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Delayed-release Diclofenac Sodium Tablets: Scaling Up the Coating Process

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Introduction

This study investigated the impact of scaling up the coating process on the quality and performance of delayed-release diclofenac sodium tablets. In particular, the intent was to evaluate the impact of the type of coating equipment on drug release from coated tablets, and gain insight into potential differences.

Methods

Diclofenac sodium tablets (each containing 50 mg of API, tablet core weight 200 mg) were prepared by means of a direct compression process using a Manesty Betapress. Tablets were initially seal coated using Aquarius™ Prime film-coating system applied to a weight gain of 3%, and then were subsequently enteric coated with Aquarius Control ENA film-coating system, employing the coating equipment and process conditions listed in Table 1.

Table 1. Coating Process Conditions Used to Apply Enteric Coating

Parameter	Trial 1	Trial 2	Trial 3
Coating pan	O'Hara LabCoat IIX (19" pan insert)	Manesty XL Cota 150	Bohle BFC 100
Type (and #) of spray guns	2 Schlick ABC (1.2 mm nozzles)	3 Manesty Opticoat (1.2 mm nozzles)	4 Schlick ABC (1.2 mm nozzles)
Pan loading (kg), seal coated cores	8	120	100
Solid content (% w/w)	20	20	20
Target weight gain (% w/w)	10	10	10
Process airflow ($m^3\ h^{-1}$)	340	2250	1500
Process air dew point (°C)	10	9.5	10
Spray rate ($g\ min^{-1}$)	24	250	300
Atomization air pressure (bar)	1.7	2	1.5
Pattern air pressure (bar)	2.3	2	1.8
Pan speed (rpm)	12	9	10
Inlet temperature (°C)	53	58	58
Bed temperature (°C)	39	38	38
Exhaust temperature (°C)	42	44.3	38
Coating process time (min)	167	241	157

Note: This work was presented at the annual meeting of the American Association of Pharmaceutical Scientists, October 25–29, 2015, Orlando, Florida.

The data shown in Table 1 underwent a thermodynamic analysis to help assess differences between each coating process. Drying efficiencies were calculated for each process. During each coating trial, coated tablet samples were selected at intermediate weight gains (3%, 4%, 5%, 6%, 8% and 10%).

Resultant tablet samples were tested using the standard USP dissolution for diclofenac sodium delayed-release tablets. In addition, 15 tablets from each coating trial, and at each weight gain, were evaluated using a 2-hour soak test in 0.1N HCl solution, and the amount of liquid uptake was determined using a weight difference method.

Coated tablets (selected at the 10% weight gain) were also weighed, and mean weights compared with those of uncoated tablets, in order to determine the actual mean weight of coating applied and, subsequently, coating process efficiency (the actual weight gain achieved, expressed as a percentage of the theoretical weight gain applied).

Results and Discussion

The photographs in Figure 1 show tablet samples coated at the final weight gain in each coating trial. All tablets can be seen to be free of obvious coating defects.

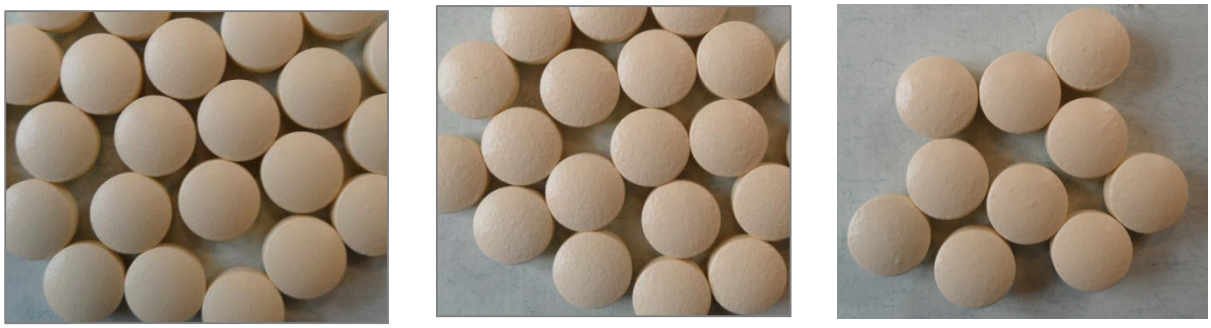

Figure 1. Photographs of Coated Tablet Samples (Final Weight Gain)

Coating Process Thermodynamic Summary: The results for the thermodynamic analysis of the three respective coating processes are shown in Table 2.

