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RESEARCH PAPER

Process and Formulation Variables Affecting the Performance of a Rupturable Capsule-Based Drug Delivery System with Pulsatile Drug Release

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ABSTRACT

The objective of this study was to optimize several process and formulation parameters, which influence the performance of a rupturable, pulsatile drug delivery system. The system consisted of a drug-containing hard gelatin capsule, a swelling layer of croscarmellose (Ac-Di-Sol®) and a binder, and an outer ethylcellulose coating. Polyvinyl pyrrolidone (Kollidon 90F) was superior to HPMC and HPC as a binder for the swelling layer with regard to binding (adherence to capsule) and disintegration properties of the swelling layer. The capsule-to-capsule uniformity in the amount of swelling layer and outer ethylcellulose coating, which significantly affected the lag time prior to rupture of the capsule, was optimized by decreasing the batch size, and by increasing the rotational pan speed and the distance between the spray nozzle and the product bed. The type of baffles used in the coating pan also affected the layering uniformity. Fully-filled hard gelatin capsules had a shorter lag time with a higher reproducibility compared to only half-filled capsules, because the swelling pressure was directed primarily to the outer ethylcellulose coating and not to the inner capsule core. Stability studies revealed that the lag time of the capsules was stable over a 240-day period when the moisture content was kept unchanged.

Key Words: Ac-di-Sol; Capsules; Coating; Ethylcellulose; Pulsatile drug delivery; Swelling agents.

INTRODUCTION

Pulsatile drug delivery systems, which release the drug rapidly and completely after a lag time, have gained increasing interest during recent years for a number of diseases and therapies.[1–3] Different types of pulsatile systems have been developed, including eroding[4–6] and rupturable systems.[7] Rupturable

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systems usually consist of a drug-containing core, an optional swelling layer, and an external water-insoluble, but water -permeable polymer coating. In gastro intestinal or dissolution fluids, water penetrates the outer coating and the core and/or the optional swelling layer expand until the outer polymer coating ruptures. Subsequently, the drug is released rapidly. Pellets, tablets, and capsules have been used as cores for such rupturable systems.[8–15]

Drug release from most rupturable systems depends on the core and therefore on the drug used (e.g., dose and solubility). Multilayered, hard gelatin capsules were investigated in this study because their release profile is more independent of the type of capsule filling. Powders, pellets, semisolids, and oily liquids can be used inside capsules.[16] The system evaluated consisted of 1) a drug-containing hard gelatin capsule, 2) a swelling layer with highly swellable substances, e.g., croscarmellose (Ac-Di-Sol®), and 3) an insoluble, but water-permeable outer polymer coating, e.g., ethylcellulose (EC).[17]

With a single-unit pulsatile system, such as the investigated capsules, a high unit-to-unit reproducibility in the drug release profile is essential. High variations in the release profile have been described in the literature.[18] The objective of this study was to identify process parameters that influence the release performance of the system in order to obtain good reproducibility.

MATERIALS AND METHODS

Hard gelatin capsules [size #3, filled with 180 mg (full capsules) or 90 mg (half-filled capsules) and size #0, filled with 386 mg (full capsules) of a mixture of microcrystalline cellulose (Avicel PH 102, FMC Corp., Newark, DE) and lactose monohydrate (Tabletose 80, Meggle, Wasserburg, Germany) in a ratio of 25:75 w/w, containing 0.3% Aerosil 200 (Degussa, Frankfurt/Main, Germany) and 0.5% magnesium stearate (Herwe, Sinsheim-Dühren, Germany), croscarmellose sodium (Ac-Di-Sol, FMC Corp., Newark, DE), polyvinyl pyrrolidone (PVP) (Kollidon® 30, Kollidon® 90F, BASF, Ludwigshafen, Germany), ethylcellulose (EC), (Ethocel® Standard 10, Dow Chemical Company, Midland, MI), hydroxypropyl cellulose (HPC), (Klucel® E and M, Hercules Ltd. Pendlebury, UK), hydroxypropyl methylcellulose (HPMC), (Methocel® E5, E15, and E50, Colorcon, Orpington, UK), dibutyl sebacate (DBS), and triethyl citrate (TEC) (Morflex, Greensboro, NC).

