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Evaluation of recent advances in continuous film coating processes

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Abstract

Background: Continuous film coating processes are recognized for their high production rates but have had slow acceptance for pharmaceutical production because of perceived high product losses during start-up and shut-down. In this article, the recent improvements in continuous coater designs were evaluated with respect to coating uniformity and reduction in product losses. Two separate studies represent trials conducted in newly redesigned continuous coating pans from two different coating pan manufacturers. *Method:* Multivitamin tablets were coated with Opadry® II, high performance film coating system, in both batch and continuous modes in the continuous coater. Tablet samples collected throughout all phases of the process were tested for color development and uniformity. Soft gelatin capsules were coated with a delayed release coating formulation, Nutrateric®, nutritional enteric coating system. Samples of the soft gelatin capsules were taken throughout the process and tested for resistance to simulated gastric fluid as a measure of coating uniformity and delayed release functionality performance. *Conclusions:* The results from both the immediate release and delayed release case studies support the assertion that continuous coating processes are capable of applying aqueous film coatings with significant improvements in coating uniformity and reduction in product loss.

Key words: *Continuous coating; dietary supplements; enteric coating; film coating; multivitamins; soft gelatin capsules; softgels*

Introduction

In recent years, advances in the formulation of aqueous film coating systems have resulted in significant improvements in coating process times and film coated tablet characteristics. Polymers such as polyvinyl alcohol (PVA) have been developed into fully formulated coating systems that offer significantly reduced viscosity and additional benefits such as improved moisture protection over more traditional coating systems[1]. A substantial benefit of these low-viscosity formulations is the ability to be applied as high as 25% weight per weight (w/w) solids in an aqueous dispersion, thus reducing the overall coating time[2]. Other benefits resulting from low-viscosity film coating systems may include efficient droplet atomization, smoother coated tablet surfaces, and less process related issues such as nozzle blockages. To realize the full advantages of these low-viscosity coating formulations, the limitations of traditional batch-oriented coating pans have to be addressed.

Traditionally, aqueous film coating is conducted in either fully or partially perforated, batch-type coating pans. As the solid concentration of the coating material increases, the time to deliver the desired quantity of coating decreases. Consequently, the overall time that the tablets will have to uniformly be presented to the spray zone will be reduced. Although process parameters such as pan speed rotation, spray distribution, and spray rates can be optimized to minimize variability in coating uniformity, there are still limitations on how fast the coating can be applied and still achieve adequate exposure of all the tablets in the pan to the coating material[3–5]. As the scale of the coating processes increases, the diameter of the coating pan increases along with the depth of the tablet bed and the number of tablets that are isolated from the spray zone at any

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given time. This is a fixed constraint associated with batch coating processes. Contrary to batch coaters, continuous coating machines have pan diameters that are half, or less, the diameter of manufacturing scale batch coaters, but the length of the pan can be as long as 15 ft. The resultant tablet bed depth, however, is more consistent with laboratory or pilot scale batch coating pans. The elongated spray zone and shallow bed depth ensure that the tablets are presented with high frequency to the spray zone. It has been proposed that this continuous coater pan configuration results in the faster development of coating uniformity, reduced process times, and shorter exposure of the tablets to the adverse thermal and mechanical stresses of the coating process[6].

Continuous film coating processes have been available for many years but have not gained wide acceptance for pharmaceutical products because of potential product losses during start-up and shut-down. In earlier versions of continuous coating pans, the initial discharge of products upon start-up and the final load of tablets in the pan upon shut-down were not typically coated to a uniform level, thus prompting rework or even discarding of the partially coated products. A review of continuous coating technology indicates that little published data exist to support the claims of improved coating uniformity and reduction in defects associated with the mechanical stresses tied to manufacturing scale batch coaters[7]. Recent innovations in the design of continuous coating machines indicate reduction in product loss during start-up and shut-down through the addition of tablets/capsules control mechanisms that ensure uniform and consistent coating for all tablets/capsules from the start to the finish of the process[8]. In this article, two case studies were carried out to investigate the continuous coater designs with respect to improvements in coating uniformity and reduction in potential product losses. The studies represent trials conducted in newly redesigned continuous coating pans from two different coating pan manufacturers. The case studies include an immediate release film coating application on tablets as well as a delayed release application on soft gelatin capsules.