Table 2. Summary of Coating Process Thermodynamics

	Process Conditions		
	Temperature (°C)	**Dew Point (°C)**	**Absolute Moisture Content (g kg^{-1})**
O'Hara LabCoat IIX			
Inlet	53	10	7.6
Exhaust	42	16.8	12
Bohle BFC 100			
Inlet	58	10	7.6
Exhaust	38	20.9	15.6
Manesty XL-Cota 150			
Inlet	58	9.5	7.4
Exhaust	44.3	17.8	12.8

These data highlight clearly that drying efficiency in an aqueous film-coating process tends to improve significantly in larger-scale coating processes. This is not unexpected, because in smaller coating pans with shallower tablet bed depths there is less resistance to air flow through the tablet bed, allowing more of the drying energy to pass through without effectively taking part in the drying process.

Coating Process Efficiency Results: The coating-process efficiencies for each coating trial are summarized in Table 3.

Table 3. Summary of Coating Process Efficiencies

Coating Process	Process Efficiency (%)
LabCoat IIX with 19" Pan	91.1
Bohle BFC 100	98.6
Manesty XL-Cota 150	90.3

Although a coating process efficiency > 90% generally is considered acceptable, and all three of these coating trials met that criterion, the coating trial conducted in the Bohle coating pan exhibits much higher process efficiency. Such a result may well be related to the fact that there is little opportunity for the process air stream, introduced from beneath the tablet bed, to interact with the atomized spray, thus, minimizing the potential for spray drying to occur.

Dissolution Results: The primary dissolution results for tablets produced in the O'Hara LabCoat IIX (lab scale), Bohle BFC 100, and Manesty XL-Cota 150 are shown in Figures 2, 3 and 4, respectively.

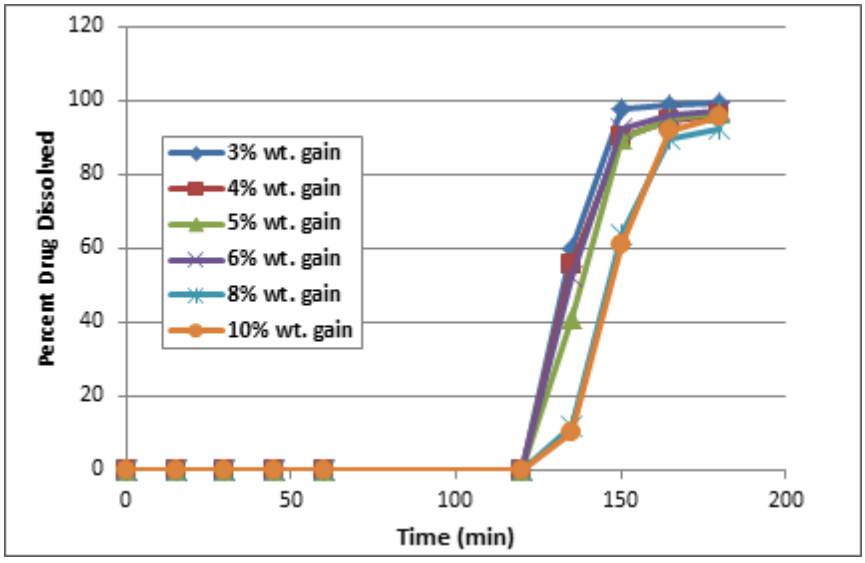

Figure 2. Tablets Coated in the O'Hara LabCoat IIX (19" Pan)