Preparation and Disintegration of Swelling Layer Films

The binder (PVP or HPC) was dissolved in ethanol under stirring. Hydroxyropyl methylcellulose, which is not soluble in pure ethanol, was first dispersed in ethanol. Water was then added under continuous stirring to obtain a clear solution. The swelling agent, Ac-Di-Sol, was dispersed in this binder solution. The homogeneous suspension was cast on a Teflon-covered petri dish to achieve a film thickness of approximately 300 μm after evaporation of the solvent (12 h at room temperature). The films were additionally dried in a desiccator for 12 h and cut in to small pieces (2×2 cm^2). The disintegration time of the films was determined in 0.1 N hydrochloric acid (HCl) at 37° C in a horizontal shaker (GFL 3033, Gesellschaft für Labortechnik, Burgwedel, Germany) at 75 rpm.

Sedimentation Studies

The suspension used to prepare the swelling layer was pumped through a transparent silicone tube (inner diameter 3 mm, length 70 cm) with a peristaltic pump at a rate of 15 g/min. Potential sedimentation in the tube was observed visually.

Coating of Hard Gelatin Capsules

Pulsatile capsules were prepared by layering a 12% w/w suspension of Ac-Di-Sol in a 4% w/w solution of Kollidon 90 in isopropanol (swelling layer) onto the hard gelatin capsules in a GC-300 Glatt pan coater (prewarming at 40° C, 10 min; spray nozzle diameter 1.2 mm; atomizing air pressure 0.8 bar; air flow rate 110 m^3/h; inlet air temperature 40° C; product temperature 30° C; spray rate 15 g/min; post coating drying at 35° C for 10 min; and post coating drying at 35° C for 10 min).

In a second step, the outer polymer coating was applied by spraying of a 4% w/w ethylcellulose (EC) solution in 96% vol. ethanol with dibutyl sebacate (DBS), (5% w/w based on EC). The EC/DBS solutions were applied in the GC-300 Glatt pan coater using standard and Fischer baffles under the conditions described above.

The actual coating level during the coating process was monitored because of polymer loss during the layering and coating process. Capsules were removed during the coating process after spraying a predetermined amount of layering suspension/coating

solution. The weight of 20 capsules was determined immediately, after drying at 40° C for 3 h, and after drying at 105° C for 3 h. The weight of uncoated capsules was determined in the same way. The actual weight gain of the coated capsules was determined by the difference between the mean weight of the coated and uncoated capsules.

Weight Uniformity of the Coating Layers

Various coating process parameters were investigated to achieve the best uniformity in weight gain during the layering of the capsules with the swelling layer. Coating was performed in a pan coater Glatt GC 300. Uncoated capsules (n=100) were weighed before and after layering with Ac-Di-Sol.

Determination of the Lag Time

The lag time of the pulsatile capsules (n=5) was determined by visual observation in a USP XXV paddle apparatus (medium: 0.1 N HCl, 37° C, rotation speed 50 rpm; VK 300, VanKel, Industries Inc., Edison, NJ). The lag time was defined as the time point when the outer polymer coating ruptured.

Stability Studies

Coated capsules were stored in open or tightly closed glass flasks in a climate chamber (Weiss Umwelttechnik GmbH, Lindenstruth, Germany) under the following conditions: room temperature (RT)—closed; RT—open; RT—desiccator; 4° C—closed; 40°C/75% relative humudity (RH)—closed.

RESULTS AND DISCUSSION

The investigated pulsatile drug delivery system consists of a drug-containing capsule as the core, an intermediate swelling layer, and an outer polymeric coating. The swelling layer was formed from an alcoholic suspension of the swelling agent, Ac-Di-Sol. A suitable binder had to be identified, which resulted in good adherence and binding of the insoluble swelling agent to the capsule surface and in an Ac-Di-Sol suspension, which did not show sedimentation during the time of the layering process. In addition, the binder did not inhibit the swelling properties of Ac-Di-Sol. Water-soluble polymers, such as PVP (Kollidon 30 and 90F), hydroxypropyl methylcellulose (Methocel E15 and E50), and hydroxypropyl cellulose (Klucel E and M) are commonly used as binders in pharmaceutical dosage forms. A screening method was developed to evaluate the different binder candidates (Table 1). Film samples containing Ac-Di-Sol and the binder were prepared by casting and drying the suspension and were evaluated with regard to their binding properties, disintegration time in 0.1 N HCl, and sedimentation. A short disintegration time would be advantageous for the use in the pulsatile Drug Delivery Systems (DDS), because it would ensure a fast drug release from the capsule after the lag time. For the sedimentation test, an alcoholic binder solution with suspended Ac-Di-Sol was pumped through a transparent plastic tube at a constant

Table 1. Evaluation of different binders for the swelling layer.