Case study 1: Immediate release multivitamin tablets

Methods

Materials

The substrates used for the coating trials were calcium + vitamin D tablets (1500 mg total tablet weight) purchased from Eagle Nutritionals (Carlstadt, NJ, USA). The coating system used in the study was a PVA-based Opadry II (85F-Orange) formulation from Colorcon, Inc. (West Point, PA, USA). This is a fully formulated dry blend system for the aqueous film coating of pharmaceutical and nutritional oral solid dosage forms. Opadry II is a water-soluble, pH-independent, immediate release film coating system. This particular coating formulation was chosen for the study because of its low viscosity. It was dispersed in water at 20% solid concentration for the trials. To aid in the assessment of color uniformity, the orange color was chosen for its moderate hiding power[9].

Coating equipment

Two coating trials were conducted using an O'Hara Model HVCC-3015 continuous coating machine (Richmond Hills, ON, Canada). The fully perforated coating pan was 30 in. (76.2 cm) in diameter and 15 ft (457.2 cm) in length (Figure 1). The machine was equipped with 28 Schlick Model S37 ABC spray guns (Untersiemau, Coburg, Germany). The spray guns were mounted on two separate manifolds, one entering from the loading side of the pan and one entering from the discharge side of the pan with both manifolds meeting in the middle. This arrangement provided for uniform spacing of the spray guns across the length of the pan and minimized the space needed for removal of the manifold for calibration, cleaning, and inspection. The two manifolds were each fed by individual Waukesha Lobe pumps (Delavan, WI, USA) and were equipped with a suspension recirculation loop. The suspension flow to the 28 individual spray guns was divided into eight separate, independently controllable zones. The number of spray guns per zone varied depending on their location in the pan. The order of zones from the front (in-feed) side of the pan and number of spray guns in each zone were as follows: Zone 1a, one gun; Zones 1 and 2, four guns; Zones 3 and 4, five guns; Zones 5 and 6, four guns; and Zone 6a, one gun. With this arrangement, spray guns at different locations in the pan could be turned on and off throughout the process as required. The continuous coating pan was also equipped with a pneumatically controlled weir plate at the discharge end of the unit that, in a lowered position, contained all tablets within the pan or when raised and controlled the flow of tablets into the discharge zone of the pan. This control mechanism is an enhancement over earlier continuous coater technology and allowed for the coating of tablets in either batch and/or continuous modes. Another difference in this equipment versus earlier continuous coating pan designs is the absence of baffles throughout the pan interior (Figure 1). There are anti slide bars in the pan and the tablet movement through the pan was controlled via tablet in-feed rates

Figure 1. Interior view of coating chamber with the spray manifolds removed.

and the height of the weir plate at the discharge end of the pan.

Operation of the coating pan in batch mode

With the weir plate at the discharge end of the pan in the closed position, the pan was loaded with tablets via a weigh belt feeder from the in-feed side of the pan to a total fill of 250 kg. The tablets were tumbled gently at 2–3 rpm pan speed during the fill process to facilitate tablet movement across the length of the pan. Care was taken to minimize exposure of the uncoated tablets to excessive tumbling, which could result in tablet breakage or damage. Once the pan was filled and weigh belt feeder stopped, the tablets were heated to the target bed temperature (44–49°C), at which point pan rotation speed was increased and the spray was commenced through all 28 spray guns simultaneously. Spray was continued until the 3% (w/w) coating weight gain (WG) was applied. Upon completion of the coating, the tablets were cooled and discharged from the pan. Tablet discharge was accomplished by raising the weir plate at the discharge end of the pan and allowing the tablets to flow out under slow (3 rpm) pan rotation. To further facilitate unloading, the entire pan was angled downward toward the discharge via a pneumatic height controller that slightly lifted the in-feed side of the pan.