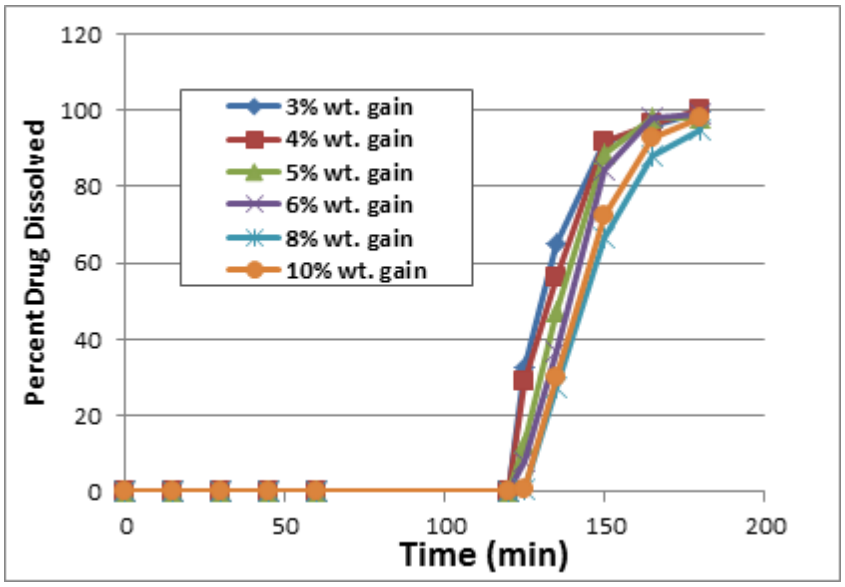

Figure 3. Tablets Coated in the Bohle BFC 100

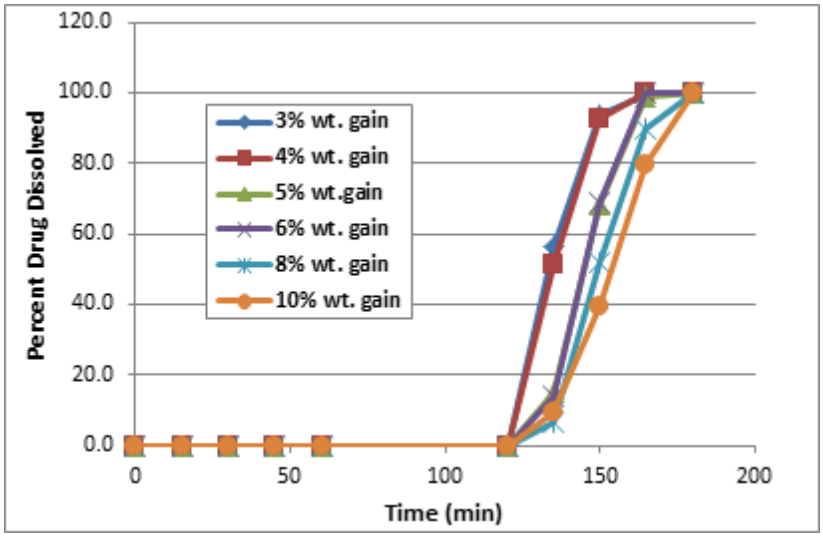

Figure 4. Tablets Coated in the Manesty XL-Cota 150

In each case, even at the lowest applied weight gains, effective gastric resistance was achieved and all coating levels from all trials met the compendial Q values (not less than 75% drug released in 45 min in phosphate buffer solution, pH = 6.8), as confirmed by the data shown in Table 4.

Table 4. Amount of Drug Released after 45 Minutes in Buffer, pH = 6.8

Coating Level (% w/w)	Quantity of Drug Released (%)		
	LabCoat IIX	Bohle BFC 100	Manesty XL-Cota 150
3	98.7	95.7	99.1
4	94.4	96.4	99.7
5	95	97.9	98.6
6	96	98.1	99.7
8	89.4	88.1	90
10	91.9	92.9	79.7

The dissolution results obtained for tablets coated on the laboratory scale in the O'Hara LabCoat IIX and in the Manesty XL-Cota 150 show the greatest similarity (with a general slowing of drug release in buffer, pH = 6.8, as coating levels increase). This is, perhaps, not unexpected because both machines exhibit similar air handling and, hence, drying characteristics. In slight contrast, the data obtained in the Bohle BFC 100 coating pan show much less differentiation in drug -release profiles as the level of coating is increased. Considering that only a small number of tablets are traditionally selected for dissolution testing, this result may potentially reflect improved coating uniformity (and thus less tablet-to-tablet variability in dissolution testing) for tablets coated in the Bohle process. Evidence for such improvements in uniformity of coating distribution in this type of equipment has been published elsewhere [1].

