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Considerations for Drug Layering of Sitagliptin on Placebo Tablets to Manufacture Fixed Dose Combination Drug Products

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Introduction

Drug layering of tablets with a film coating process has long been used to manufacture fixed-dose combination products (FDC). During the large-scale manufacture of drug layered FDC products, the use of drug dispersion at high solids content may be challenging due to potential variations in content uniformity of the finished dosage form. Upon increasing the drug content in the dispersion, higher coating pan speed is commonly utilized to assure processing time is not increased. At a higher speed, tablets pass the spray zone more frequently, imposing higher mechanical stress onto the batch which could, in turn, lead to edge chipping or cracking of the drug layer. Therefore, an optimized film coating formulation with superior adhesion, a high API-loading capacity and an elevated tensile strength is required.

Objectives

The objective of this study is to evaluate the effect of the coating parameters at pilot (24" pan) and production (48" pan) scales on tablet appearance and content uniformity when sitagliptin phosphate monohydrate (PM) is drug layered using a 1:1 ratio of drug to Opadry, employing an Opadry formulation as a binder.

Methods

Drug Layering Dispersion Preparation: A fully formulated, HPMC-based, immediate release film coating system (Opadry®) was used for layering sitagliptin PM USP (Fuxin Long Rui Pharmaceutical CO.). The drug layering dispersion was applied on placebo caplets. A sitagliptin PM to Opadry ratio of 1:1 was employed for drug layering to 14.28% w/w theoretical weight gain, achieving 64.25mg dose of sitagliptin PM (equivalent to 50mg of sitagliptin as free base).

Sitagliptin PM drug layering dispersion was prepared by adding the drug to ambient water temperature and mixed using a variable-speed mixer for 30 minutes until an API translucent solution was obtained. Then Opadry was added and mixed for 45 minutes, it was de-aerated overnight and screened through a 60 mesh.

Coating Process Parameters and Equipment: Three coating runs were carried out in two coating machines, as follows:

- An O´Hara Lab coat II with a 24" pan, four ploughshare baffles and two spray guns Schlick 930-7-1- S35 were employed to conduct one coating run, with a pan charge of 15kg of placebos tablets.
- An O´Hara Fast coat II with a 48" pan, four ploughshare baffles and three spray guns Schlick 930-7-1- S37 were employed to conduct two coating runs, with a pan charge of 120kg of placebos tablets.
- Pattern air pressure was adjusted to achieve full coverage of the tablet bed and a uniform spray pattern for even coating.
- Baffle design, pan speed and the number of spray guns are key factors that influence uniformity of solid distribution; on the 48" scale, these factors were kept constant.

The coating process parameters are shown in Table 1.

Table 1. Coating Process Parameters

Parameter	units	24#	48"	
Batch size	kg	15	120	120
Inlet air volume	cfm	276	2000	2000
Inlet air temperature	(°C)	66	60	55
Pan differential pressure	"w.c.	-0.15	-0.15	-0.15
Spray rate	g/min	60	350	350
Solids	(%)	12	12	15
Tablet bed temperature	(°C)	41.0	42	38.5
Pan speed (angular velocity)	RPMs	14	8	8
Pan speed (linear velocity)	ft/min	88	101	101
Number of guns	#	2	3	3
Gun to bed distance	inches	6.0	7.5	6.5
Atomizing air pressure	psi	25	25	20
Pattern air pressure	psi	25	30	30
Total drug layering dispersion	Kg	17.9	142.8	114.2
Process time	hours	5.0	6.8	5.4
EEF - Environmental Equivalency Factor	-NA	3.0	3.2	2.9

Analytical Methods: Sitagliptin PM was quantified by liquid chromatography following the USPNF 2022 (Issue 2) monograph for sitagliptin immediate release (IR) tablets. Tablet content uniformity testing was carried out according to the USP general chapter: <905> Uniformity of Dosage Units, where an acceptance value of >15.0 does not meet USP criteria. Drug layered tablets were pulled from the coater at the following weight gains to assay API content uniformity: 5, 7.5, 10, 12.5 and 14.3%.

