Impact of Coating Process Parameters on Drug Layering of Sitagliptin Over Metformin HCl ER Tablets

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Introduction

The purpose of this study was to develop a tablet formulation containing metformin HCl as an extended release (ER) tablet followed by drug layering of sitagliptin as an immediate release (IR) layer.

Fixed-dose combination (FDC) drug products combine two or more APIs (Active Pharmaceutical Ingredient) in a single dosage form. Bilayer tablet technology is commonly used for FDC formulations to achieve desired therapeutic benefits; however, bilayer tablet formulations can present challenges such as lack of interfacial bonding, crack development, or layer separation.[1] The most common FDC formulations contain an immediate release (IR) low dose API and an extended release (ER) mid to high dose API. If the IR layer API has good aqueous solubility, drug layering using a suitable film coating system over the ER tablet can overcome the challenges of bilayer tablet formulation. For drug layering, the selection of a suitable coating system along with optimized coating process parameters plays an important role in achieving good uniformity of the API on the tablet surface and throughout the production batch.[2]

Methods

Metformin HCl ER tablets were manufactured using METHOCEL™ K100M (hypromellose) as the rate controlling polymer, with a drug layer of sitagliptin added using an Opadry® complete film coating system. Coating process parameters were studied to investigate the impact on tablet appearance and content uniformity (CU). The resulting sitagliptin IR/metformin ER tablets were then film coated with Opadry® II High Performance Film Coating System followed by a top-coat of Opadry® EZ, Easy Swallow Film Coating System. (Table 1).

Manufacturing of Metformin HCl ER Tablets:

While mixing constantly, a specified quantity of water was added to the MCC (microcrystalline cellulose). The wetted MCC was passed through ASTM #18 mesh screen and further mixed with metformin, METHOCEL™ K100M and colloidal silicon dioxide (ASTM #40 mesh screen) in a DCM blender (Rimek Kalweka, India) for 10 mins at 20 rpm. The powder blend was lubricated for an additional 2 mins. with magnesium stearate (ASTM #60 mesh screen) for 2 mins at 20 rpm. Tablets were compressed on a rotary tablet press (Rimek Minipress SF II, India) using 21.2 x 10.6 mm, oval shaped, D-type standard concave tooling. The dissolution profile of uncoated tablets was obtained using USP Apparatus II with sinkers at 100 rpm using 1000 mL of phosphate buffer pH 6.8.

Drug Layering of Sitagliptin Over Metformin HCl ER Tablets:

Drug layering was done using an Opadry coating system and the impact of coating process parameters, such as % solids, spray rate, and pan speed on tablet appearance and CU studied (Table 2). Coated tablets were evaluated for surface roughness, CU, and drug assay. Dissolution of drug layered sitagliptin tablets was obtained using USP Apparatus II at 75 rpm using 900 mL of 0.1 N HCl.

Table 1. Composition of Metformin HCl ER (1000 mg) and Sitagliptin (100 mg) Tablets

Ingredients	% w/w	mg/tablet
Metformin HCl ER (Partial)		
Metformin HCl	76.92	1000.00
METHOCEL K100M Premium	17.78	231.14
MCC PH 101	4.00	52.00
Colloidal silicon dioxide	0.90	11.70
Magnesium stearate	0.40	5.20
Total	100.00	1300.04
Drug Layering with Sitagliptin (20% WG)		
*Sitagliptin phosphate monohydrate	51.35	133.50
Opadry 03F180011 White	48065	126.50
Purified water (10% w/w solids)	Q.S.	
Total		260.00
Drug layered tablet weight		1560.04
Film Coating with Opadry II 85F (3%WG)		
Opadry II 85F570018	100.00	46.80
Purified water (20% w/w solids)	Q.S.	
Film coated tablet weight		1606.84
Film Coating with Opadry EZ (1% WG)		
Opadry EZ 254U570001 Beige	100.00	16.07
Purified water (10% w/w)	Q.S.	
Film Coated tablet weight		1623