Operation of the coating pan in continuous mode

Operation of the coating machine in continuous mode was started as described above for batch mode. Once the entire batch reached the targeted coating WG of 3% (w/w), the weir plate at the discharge end of the machine was lifted, allowing coated tablets to begin discharging. At the same time, the weigh belt feeder was started and uncoated tablets began entering the in-feed side of the pan. Simultaneously, all spray guns were turned off except for the first spray gun zone at the in-feed side of the pan. A computerized automatic recipe control system then began sequencing, to the "on" position, the subsequent spray gun zones incrementally as the partially coated tablets progressed down the length of the pan. This was continued until all spray guns were delivering spray and a full continuous coating mode was achieved. The indexing of the spray guns was controlled to coincide with the rate of tablet feed into the coater. Spray rates were controlled to ensure the target WG of coating applied versus tablet feed rate was consistent. The total throughput rate of the coater was determined by the rate (kg/h) setting of the weigh belt feeder introducing tablets into the coater. To shut down the coating process, the start-up process was reversed with closure of the discharge end of the pan and reverse sequencing of the spray guns. The aim of this process was to ensure that all of the tablets were uniformly coated to the same level throughout the start-up, continuous process, and shut-down modes. Once all the spray gun zones were turned off, the pan was fully discharged as described above in batch mode. The process parameters were controlled to maintain coating temperatures and conditions similar to those in a typical (noncontinuous) fully perforated batch coater (Table 1).

Color development and color uniformity testing

In the batch mode operation, tablet samples were taken every minute from the center of the pan for the duration of the trial using a specially designed sample thief that reached from the discharge end of the pan to the center of the pan. In the continuous mode of operation, samples were taken every 10 minutes from the discharge of the pan for the duration of the trial and every minute during the tablet unloading cycle. These samples were

Table 1. Process parameters for batch and continuous modes of operation.

Process parameter	Batch mode settings	Continuous mode settings
Inlet temperature (°C)	80–85	80–85
Exhaust temperature (°C)	50–52	47–52
Product temperature (°C)	44–49	44–49
Airflow (cfm)	9500	9500
Pan pressure (ΔP)	−0.01	−0.01
Pan speed (rpm)	16	16
Bed depth (in.)	5.5	5.5
Weigh belt feed rate (kg/h)	n/a	1100–1300
Solution flow rate (g/min)	3000	3000
Solids concentration (%)	20	20
Batch size (kg)	250	250 initial fill – continuous thereafter

tested instrumentally for color development and uniformity testing using a Diano Color Products Milton Roy Colormate employing the Commission Internationale de l'Eclairage L^* a^* b^* system. Total color difference from target reference was determined by calculating the distance between two points in the color space using the following equation:

$$\Delta E^* = \left[(L^*1 - L^*2)^2 + (a^*1 - a^*2)^2 + (b^*1 - b^*2)^2 \right]^{1/2}$$

The standard deviation (SD) of color difference between calculated ΔE values of the individual tablets from each set of samples was compared as a measure of coating uniformity. A ΔE value of <2 indicates no visual difference in color from the target reference color. This spectrophotometric method for assessing the color development and uniformity of coated tablets in relation to coating process parameters is well documented[9].

Results and discussion

For the trial conducted solely in batch mode, the total coating time to reach the target 3% (w/w) WG was 14 minutes. The resultant coated tablets appeared visually uniform in color and free of defects. The coating surface was smooth and glossy (Figure 2). Instrumental color testing indicated that the batch uniformly reached the target color of less than 2 ΔE from reference (actual 0.4 ΔE) in less than 9 minutes of total coating time (Figure 3) and an applied WG of ~1.9%. In comparison, a similar application (tablet size, shape, coating material, and coating WG) conducted in a traditional 48-in. diameter (noncontinuous design) batch coater, color uniformity

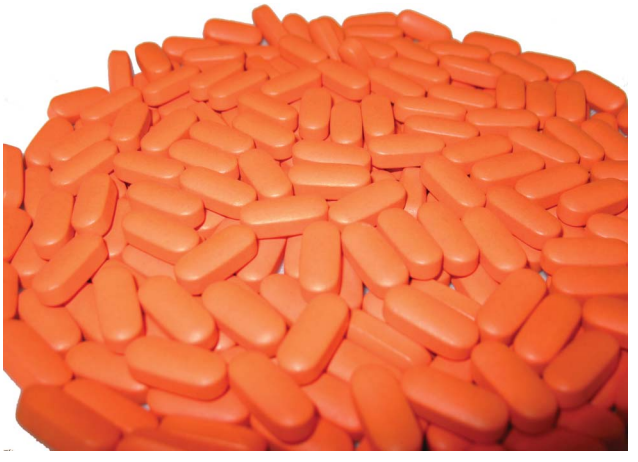

Figure 2. Coated tablet appearance.