Binder	Conc., % w/v	Solvent	Ac-Di-Sol/binder ratio	Film properties: Binding	Film properties: Disintegration time, min	Sedimentation in tube
Kollidon 30	6	ethanol	4/1	good	2–3	yes
Kollidon 90F	3	ethanol	5/1	good	2–3	no
	3		6/1	good	2–3	no
	3		7/1	good	2–3	no
HPMC E 50	2.5	ethanol/water	6/1	poor	>20	no
HPMC E15	2.5	90/10	8/1	poor	>20	no
	3		5/1	poor	2–3	yes
HPC-E	7.5	ethanol	5/1	poor	2–3	yes
HPC-M	2		5/1	good	10–15	no
HPC E/M 8/2	3		5/1	good	8–12	no

rate (15 g/min, same as in the coating process). The binder should increase the viscosity of the coating suspension sufficiently to eliminate sedimentation, which otherwise could cause difficulties in the coating process (e.g., nozzle clogging, uneven spraying of the swelling agent). An alcoholic suspension of Ac-Di-Sol was preferred to an aqueous suspension because of the lack of swelling of Ac-Di-Sol in alcohol when compared to water.

Among the binders investigated, PVP (Kollidon 30 and 90F) was most suitable. It resulted in good binding properties, a short disintegration time, and no sedimentation. The higher molecular weight Kollidon 90F was selected for further experiments because a lower concentration was necessary to achieve the desired solution viscosity when compared to the lower molecular weight Kollidon 30. The amount of Kollidon 90F in the swelling layer was therefore lower. Both HPMC grades resulted in poor binding properties, which was indicated by highly brittle films, and also longer disintegration times. The HPC grades had intermediate properties but were inferior to PVP.

The rupture of the outer polymer coating layer will be determined primarily by the thickness of the swelling layer and the thickness of the coating layer. It was therefore important to correlate the amount of the Ac-Di-Sol layering suspension or of the ethylcellulose coating solution sprayed with the actual amount coated onto the capsules. Ideally, this should be done as an in-process control. Capsules were therefore taken from the capsule bed during the layering or coating process and analyzed for weight

