20% (w/w) solid content with talc and triethyl citrate. The target quantity of Eudragit® L30 D-55 per capsule surface area was 3.5 mg/cm^2 (very low level), 5.1 mg/cm^2 (low level), 6.6 mg/cm^2 (medium level), and 9.2 mg/cm^2 (high level).

For each target coating level, an aliquot was cured onto aluminum trays at laboratory room conditions for at least 12 hours. The remaining capsules were packed into double LDPE bags.

Following coating, the capsules were checked for appearance, and a dual stage dissolution testing was conducted (USP apparatus II, gastric stage: 120 min in HCl 0.1N; intestinal stage: 85 min pH 6.0 phosphate buffer). The amount of niacin dissolved was determined by UV spectrophotometry at 262 nm wavelength. Uncoated and coated capsules, at the lowest and highest levels, were analyzed by Scanning electron microscope (SEM) focusing on the body-cap joint.

REFERENCE

Piccinni, P. (2022). An Assessment of the Gastro-Resistance and Dissolution Rate of Banded and Not-Banded Capsules Coated with an Enteric Coating Film. AAPS 2022 Poster.

RESULTS

The batches of gelatin and HPMC capsules were coated without any issues and the product temperature during spraying was kept above the film forming temperature of Eudragit® L30 D-55. Overall, the capsule weight gain following coating was within the required range (Table 1). The coated capsules presented a smooth surface as the enteric film appeared homogeneously applied by visual assessment. SEM confirmed the presence of a uniform layer of coating material spread onto the capsule surface. Although, the body-cap gap was visible at all levels of coating, at the lowest coating level the body-cap joint was not as much filled with material as at the highest coating level (Figure 1).

The HPMC capsules showed gastro-resistance at low level of coating while, the gelatin capsules only at highest coating level. Nevertheless, all the gelatin coated capsules presented shape deformation at the body-cap joint during the gastric stage.

The release of niacin was at least 80% in pH 6.0 phosphate buffer within 60 minutes and, the dissolution rate was faster as the level of coating lowered. The capsule filling weight appeared not to impact the drug release rate. Within 15 minutes testing in phosphate buffer, only a limited number of capsules started to dissolve (Table 2).

Three different cured batches were tested for dissolution and only the 10 mg gelatin medium level coated capsules had gastro-resistance versus the not cured batch.

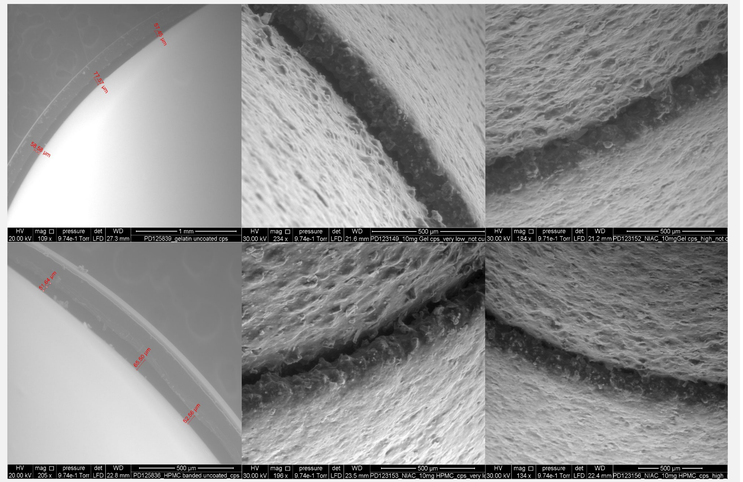

Figure 1 - SEM pictures of Gelatin uncoated capsule, coated at very low level and high level, HPMC uncoated capsule, coated at very low level and high level (from left to right and top to bottom; 10 mg capsules only)

CONCLUSIONS

The coating process parameters were selected to provide suitable capsule's movement in the rotating pan and obtain a visually homogeneous coat which was confirmed also by SEM pictures. In general, the enteric coat applied to the capsules guaranteed the closure of the cap-body junction gap depending on the material of the capsule shell. As this gap was larger on uncoated gelatin capsules, gastro-resistance was achieved only at the highest coating level. Whereas HPMC capsules showed gastro-resistance at the low coating level. Thus, gastro-resistance and full API release in pH 6.0 phosphate buffer was achieved with both gelatin and HPMC capsules.

The curing step as well as the capsule filling weight appeared not to have any relevant impacts on the gastro-resistance of the capsules and dissolution rate of API. More information should be generated to evaluate the stability and the impact of a banding step on the drug product.

