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An Accurate Method of Coating Tablets with Active Pharmaceutical Ingredients

A summary of the
poster presented at the
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Symposium
September 17-19, 2003
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Freiburg, Switzerland

INTRODUCTION

Coating technology is used extensively in the pharmaceutical industry, e.g. for the application of non-functional or functional coats (aesthetic, protective or rate controlling polymer films) and for the deposition of Active Pharmaceutical Ingredients (APIs) onto nonpareils (multi-particulate dosage forms). In addition to efficient techniques for API layering of multiparticulate systems, an accurate method of coating objects 3 to 30 mm in length with APIs is also desired in the pharmaceutical industry as this is the size range of most single-unit solid dosage forms. These include tablets for oral administration and forms for other methods of delivery including human implantation. Existing methods of coating objects in this size range have limitations, e.g. in terms of coating speed and accuracy/uniformity, particularly for the deposition of low dose API onto single unit tablet dosage forms which requires a greater degree of accuracy than can be achieved using current tablet coating techniques¹.

A novel method of coating small objects has been developed that has demonstrated the ability to uniformly coat inert objects of sizes between 3 and 30 mm in length with a high degree of accuracy. Using the coating method, Relative Standard Deviations (RSDs) below 2% have been achieved for total coating contents as low as 200 micrograms per object. However, it is unknown how accurately the deposition will be on conventional pharmaceutical tablets (which have a higher degree of friability and more irregular surface compared to the inert objects used).

Methods of evaluating coating uniformity include mass variance of the coated tablets and variance of the tablet API content^{2,4}. However, the United States Pharmacopoeia (USP) states that "The test for content uniformity is required for coated tablets, other than film-coated tablets containing 50 mg or more of an active ingredient that comprises 50% or more (by weight) of one tablet."⁴ In this study, the RSD of the API content will be used to evaluate the inter-tablet coating uniformity of this novel coating method in applying low doses of API onto conventional tablets.

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Figure 1:
Prototype Coating
Apparatus
(Niro Pharma Systems)

OBJECTIVES

- To determine the accuracy and uniformity of the coating method in applying small amounts (theoretical doses of 200 and 400 micrograms per tablet) of an API onto conventional tablets.
- To investigate the influence of the following process parameters on the uniformity and yield of API content per tablet:
 1. Batch weight
 2. API solution concentration
 3. API dose
 4. Solution spray rate
 5. Atomizing gas pressure

Coating Process

The coating apparatus shown in Figures 1 and 2 is described in US patent 6,209,479 and EP patent 1 140 366 and eqv.^{5,6} The apparatus consists of a processing chamber that sits on top of an air distribution plate (roto-nozzle). The roto-nozzle contains gas jets designed to accelerate the object through the coating zone in a ballistic flight path. Additionally, the gas jets impart momentum such that the object is rotating as it passes through the coating zone. The spray zone is created by a low-momentum two-fluid nozzle beneath the gas distribution plate that atomizes the stream of coating solution into fine droplets. Tangentially located slots around the nozzle that mix high-pressure atomization gas with low-pressure processing gas muffle the energy from the two-fluid nozzle. The objects are loaded into the processing chamber and are coated co-currently with the drying gas.

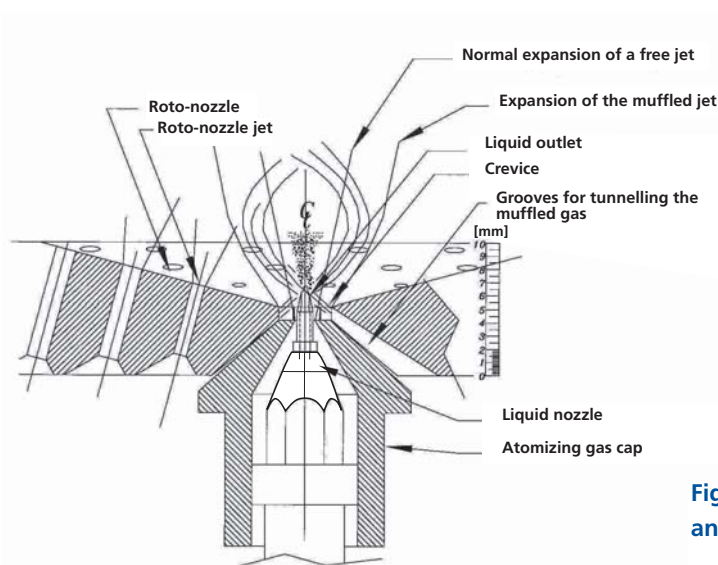


Figure 2: Cutaway of roto-nozzle and liquid nozzle

MATERIALS AND METHODS

The materials and methods used in this study are given in Tables 1 - 3 and Figures 3 and 4:

Table 1: Formulation for Granulation in a PRECISION GRANULATOR™

Material	Amount (wt. %)
Lactose 200M* (Pharmatose 200M, DMV)	88
Polyvinylpyrrolidone (K29/32, ISP)**	5
Microcrystalline cellulose (Avicel PH-101, FMC)	5
Crospovidone (Polyplasdone XL10, ISP)	2

* From DMV product literature:
Lactose 200M - average particle size 0.040 mm; % <0.045 mm : 50-65

** As a 15 wt.% polyvinylpyrrolidone solution

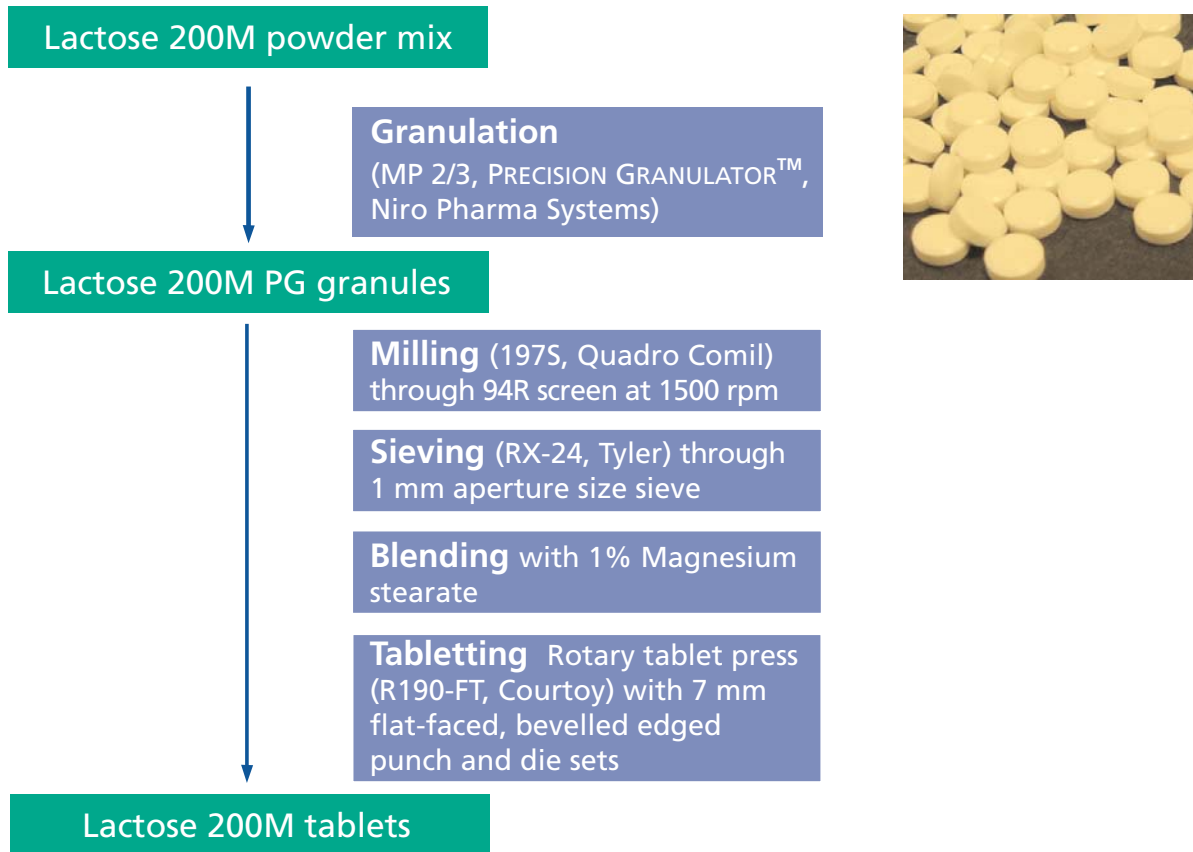
Table 2: Base and API Formulations for Coating