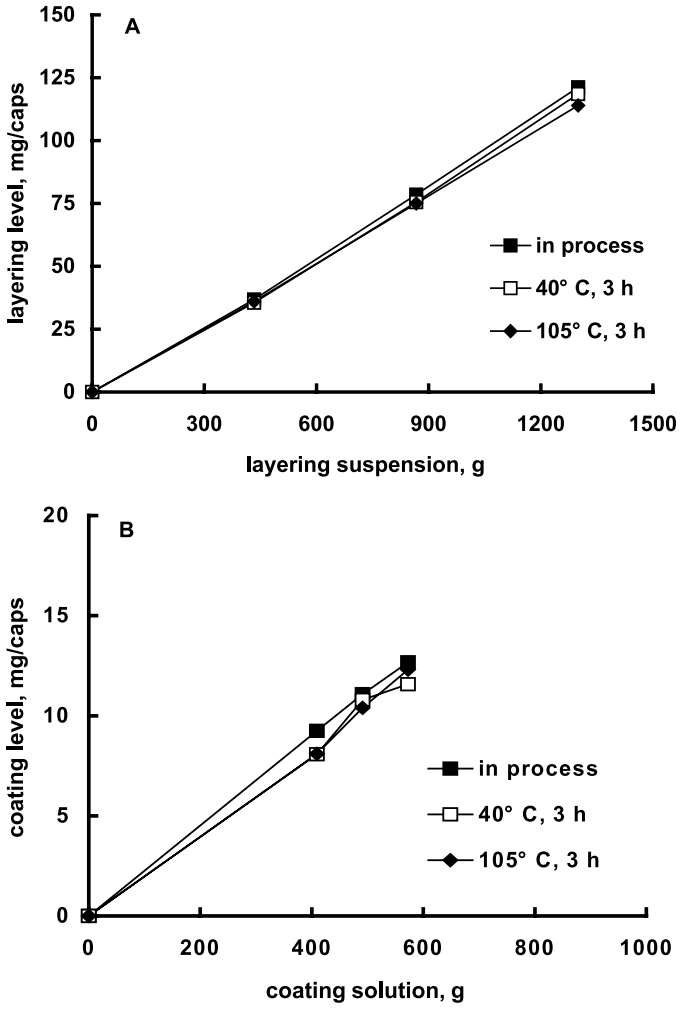

Figure 1. Actual weight gain (mg/capsule) of (A) the swelling layer as a function of the amount of sprayed Ac-Di-Sol suspension (layering suspension) and (B) the outer ethylcellulose coating as a function of the amount of sprayed ethylcellulose solution (coating solution). The weight of 20 capsules was determined for each data point.

Table 2. Optimization of the Ac-Di-Sol layering process parameters of gelatin capsules size #3 in a pan coater Glatt GC 300 (standard baffles).

Batch size, l	1.0		1.5			
Pan rotation, rpm	24	30	15	24		
Distance nozzle-bed, cm	11	11	8		11	Uncoated capsules size #3
Average weight, mg	172.0	173.0	173.5	175.1	171.6	136.3
SD, mg	3.4	2.6	6.3	4.9	4.3	1.4
C.V., %	2.0	1.5	3.6	2.8	2.5	1.0
Max, mg	178.9	180.4	189.5	188.5	182.2	139.7
Min, mg	162.4	167.1	155.7	165.3	160.4	133.1
Range, mg	16.5	13.3	33.8	23.2	21.8	6.6

gain immediately after sampling or after drying for 3 h at 40° C or 105° C. A good linear relation between the amount of layering suspension or coating solution and the actual layering or coating level was obtained for all three weight determinations (Figure 1A and B). The weight of the oven-dried samples was very similar to the weight of the in-process weighed capsules for the layering process and slightly lower for the coating process of the ethylcellulose coating (this coating layer had a smaller weight gain, and residual moisture in the original capsules therefore had a stronger influence on the weight when compared to the layered capsules). The desired layering or coating level could therefore be predicted from the amount of liquid sprayed. This method was used for the monitoring of the weight gain during the layering/coating to reach the desired layering/coating level.

During preliminary studies, variations in the lag time (time to rupture of the capsules in aqueous fluids) were observed from capsule to capsule of the same batch, and these variations in lag time were caused by variations in the weight gain of the swelling or polymer coating layer. In order to obtain reproducible lag times with a narrow standard deviation, it was important to obtain a uniform layering of the swelling layer followed by a uniform ethylcellulose coating layer. The influence of the process parameters—batch size, pan rotation speed, and the distance between the spray nozzle and the product bed—on the uniformity in weight gain of the swelling layer was investigated (Table 2).

The weight variability (as indicated by the coefficient of variation and the range in capsule weight) was reduced with an increasing distance between the nozzle and the capsule bed (Table 2). This was attributed to a wider distribution of the spray droplets over the product bed at a larger distance, and more capsules were therefore hit by the droplets at the same time. Increasing the pan rotation from 15 to 30 rpm also reduced the variation. Increasing the rotation speed increased the number of passages of the capsules through the spraying zone, and the amount sprayed was

Table 3. Effect of baffle type on the layering uniformity of hard gelatin capsules size #0 in a pan coater Glatt GC 300.

	Standard baffles			Fischer baffles		
Pan rotation, rpm	30			30		
Distance nozzle-bed, cm	11			11		
Batch size, l	1	1.5	2	1.5	2	Uncoated capsules size #0
Average weight, mg	542.3	542.5	544.8	545.5	544.1	475.4
SD, mg	3.8	5.1	5.4	14.3	12.8	2.8
C.V., %	0.7	0.9	1.0	2.6	2.3	0.6
Max, mg	552.2	554.8	556.5	585.0	581.7	483.5
Min, mg	533.0	526.9	526.3	514.4	512.5	468.8
Range, mg	19.2	27.9	30.2	67.3	72.5	14.7