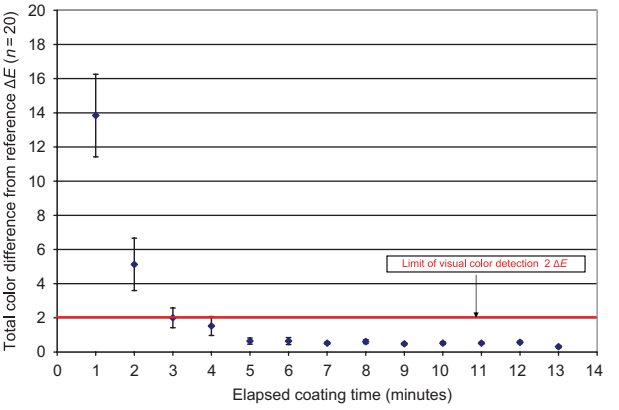

Figure 3. Batch mode color development and uniformity plot.

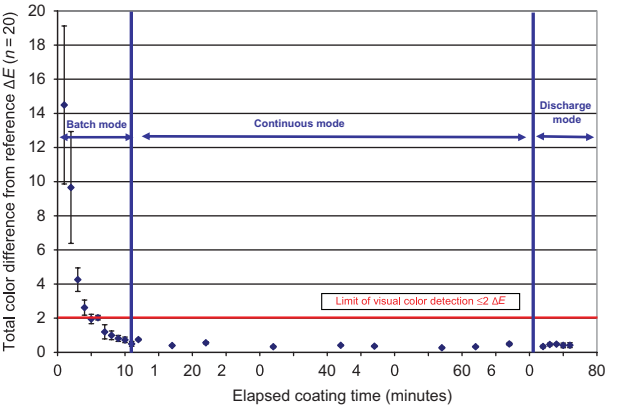

Figure 4. Continuous mode color development and uniformity plot.

was only achieved after 40 minutes of coating time rather than the 9–10 minutes achieved in this continuous coater[10]. For the trials in the continuous coating mode, a coated tablet throughput rate of 1300 kg/h was achieved with no sample exceeding the 2 ΔE color limit throughout the start-up, continuous, and discharge modes (Figure 4). In both the batch operation and batch start-up for the continuous mode of operation, color development and color uniformity were achieved in significantly less time than in a traditional batch coater. One significant difference between a traditional batch coater and a continuous coater is the depth of the tablet bed which is significantly greater in a traditional batch coater than in the continuous coater. Consequently, in the shallower bed, the tablets are exposed much more frequently to the spray zone and the duration that the tablets are isolated from the spray is significantly reduced. The increased number of spray guns and elongated coating chamber may also play a role in enhanced coating uniformity by improving the consistency of spray distribution across the tablet bed. While it

can be concluded that under the conditions and test methods used in this study, all tablets received a sufficient amount of coating to achieve color uniformity, it was not determined whether instances occurred where tablets received excess coating material.

Case study 2: Delayed release mineral oil soft gelatin capsules

Methods

Materials

Placebo soft gelatin capsules (softgels) filled with mineral oil (1000 mg) obtained from Nutra Manufacturing Inc. (Greenville, SC, USA) were used as the substrate for delayed release coating trials. The coating system used for the trials was Nutrateric, which is based on Surelease®, aqueous ethylcellulose dispersion (E-7-19040), and NS Enteric®, nutritional enteric component, all supplied by Colorcon, Inc. (West Point, PA, USA). Nutrateric is an aqueous delayed release coating system designed specifically to meet the regulatory requirements for dietary supplement, nutritional, and herbal products in Europe, the United States, and other North American regions. The self-affirmed Gras status of Nutrateric and adoption of Council Directive 2006/52/EC allows it to be used on dietary supplements across the United States and Europe. The ratio of Surelease to NS Enteric can be varied to meet specific release and process constraints. For this study, the Surelease and NS Enteric were used at an 85:15 ratio, respectively. The coating dispersion was prepared at 10% solid concentration by hydrating the NS Enteric powder in water for 60 minutes and then adding the Surelease to the dispersion. The dispersion was gently mixed for an additional 30 minutes prior to spraying.