Material	Base Coat (wt. %)	API Coat 1 (wt. %)	API Coat 2 (wt. %)
Purified water	94.45	94.35	93.45
Hydroxypropyl methylcellulose (Methocel E3 PREM LV, Dow)	5	5	5
Polyethylene glycol (Carbowax 3350, Union Carbide)	0.05	0.05	0.05
Polyvinylpyrrolidone (Plasdone C-15, ISP)	0.5	0.5	0.5
Propranolol	0.0	0.1	1.0

Table 3: Coating Process Conditions

Batch ID	Batch Weight (g)	Airflow Rate (CMH)	Inlet Air Temperature (°C)	Plenum Pressure (cm WC)	Atomizing Gas Pressure (Bar)	API Solution Concentration (wt. %)	Volume Applied (mL)	Spray Rate (mL/min)
F	30.00	17.4	120	1000	2.3	0.1	89.80	4.0
G	30.00	17.4	120	1000	3.0	0.1	89.80	6.0
A	60.00	21.3	120	1700	3.0	0.1	89.80	8.0
H	60.00	21.3	120	1700	2.3	0.1	89.80	6.0
E	30.00	17.4	120	1000	2.3	0.1	44.90	6.0
J	30.00	17.4	120	1000	3.0	0.1	44.90	6.0
K	30.00	17.4	120	1000	2.3	0.1	44.90	4.0
B	30.00	17.4	120	1000	3.0	0.1	44.90	4.0
C	30.00	17.4	120	1000	3.0	0.1	44.90	4.0
D	30.00	17.4	120	1000	2.3	1.0	4.49	4.0