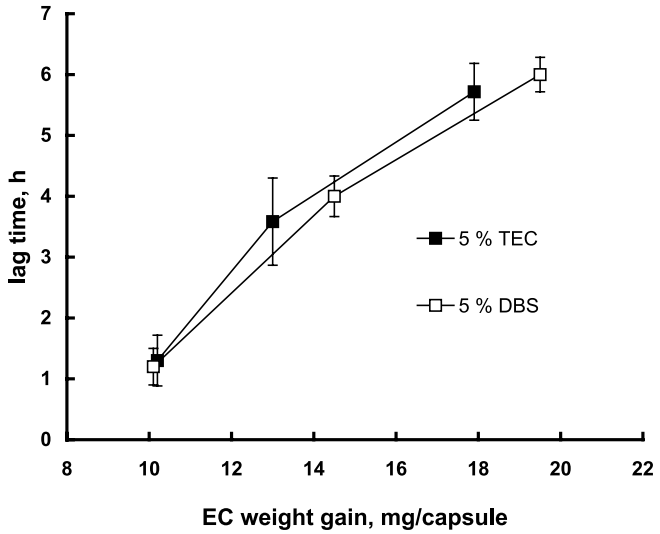

Figure 2. Lag time as a function of the ethylcellulose coating level and of type of plasticizer (n=5).

therefore distributed more uniformly onto the capsules. The highest possible pan speed to still obtain a waterfall like movement of the capsules was 30 rpm. At higher speeds, a circle-like movement occurred, which was undesirable.

The proposed loading volume for the lab scale coater Glatt GPCG 300 is 2 liter. Overloading usually leads to a reduced coating homogeneity because proportionally fewer capsules are hit by the coating droplets. Underloading the pan led to an increased loss of the coating droplets to the pan wall, which was not fully covered by the capsules. The volume increase from uncoated to layered capsules caused by the application of the Ac-Di-Sol layering suspension was up to 50% in the case of a 120 mg weight gain of the swelling layer/capsule. The coating pan was therefore not fully loaded. A further decrease in the batch size from 1.5 L to 1.0 L improved the weight uniformity of the capsules. The reason was the same as above. Proportionally, a larger number of capsules was hit by the droplets.

The type of baffles in the coating drum also affected layering uniformity (Table 3). Fischer baffles, which are higher than the standard baffles, were not fully covered by the capsule bed and resulted in a higher variability than the standard baffles.

In conclusion, all relevant process parameters that contribute to the overall coating uniformity, including batch size, rotational batch size, and nozzle-to-product bed distance, had to be optimized. The key to good weight uniformity of the capsules was a large number of passages of the capsules through the spray cone at a fixed amount of spray liquid.

Next, the lag time prior to the rupture of the pulsatile capsules was determined as a function of the ethylcellulose (EC) coating level with two different plasticizers (Figure 2). The lag time increased with increasing EC level because of the reduced water

Table 4. Lag time of pulsatile capsules as a function of the amount of Ac-Di-Sol (swelling layer) and filling state of the capsules (coating: ethylcellulose, 5% DBS, 12 mg/capsule).

	Ac-Di-Sol weight gain, mg/capsule		
	60	90	120
Capsule #	Lag time, h:min		
Fully filled capsules			
1	3:00	01:58	01:30
2	>6 h	03:40	01.57
3	>6 h	02:30	02:20
4	>6 h	00:30	01:43
5	>6 h	>6 h	02:35
Mean, h:min	n.c.	02:09	02:01
SD, h:min	n.c.	01:08	00:23
Half-filled capsules			
1		03:01	03:30
2		>6 h	01:30
3		>6 h	>6 h
4		>6 h	>6 h
5		>6 h	>6 h
Mean, h:min		n.c.	n.c.
SD, h:min		n.c.	n.c.

n.c.: not calculated.

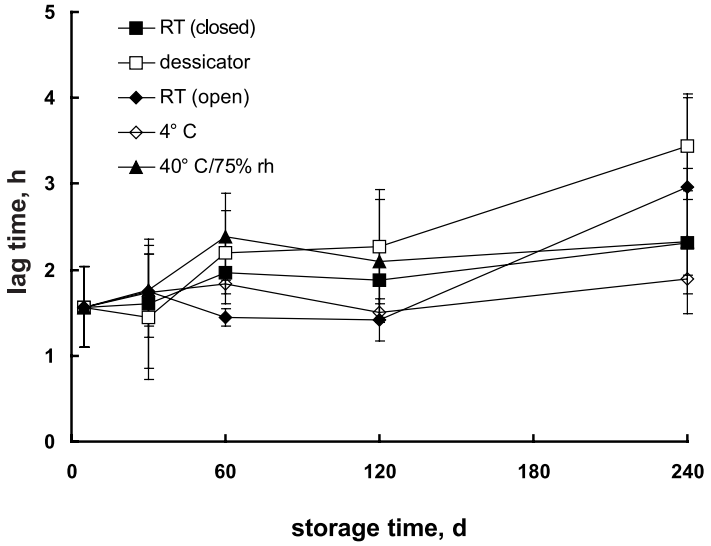

Figure 3. Lag time after storage of the capsules at different conditions in open or closed containers (n=5).