Coating equipment

Three delayed release coating trials were conducted using a Thomas Engineering continuous coating system (Hoffman Estates, IL, USA). This fully perforated coating pan was 24 in. (61.0 cm) in diameter and 13.3 ft (405.4 cm) long. The coater was equipped with a modular spray bar (Thomas Engineering) comprising 24 independently controlled Schlick ABC spray guns (Untersiemau, Coburg, Germany). The continuous coating pan was equipped with a pneumatically controlled barrier at the discharge end of the unit to prevent the substrate from exiting the pan in the initial stages of loading and coating.

Process start-up and shut-down procedure

The pan was loaded with softgels via a weigh belt feeder from the in-feed side of the pan to a total fill of 95 kg (Figure 5). The softgels were tumbled gently at 2–3 rpm pan speed during the fill process. Once the pan was filled, the softgels were heated to the target bed temperature (30–33°C), at which point pan rotation speed was increased and the spray was commenced only through the spray gun closest to the discharge end of the pan. As the softgels closest to the discharge of the pan obtained necessary coating levels (calculated as a fraction of the total amount of coating to be applied across the horizontal pan load), the next spray gun in line began spraying. This sequencing of the spray guns continued until the softgels at the discharge end of the pan were fully coated (3.5% or 4.0%, w/w, coating WG) and softgels in the remaining section of the pan obtained the equivalent level of coating that would be seen in that location during the continuous mode of processing. This start-up mode was controlled via computerized automatic recipe control. At the conclusion of the start-up mode, the pneumatically controlled barrier at the discharge end of the coater was opened allowing the fully coated softgels to enter the discharge zone of the coater. At the same time, the automatic weigh belt feeder began introducing uncoated softgels into the in-feed side of the coater. For process shut-down, the start-up process was essentially reversed. The weigh belt feeder was stopped with simultaneous closure of the discharge end of the pan and reverse sequencing of the spray guns. The aim of this start-up and shut-down process was to ensure that all of the softgels were consistently coated to the same level throughout the start-up, continuous process, and shut-down modes. The throughput rate of the coater was determined by the rate (kg/h) setting of the

Figure 5. View of continuous coating pan loaded with 95 kg of soft gelatin capsules.

Table 2. Process parameters for continuous enteric coating trials.

	Trial 1	Trial 2	Trial 3
Target weight gain (%)	4	3.5	4
Target throughput rate (kg/h)	130	200	200
Solids concentration (%)	10	10	10
Spray rate (g/min)	865	1165	1335
Process airflow (cfm)	6800	6800	6800
Inlet temperature (°C)	47	55	57
Exhaust temperature (°C)	35	38	38
Bed temperature (°C)	33	33	33
Product temperature at discharge (°C)	30	33	32
Pan speed (rpm)	10	10	12
Process run time in continuous mode (min)	**60**	**30**	**30**

weigh belt feeder introducing softgels into the coater. Spray rates were adjusted to ensure the target WG of coating applied versus softgel capsules feed rate. The production throughput rates of each trial were assessed from 130 to 200 kg/h at WGs from 3.5% to 4.0% (Table 2). With regard to the process airflow settings, it should be noted that the typical process airflow for this machine should be 10,000 cubic feet per minute (cfm). Samples of the coated softgels were taken from the discharge of the coating pan every 5 minutes for the duration of each trial for evaluation of delayed release functional properties. Additional samples were taken from the final discharge of the coated product at the completion of the trials.

Enteric disintegration testing

All coated softgel samples taken from the process were tested for delayed release (enteric) properties in simulated gastric fluid (SGF), using the six chamber basket rack disintegration apparatus as described in USP test method 701. The softgels were exposed to SGF for 60 minutes and then removed from the apparatus and examined for any signs of disintegration, deformation, leaking, or defects in the coating. Although there is no specification for the duration that placebo (mineral oil) softgels must resist simulated intestinal fluid (SIF), a 60-minute exposure to SGF is typical for enteric coated dietary supplement products such as fish oil softgels. Select samples from each trial were then transferred to SIF and the time for full disintegration of the softgel recorded. This test was carried out to ensure that the coating and the softgel completely disintegrated with no residue left in the basket within 60 minutes exposure to high pH media.