In all cases, the levels of coating applied are theoretical. Because the data shown in Table 3 indicate that the coating trial performed in the Bohle coating pan exhibited a higher coating-process efficiency, the fact that the actual amount of coating deposited was also higher in this trial may partially explain the dissolution results obtained.

Liquid Uptake Results: Data for tablets exposed for two hours in 0.1 N HCl solution ("gastric soak test") are shown in Figure 5.

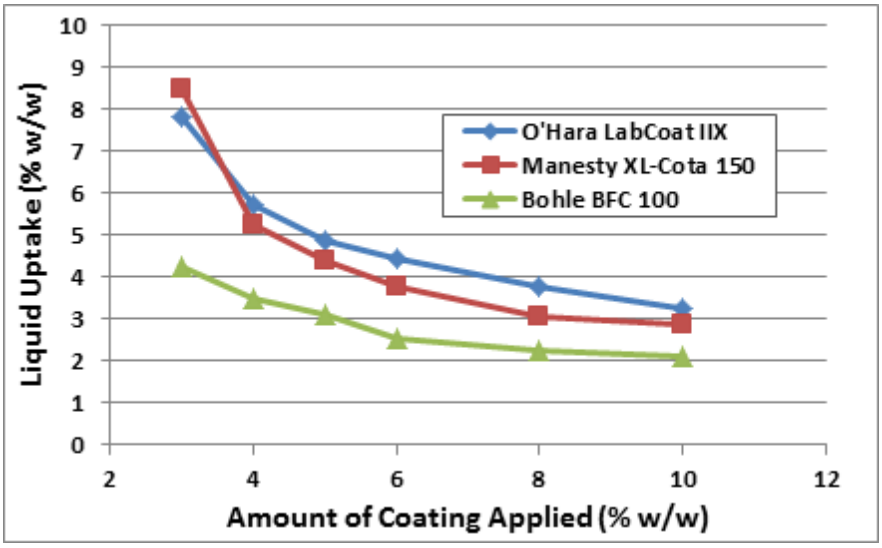

Figure 5, Liquid Uptake After 2 Hours in 0.1N HCl Solution

As with the results obtained in the dissolution test, the greatest similarity in the case of the liquid uptake test is shown between tablets coated in the O'Hara LabCoat IIX (laboratory scale) and the Manesty XL-Cota 150. On the other hand, tablets coated in the Bohle BFC 100 appear to offer greater resistance to the ingress of liquid in this test. While such a test has no well-defined and commonly accepted standards covering its application and, generally, has not been correlated to delayed-release performance as required by global compendia, the results are indicative of potential impacts of differences in the coating

processes (and process conditions) on gastric resistance of the applied coating, as reflected by coating permeability.

As with the dissolution results, the greater gastric resistance of tablets coated with the Bohle process can also be explained by a higher coating-process efficiency, because this would result in more coating actually being deposited.

Conclusions

Overall, tablets coated in each of the coating trials possessed acceptable delayed-release properties, in each case meeting compendial requirements for diclofenac sodium delayed-release tablets. The fact that effective gastric resistance could be achieved in all cases with coating weight gains of as little as 3–4% is particularly noteworthy. That said, in spite of the fact that all three coating processes operate under the same general principles, the results show that differences in the specific operating characteristics of a coating pan, especially during scale up, can potentially have an influence on the functional behavior of tablets coated in those processes. Thus, scaling up a film-coating process, especially for a modified-release product, should never be taken as a trivial matter, and is particularly important when scale up involves transfer to another manufacturing site where process equipment may differ from that of the development site.

Reference

[1] Optimization of the inter-tablet coating uniformity for an active coating process at lab and pilot scale; Just, et al, Int. J. Pharm., 457, (2013) , 1–8.