Results

The main purpose of the coating trial at the 24” pan scale was to determine if the optimized Opadry formulation at a 1:1 drug to Opadry ratio could withstand the mechanical stress of a pan speed linear velocity of ≥ 88 ft/min (Table 1), which is expected to yield acceptable content uniformity results when an API is drug layered at the 48” pan scale. Previous coating trials revealed that tensile strength is a critical film coating formulation attribute that needs optimizing to prevent defects when a high API load is present.

No edge-chipping or cracking was detected from all three coating runs and a smooth coating was achieved in all cases.

Drug Content Uniformity Testing: Content uniformity for the drug layered tablets is presented in Table 2; acceptance values were calculated using content of sitagliptin PM.

Individual drug layered tablets assayed for drug content complied with the USP requirements for content uniformity for both coating trials at 12% solids in the 24” and 48” scale; acceptance values were below 15 at all weight gains and tended to decrease toward the end of the process when approaching the final weight gain (14.3%).

In the coating run at 15% solids in the 48” pan, a higher solid content generated higher acceptance values at all weight gains (when compared to the 12% solids); the acceptance value failed the specification at the end of the process.

As expected, increasing solid content decreased the degree of uniformity with which atomized solids (including the API) were distributed among individual tablets, this is mainly due to a decrease on the total number of times that the tablets passed through the spray zone during the full process. In other words, at a constant spray rate of 350 g/min, total drug layering dispersion decreased from 142.8kg to 114.2kg, and therefore process time decreased from 6.8 hrs. to 5.4 hrs. Also, it is important to highlight that no adjustment was made to pan speed to compensate the decrease in process time as previous trials had showed that the drug layer was susceptible to edge chip.

Process Efficiency: Process efficiency for all three coating runs is presented in Table 3. Spray drying was observed in all three coating trial cases in different orders of magnitude which depended on the scale and parameters employed.

Parameters influencing process thermodynamics, droplet size and gun-to-bed distance might be optimized to decrease the incidence of spray drying:

- The 12% solids / 48" pan trial exhibited the highest magnitude of spray drying; in this case, an EEF thermodynamic factor of 3.2 in combination with a 7.5-inch gun-to-bed distance, and an atomization air pressure of 25 psi yielded a process efficiency of 85.9%.
- Some adjustments were made for the 15% solids / 48" pan trial: (i) a decrease on the inlet air temperature led to a decrease on the EEF to 2.9, which in combination with a decrease on both, (ii) gun-to-bed distance and (iii) atomization air pressure, led to an increased process efficiency of 94.2%. As a result of these adjustments on the process parameters, a significant decrease of spray-drying was observed.

Table 2. Content Uniformity Results

	24" pan/Solids: 12%				
WG (%)	5.0	7.5	10	12.5	14.3
Process time (hr.)	1.7	2.6	3.6	4.3	5.0
RSD (%)	5.2	4.3	4.0	3.9	2.3
Acceptance value	12.5	10.2	9.6	9.3	5.5
Meets specification?	PASS	PASS	PASS	PASS	PASS

48" pan/Solids: 12%				
5.0	7.5	10	12.5	14.3
2.4	3.6	4.8	6.0	6.8
5.9	5.5	5.5	4.2	4.4
14.0	13.1	13.3	10.1	10.6
PASS	PASS	PASS	PASS	PASS

48" pan/Solids: 12%				
5.0	7.5	10	12.5	14.3
1.9	2.9	3.8	4.8	5.4
7.6	7.5	6.1	5.0	8.1
18.3	18.1	14.6	12.0	19.4
FAIL	FAIL	PASS	PASS	FAIL

Table 3. Coating Process Efficiency

	Units	24"	48"	
Solids	(%)	12	12	15
Theoretical content	mg	64.4	64.4	64.4
Measured content	mg	59.5	55.3	60.7
Process efficiency	%	92.4	85.9	94.2
RSD	%	2.3	4.4	8.1

Conclusions

The purpose of this film coating study was to generate experimental data to serve as a starting point for the optimization of a drug layering coating process at production scales.

A solid concentration of 12% (drug: Opadry at 1:1 ratio) complied with the USP requirements for content uniformity of drug layered sitagliptin PM. These results can be replicated under the similar setup i.e.: perforated side-vented pan with similar pan dimensions, baffle design and number; the number and type of spray guns; and pan speed. However, it is also recommended to verify and adopt the adjustments made to the thermodynamic parameters of the process to increase process efficiency and decrease spray drying.

References

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