	10 mg HPMC Capsules			30 mg HPMC Capsules			10 mg Gelatin Capsules			10 mg Gelatin Capsules		
Coating phase	**Warming**	**Spraying**	**Drying**	**Warming**	**Spraying**	**Drying**	**Warming**	**Spraying**	**Drying**	**Warming**	**Spraying**	**Drying**
Inlet air temp. (°C)	35.2 – 40.0	40.0 – 56.7	39.6 – 42.2	35.0 – 40.0	40.0 – 52.7	35.9 – 49.6	35.0 – 39.8	38.0 – 52.6	34.9 – 52.1	36.4 – 44.9	47.9 – 56.2	35.9 – 49.6
Exhaust air temp. (°C)	23.6 – 30.9	30.9 – 35.2	25.8 – 35.0	24.4 – 32.1	31.3 – 33.9	27.1 – 33.9	25.1 – 33.9	29.7 – 34.0	26.6 – 33.1	25.4 – 32.9	30.5 – 33.6	27.1 – 33.9
Product bed temp. (°C)	23.6 – 31.7	29.5 – 35.0	25.8 – 35.0	24.4 – 33.3	30.7 – 34.9	28.3 – 34.9	26.1 – 34.7	29.5 – 33.1	28.6 – 34.9	24.7 – 33.4	31.1 – 34.3	28.3 – 34.9
Inlet air volume (CFM)	55 ± 10	55 ± 10	55 ± 10	55 ± 10	55 ± 10	55 ± 10	55 ± 10	55 ± 10	55 ± 10	55 ± 10	55 ± 10	55 ± 10
Pan Speed (rpm)	5*	18	5*	5*	18	5*	5*	18	5*	5*	18	5*
Phase duration (min)	5	100	9	9	127	5	15	114	5	11	112	5
Atomizing pres. (psi)	--	13	--	--	14	--	--	14	--	--	14	--
Fan width pressure (bar)	--	0.4	--	--	0.5	--	--	0.4	--	--	0.4	--
Nozzle size (mm)	--	1.0	--	--	1.0	--	--	1.0	--	--	1.0	--
Spray rate (g/min) / time (min)	--	6.0 / 5 13.8 / 57 14.5 / 9 15.2 / 29	--	--	6.0 / 5 12.1 / 31 14.9 / 45 16.0 / 46	--	--	6.0 / 12 12.8 / 25 13.2 / 25 13.7 / 10 14.5 / 42	--	--	6.0 / 6 12.0 / 23 13.0 / 23 13.8 / 25 16.0 / 37	--
Solid content added to the capsule												
	Not cured		**Cured**	**Not cured**		**Cured**	**Not cured**		**Cured**	**Not cured**		**Cured**
Very low level 28.0 mg (25.2 mg – 30.8 mg)	26.8**		31.9	28.7**		29.5	29.6**		29.0	28.8**		30.2
Low level 40.7 mg (36.6 mg – 44.8 mg)	49.9**		49.7	40.7**		41.6	40.2**		41.4	42.0**		41.4
Medium level 57.0 mg (52.0 mg – 62.0 mg)	59.4**		58.1	56.5**		57.9	57.0**		56.2	58.4**		59.7
High level 73.3 mg (68.3 mg – 78.3 mg)	73.3**		73.0	73.7**		74.7	73.4**		72.9	74.0**		73.3

**pulse mode; **not dried capsules;*

Table 1 - Coating process parameters and capsule's weight gains.

	Gastric stage	Intestinal stage					
Sampling time (min)	**T120 (RSD%)**	**T15 (RSD%)**	**T30 (RSD%)**	**T45 (RSD%)**	**T60 (RSD%)**	**T75 (RSD%)**	**T85 (RSD%)**
10 mg HPMC Capsules							
Very low level not cured	9.3 (84.8)	46.3 (66.6)	85.0 (24.3)	93.3 (16.3)	97.8 (9.6)	100.7 (4.6)	104.5 (4.3)
Very low level cured	6.4 (183.0)	69.2 (33.2)	95.7 (7.3)	100.7 (3.5)	101.5 (3.3)	101.8 (3.4)	102.0 (3.6)
Low level not cured	0.0 (0.0)	20.7 (79.7)	47.8 (61.3)	68.8 (39.8)	87.3 (17.8)	97.0 (9.2)	104.8 (1.9)
Medium level not cured	0.0 (0.0)	13.0 (244.9)	35.2 (99.2)	69.5 (39.3)	87.3 (20.4)	96.0 (11.1)	103.2 (3.5)
High level not cured	0.0 (0.0)	0.0 (0.0)	26.0 (123.9)	63.2 (39.7)	83.8 (19.3)	93.5 (9.8)	102.3 (2.9)
30 mg HPMC Capsules							
Very low level not cured	12.8 (90.1)	49.3 (23.7)	78.8 (18.9)	89.8 (13.3)	93.8 (8.5)	91.7 (5.9)	94.8 (1.2)
Low level not cured	0.0 (0.0)	30.5 (72.1)	69.8 (36.3)	81.7 (25.0)	82.0 (18.4)	90.5 (8.2)	96.3 (3.1)
Medium level not cured	0.0 (0.0)	0.0 (0.0)	25.5 (90.7)	68.3 (24.6)	86.3 (12.1)	94.0 (7.2)	98.8 (1.7)
10 mg Gelatin Capsules							
Very low level not cured	38.5 (63.7)	58.2 (47.9)	78.7 (30.2)	87.0 (32.4)	102.5 (9.8)	107.3 (4.9)	111.8 (2.1)
Low level not cured	8.5 (142.1)	48.2 (60.7)	94.5 (13.1)	105.3 (6.1)	108.8 (3.6)	109.7 (3.1)	110.8 (2.6)
Medium level not cured	3.7 (244.9)	15.0 (110.1)	36.7 (110.6)	84.2 (26.7)	108.8 (25.5)	105.2 (4.3)	108.2 (1.6)
Medium level cured	0.0 (0.0)	5.5 (244.9)	50.8 (54.7)	88.7 (15.3)	98.0 (8.9)	102.0 (5.8)	107.0 (1.6)
High level not cured	0.0 (0.0)	14.2 (169.7)	32.3 (154.9)	65.7 (64.5)	102.2 (10.5)	107.8 (3.9)	109.7 (2.2)
30 mg Gelatin Capsules							
Medium level not cured	4.3 (178.0)	28.3 (64.4)	76.8 (21.7)	96.5 (4.4)	100.5 (2.2)	101.0 (1.9)	101.0 (2.3)
Medium level cured	15.2 (135.5)	23.8 (103.1)	62.2 (53.3)	94.3 (5.9)	99.2 (3.5)	100.2 (3.2)	100.3 (3.3)
High level not cured	0.0 (0.0)	2.2 (244.9)	30.5 (96.3)	85.0 (13.1)	96.7 (4.8)	99.7 (2.4)	100.7 (0.5)

Table 2 - Dissolution data