Figure 3: Preparation and characterization of tablet cores



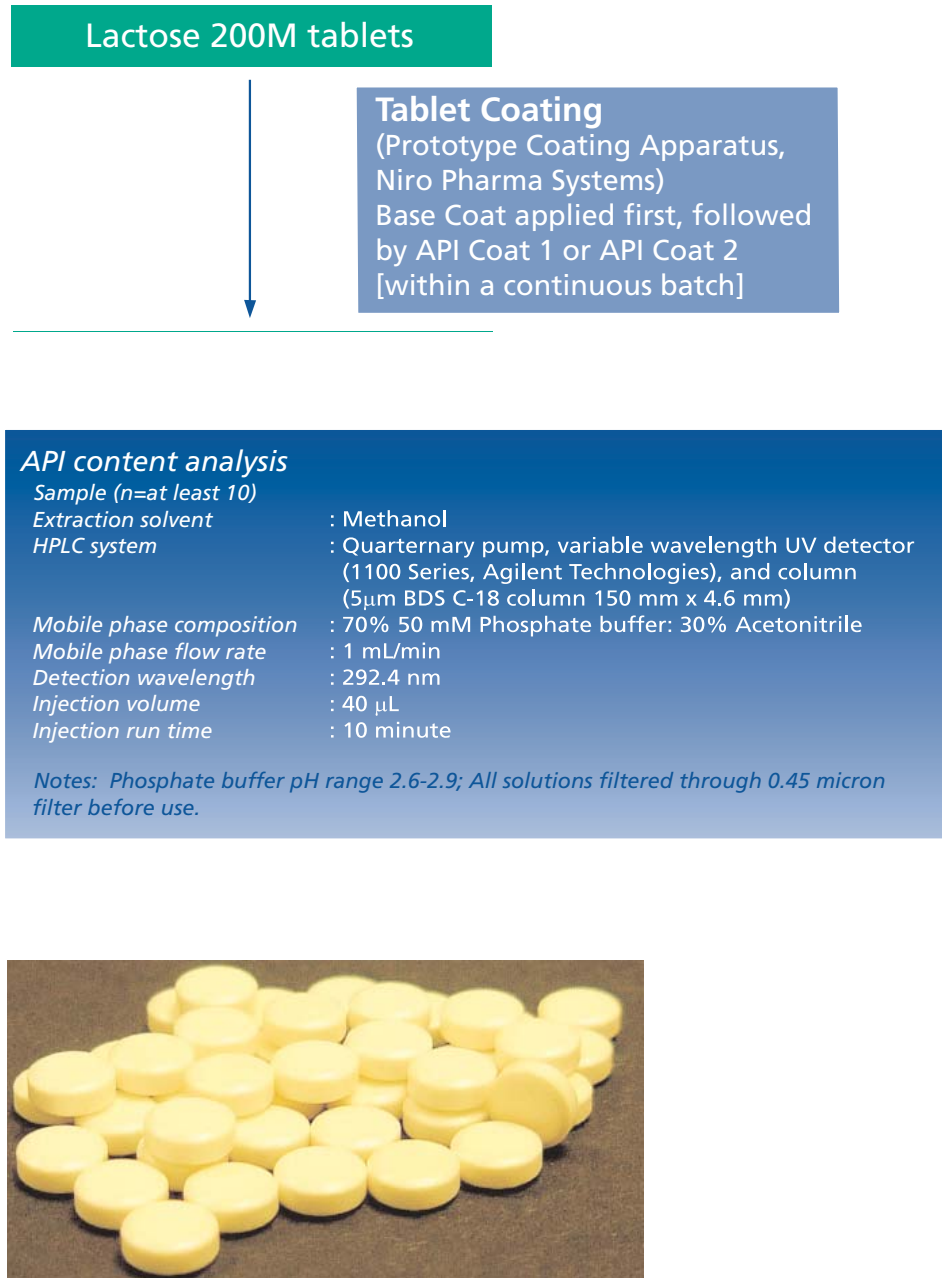
Tablet properties	Thickness (mm)	Width (mm)	Weight (mg)	Hardness (N)	Friability (% wt. loss)
Mean	2.59	7.03	0.131	80.9	0.06
Standard deviation	0.01	0.003	0.001	5.9	0.002
RSD	0.52	0.04	1.11	7.3	3.33

Weight variation (MC5 Balance, Sartorius)

Hardness (PTB 300, Pharmatest)

Friability (Electrolab)

Figure 4: Tablet Coating and API content analysis of coated lactose 200M tablets



RESULTS

Uniformity of Coating Process

The results from the HPLC analysis of the API content are presented in Figure 5 and Table 4. The best results were from Batch H, which had the lowest API content RSD of 3.0% and the second highest API yield of 78.9%. The ability of the coating process to uniformly apply low doses of an API to single-unit dosage forms was demonstrated, as the API content RSDs were 5.0% or less for all but two batches. The causes of these two high values are discussed in the second part of this section under Influence of Process Variables on API Content Uniformity and Yield.

Batch ID	API Content RSD (%)	API Yield (%)
F	3.8	70.0
G	4.6	67.1
A	8.9	79.4
H	3.0	78.9
E	4.9	67.3
J	4.4	63.6
K	4.7	61.8
B	3.8	63.1
C	5.0	61.6
D	13.0	65.0