Stability testing

Enteric coated softgels sampled from Trial 2 were packaged in foil-sealed 250cc HDPE bottles (50 capsules per bottle). The bottles were stored in stability chambers at 40°C/75% RH and 30°C/65% RH conditions for a period of 3 months. Disintegration testing in both SGF and SIF was conducted on the capsules at 1 and 3 month storage time points. The capsules were also visually examined for any signs of leaking or deformation.

Results and discussion

Coating process and enteric test results

The coating processes for each of the three trials were free of any problems. Exposure of softgels to elevated temperatures can soften the shell, making a uniform application of film difficult. In each of the three trials, process temperatures were successfully maintained to ensure that the softgels were never exposed to temperatures above 35°C. The resultant enteric coated softgels were uniform in appearance and exhibited no visual defects. The samples from the three trials subjected to enteric testing were intact with no ruptures or signs of deformation after 60 minutes of exposure to SGF. The disintegration time of all samples in SIF were within 60 minutes, indicating that all samples from the three trials met the disintegration test requirements (Tables 3 and 4). Consistent enteric performance was achieved for each trial at enteric coating WGs as low as 3.5% with all softgels passing disintegration testing irrespective of whether they were sampled from continuous mode or product discharge modes in the process. This testing indicates that the coating uniformity throughout the batch was excellent as uncoated or partially coated softgels will rapidly fail and deform with exposure to SGF. This is in contrast to historical continuous film coating processes where some products had to be discarded during start-up and shutdown stages of the process.

Table 3. Resistance to simulated gastric fluid.

Sample time point (minutes)	Time (minutes) of resistance to simulated gastric fluid with no signs of disintegration ($n = 6$)		
	Trial 1	Trial 2	Trial 3
0	>60	>60	>60
5	>60	>60	>60
10	>60	>60	>60
15	>60	>60	>60
20	>60	>60	>60
25	>60	>60	>60
30	>60	>60	>60
35	>60	Trials 2 and 3 ended at 30 minutes of continuous running time	
40	>60		
45	>60		
50	>60		
55	>60		
60	>60		

Table 4. Disintegration time in simulated intestinal fluid.

Sample time point (minutes)	Disintegration time (minutes) ($n = 6$)		
	Trial 1	Trial 2	Trial 3
0	27.5 ± 4.3	27.3 ± 3.4	28.2 ± 4.5
15	22 ± 6.4	36.8 ± 5.2	29.6 ± 3.6
30	29.5 ± 4.8	31.5 ± 6.1	26.8 ± 5.2
45	34.5 ± 7.3	Trials 2 and 3 ended at 30 minutes of continuous running time	
60	29.4 ± 8.2		

Table 5. Disintegration test results after exposure to elevated storage conditions.

Storage time point	Time (minutes) of resistance to simulated gastric fluid with no signs of disintegration ($n = 6$)	Disintegration time (minutes) in simulated intestinal fluid ($n = 6$)
40°C/75% RH Storage conditions		
Initial	>60	19.3 ± 6.3
1 month	>60	22.5 ± 4.8
3 months	>60	18.5 ± 5.3
30°C/65% RH Storage conditions		
Initial	>60	19.3 ± 6.3
1 Month	>60	20.8 ± 5.4
3 Months	>60	16.7 ± 4.2

Stability testing results

At both accelerated storage conditions, the enteric coated softgel samples retained their resistance to SIF and the disintegration time in SIF was unaffected (Table 5).

Conclusions

The results from both the immediate release and delayed release trials support the assertion that continuous coating processes are capable of applying aqueous film coatings with significant improvements in coating uniformity. For the immediate release Opadry II coating applications, color uniformity was obtained in significantly faster times than are achievable in traditional batch coaters. Similarly, the successful application of a functional coating at very low WGs on soft gelatin capsules further supported these observations. Improved continuous coater designs have successfully addressed earlier issues with product loss at start-up and shut-down. Recent advances in the development of low-viscosity immediate release film coating formulations have provided for coating systems that are ideally suited for these processes.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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