permeability and an increased mechanical resistance of the EC coating.[19] No significant differences were found between triethyl citrate (TEC), a hydrophilic plasticizer, and dibutyl sebacate (DBS), a lipophilic plasticizer, because the mechanical properties of ethylcellulose films are not strongly affected by the type of plasticizer,[20] and the differences in water permeability were apparently also not affected by the small amount (only 5%) of plasticizer added. The variability in lag time was low, indicating good control of the lag time by the choice of the coating level and process conditions.

The rupturing of the outer ethylcellulose coating was caused by the swelling of the Ac-Di-Sol swelling layer. The swelling pressure developed by the swelling layer, however, is not only directed to the outer ethylcellulose coating but also towards the inner hard gelatin capsule shell. The resistance, which this shell provides, strongly depends on the filling state of the capsule. Therefore, the effect of two different filling states of the capsules on the lag time was investigated at three different Ac-Di-Sol layering levels (Table 4). The hard gelatin capsules were either completely filled (fully filled capsules) or half-filled. The lag time was

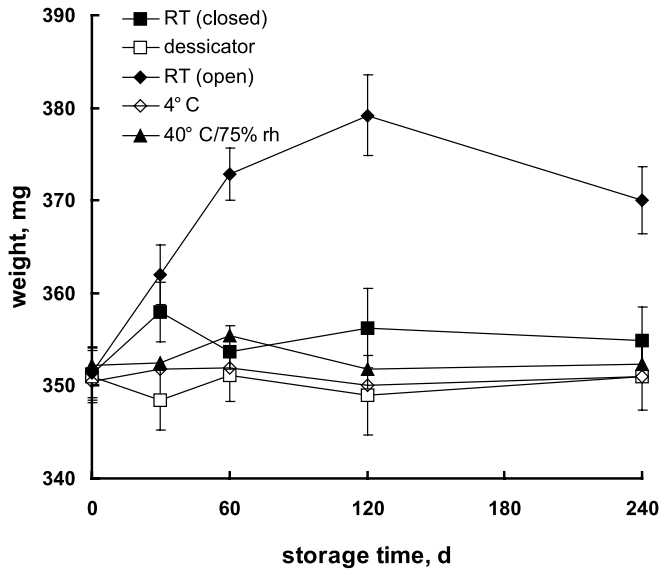

Figure 4. Weight of the capsules after storage at different conditions in open or closed containers (n=6).

significantly higher with the half-filled capsules (mostly in excess of 6 h when compared to 2 h for the fully filled capsules). This was attributed to the lower mechanical resistance of the capsule core against the rising pressure exerted by the swelling Ac-Di-Sol-layer. When the rupturable dosage form contained a core of higher resistance, as in the case of fully filled capsules, the swelling pressure was directed more towards the outer EC coating and the system ruptured earlier. The reproducibility in the lag time was higher with fully filled capsules in comparison to half-filled capsules.

The rupturing of pulsatile capsules was triggered by penetrating water and could therefore potentially be dependent on storage conditions (e.g., moisture). Stability studies on the lag time of the capsules were therefore performed. The capsules were stored at different storage conditions in order to see the effect of temperature, humidity, and time on lag time (Figure 3). The lag times of capsules stored in closed containers at room temperature, at 4° C or at 40° C/75% r.h. did not change over the entire test period of 240 days. The lag times changed when the capsules were stored in open containers at room temperature or in a desiccator. In parallel, the weight of the capsules was followed with storage time (Figure 4). As expected, the weight did not change significantly when the capsules were stored in closed containers. A weight increase was observed with open storage, indicating a moisture uptake of the capsules.

These results indicated that the dosage form was sensitive to moisture changes (open storage or desiccator storage). Therefore, a tight packaging with adequate moisture protection is recommended.

In conclusion, process and formulation parameters have to be optimized in order to obtain the desired lag times prior to rupture of the pulsatile capsules and a good capsule-to-capsule reproducibility.

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