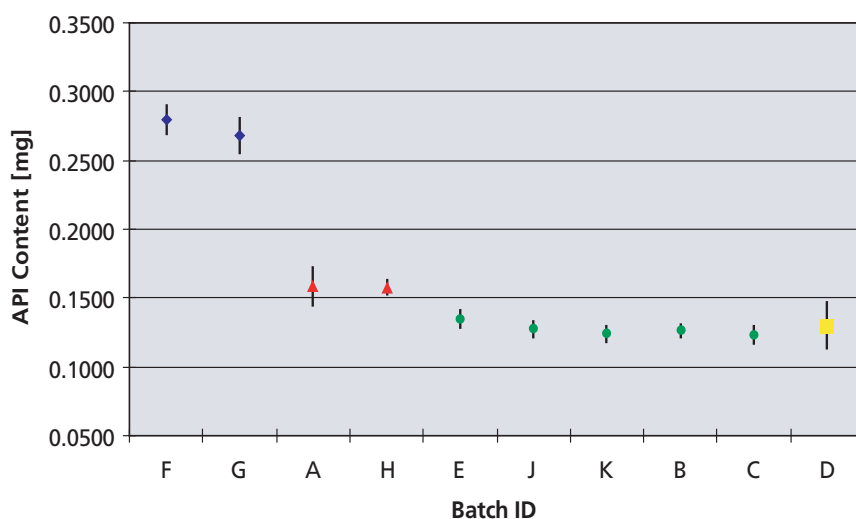


Table 4: API content RSDs and API yields

Figure 5: Mean API content per tablet

Influence of Process Variables on API Content Uniformity and Yield

1. Batch weight

Two batch weights of 30 g (229 tablets) and 60 g (458 tablets) were used. The theoretical API dose per tablet for both batch weights was 200 micrograms. The plenum pressure was increased from 1000 cm WC in the 30 g batches to 1700 cm WC in the 60 g batches to maintain proper tablet movement during coating. The results are shown in Figure 6 and Table 5.

Batch ID	Batch Weight (g)	API Content RSD (%)	API Yield (%)
A	60	8.9	79.4
H	60	3.0	78.9
E	30	4.9	67.3
J	30	4.4	63.6
K	30	4.7	61.8
B	30	3.8	63.1
C	30	5.0	61.6

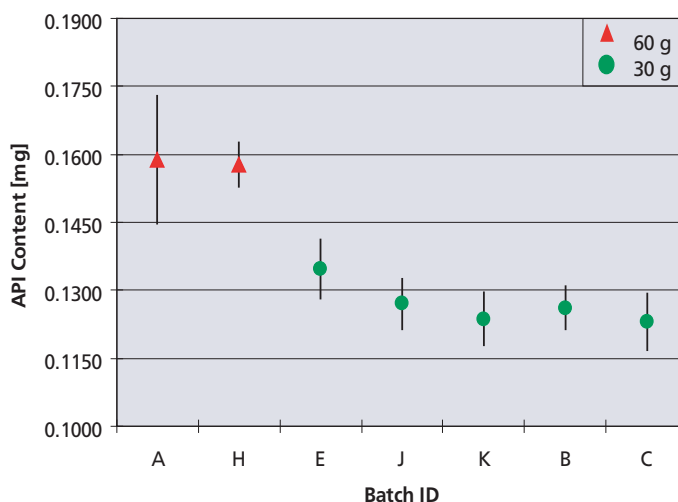


Table 5: API content RSDs and API yields—30 and 60 g batches

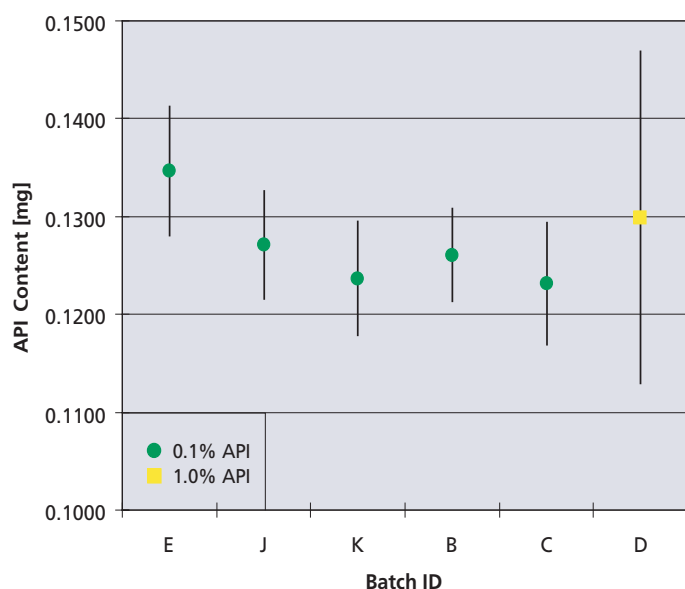
Figure 6: Mean API content per tablet—30 and 60 g batches

The two 60 g batches had a significantly higher mean API yield (79.2%) than the 30 g batches (63.5%). With a larger batch size, there is more surface area to collect the liquid droplets, which results in higher API yields.

The trend in the RSDs of API content is not as clear compared to the yield. Although the 60 g batches had a higher average RSD of 6.0% versus 4.6% for the 30 g batches, the API content RSD of batch A is most likely high because the highest spray rate was used for this batch. This effect is discussed later.

2. API solution concentration

Two API solution concentrations were used in the coating formulations, 0.1% (API Coat 1) and 1.0% (API Coat 2) by weight. In order to maintain the theoretical API dose of 200 micrograms per tablet, the total volume of coating solution was decreased by a factor of ten for the batch coated with API Coat 2. The results are shown in Figure 7 and Table 6:



Batch ID	API Solution Concentration (wt. %)	API Content RSD (%)	API Yield (%)
E	0.1	4.9	67.3
J	0.1	4.4	63.6
K	0.1	4.7	61.8
B	0.1	3.8	63.1
C	0.1	5.0	61.6
D	1.0	13.0	65.0

Table 6: API content RSDs and API yields— 0.1% and 1.0% API solution concentration batches

Figure 7: Mean API content per tablet—0.1% and 1.0% API solution concentration batches

The mean API contents (and therefore API yields) of the various batches were found not to be significantly different from each other. While the concentration of the API solution did not appear to have a significant effect on API yields, the content RSD values indicated that API solution concentration influenced coating uniformity. The average content RSD of the 0.1% API solution batches was 4.6 while that of the 1.0% API solution batch, at 13.0%, was the highest RSD among all of the batches. With a lower API solution concentration, the API is distributed into a larger volume of coating solution. Deposition of the API onto the tablets then takes place over a longer period of time, resulting in a more random coating process.

3. API dose

Two theoretical API doses were used in this study, 200 and 400 micrograms. The spray times for the 400 microgram batches were twice as long as the 200 microgram batches in order to keep all other parameters constant. The results are shown in Figure 8 and Table 7:

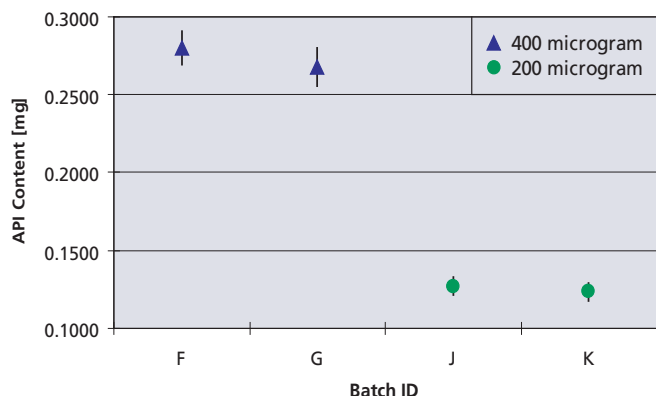


Figure 8: Mean API content per tablet —200 and 400 microgram theoretical doses

Batch ID	API Theoretical Dose (microgram)	API Content RSD (%)	API Yield (%)
F	400	3.8	70.0
K	200	4.7	61.8
G	400	4.6	67.1
J	200	4.4	63.6

Table 7: Mean API content RSDs and API yields —200 and 400 microgram theoretical doses

All of the batches had API content RSDs less than 5.0%. The batches with the 400 microgram theoretical API dose had a mean API content RSD of 4.2% while the 200 microgram batches had a mean API content of 4.6%. The 400 microgram batches were observed to have a slightly higher mean API yield than the 200 microgram batches.

4. Solution spray rate

Three different spray rates were used, two for each batch size. The maximum spray rate differs for each batch size as the rate of drying increases with an increased amount of surface area and therefore the same two spray rates could not be used for both batch sizes. The results are shown in Figure 9 and Table 8:

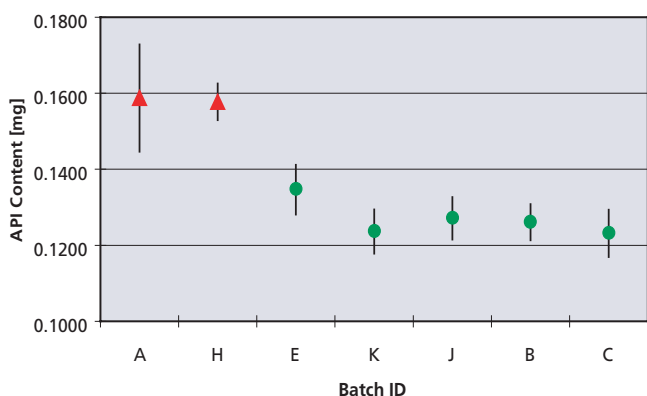


Figure 9: Mean API content per tablet —4.0, 6.0, and 8.0 mL/min spray rates

Batch ID	Solution Spray Rate (mL/min)	Batch Weight (g)	API Content RSD (%)	API Yield (%)
A	8.0	60	8.9	79.4
H	6.0	60	3.0	78.9
E	6.0	30	4.9	67.3
K	4.0	30	4.7	61.8
J	6.0	30	4.4	63.6
B	4.0	30	3.8	63.1
C	4.0	30	5.0	61.6

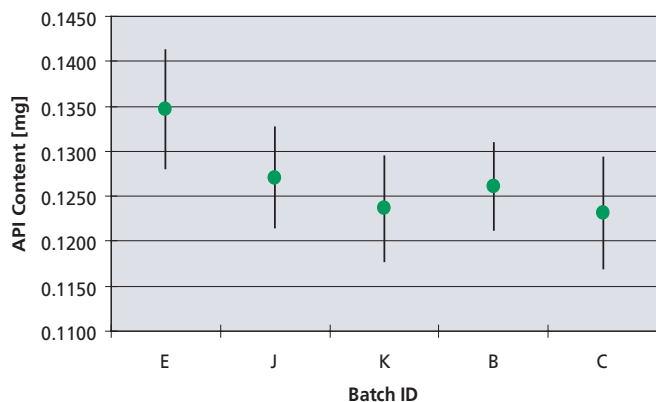
Table 8: Mean API content RSDs and API yields —4.0, 6.0, and 8.0 mL/min spray rates

For the 60 g batches, the API content RSD increased significantly when the spray rate was increased from 6.0 mL/min to 8.0 mL/min. With a spray rate of 8.0 mL/min, batch A had an RSD of 8.9%, one of only two batches higher than 5.0%. However, large differences in RSDs were not observed for the 30 g batches at the spray conditions used. All of the 30 g batches had RSDs less than or equal to 5.0%.

When the spray rate was increased from 4.0 to 6.0 mL/min, the API yields of the 30 g batches ranged between 61.6% and 67.3%.

5. Atomizing gas pressure

Two different atomizing gas pressures were used in the experiments, 2.3 and 3.0 bar. The results are shown in Figure 10 and Table 9:



**Figure 10: Mean API content per tablet
—2.3 and 3.0 bar atomizing gas pressures**

Batch ID	Atomizing Gas Pressure (Bar)	Spray Rate (mL/min)	API Content RSD (%)	API Yield (%)
E	2.3	6.0	4.9	67.3
J	3.0	6.0	4.4	63.6
K	2.3	4.0	4.7	61.8
B	3.0	4.0	3.8	63.1
C	3.0	4.0	5.0	61.6

**Table 9: Mean API content RSDs and API yields
—2.3 and 3.0 bar atomizing gas pressures**

At the atomizing gas pressures selected, all of the API content RSDs were less than or equal to 5.0% and the API yields ranged from 61.6% to 67.3%.

CONCLUSIONS

Based on the results of this preliminary study, the coating process has the potential to uniformly apply low doses of APIs to single-unit dosage forms such as pharmaceutical tablets. API content RSDs of less than 5.0% can be achieved for doses as small as 200 micrograms. The API yields obtained ranged from 61.6% to 79.4%, with the 60 g batches having the highest values. For the purpose of applying low doses of APIs to single-unit dosage forms, the goal is to obtain the lowest API content RSD and the highest API yield. Optimization of the process is necessary to further improve the coating uniformity and coating yield and to better understand the relationships between the process and formulation variables in this novel coating technique.

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