Table 2. Drug Layering Process Parameters

Process Parameters	R&D Batch Size Trial		
	Trial 1	Trial 2	Trial 3
Pan load, kg	0.65		
Coating machine	O'Hara LCM 5		
Pan Size	10.5-inch pan		
Number of spray guns	1		
Nozzle diameter, mm	1.0		
Drug layering dispersion Drug: Opadry Ratio	51.35:48.65	51.35:48.65	51.35:48.65
% Weight Gain	20		
Coating media	Purified water		
% Solids	12.5	10	10
Spray rate, g/min	4-6	4-6	2-4
Pan speed, rpm	5-8	5-8	7-10
Inlet air temperature, °C	57-61	57-61	55-59
Exhaust temperature, °C	43-45		
Bed Temperature, °C	42-44		
Atomization air pressure, bar	1.3-1.5		
Pattern air pressure, psi	1.3-1.5		
Air flow, m3/hr	120-125		

Film Coating of Drug Layered Tablets:
Sitagliptin-metformin FDC tablets were subsequently coated with Opadry II film coating at 3% weight gain followed by a final top-coat of Opadry EZ at 1% weight gain.

Results

a. Metformin ER Tablet Physical Properties:

The metformin ER formulation displayed satisfactory flow properties with good compressibility. Tablets showed good hardness ~24 kP and very low friability ~0.3 % (Table 3).

b. Drug Layering of Sitagliptin onto Metformin ER Tablets:

Drug layered sitagliptin-metformin HCl FDC tablets in Trials 1 and 2 (higher spray rate with 12.5% and 10% solids) produced tablets with a slightly rough surface; whereas drug layered sitagliptin tablets prepared using Trial 3 (low spray rate and 10% solids) had a smooth surface (Figure 1). An additional coating trial (Trial 4) was performed on a 12 kg scale using an ACG Quest TCM machine with the process parameters based on Trial 3 (Table 4). The coated tablets resulting from Trial 4 had a smooth surface appearance (Figure 1).

Table 3. Physical Properties of Powder Blend

Parameters	Metformin HCl ER lubricated Blend
Bulk density, g/ml	0.47
Tapped density, g/ml	0.64
Compressibility index, %	26.4
Hausner ratio	1.36
LOD, %	3.70

Table 4. Drug Layering Process Parameters

Process Parameters	Scale Up Trial 4 Size
Pan load, kg	12
Coating machine	ACG Quest TCM
Pan Size	24L Pan
Number of spray guns	2
Nozzle diameter, mm	1.2
Drug layering dispersion Drug: Opadry Ratio	51.35:48.65
% Weight Gain	20
Coating media	Purified water
% Solids	10
Spray rate, g/min	40-50
Pan speed, rpm	4-5
Inlet air temperature, °C	48-52
Exhaust temperature, °C	42-44
Bed Temperature, °C	41-43
Atomization air pressure, bar	3.0
Pattern air pressure, psi	2.5
Air flow, m3/hr	490-510

Figure 1. Drug Layered Sitagliptin-Metformin HCL ER Tablets

c. Content Uniformity, Assay and Dissolution Testing for Sitagliptin:

Drug layered sitagliptin tablets from Trials 1 and 2 provided acceptance value (AV) of 22 and 23, respectively for CU assay, indicating nonuniform distribution of the drug. However, Trials 3 and 4, in which optimized coating process parameters were used (lower % solids, lower spray rate and higher pan speed) gave lower AV values ~11, indicating the uniform distribution of the drug. (Fig 2). Similarly, sitagliptin content in drug layered and film coated tablets was 100.6 and 101%, respectively. No significant difference in drug release, was observed in drug layered and film coated tablets within 45 minutes of dissolution cycle. (Fig 3), both the portions, drug layer as well as film coated tablet resulted in more than 95% of drug in 45 minutes.

d. Film Coating of Drug Layered Tablets:

Sitagliptin layered metformin ER tablets prepared in Trial 4 were further coated with Opadry II Beige at 3% weight gain followed by Opadry EZ Clear coating at 1% weight gain. Film coated tablets showed smooth and uniform appearance (Figure 4).

e. Assay and Dissolution Testing for Metformin HCl:

The assay content ~ 98.0% was obtained for the metformin ER tablet with no significant difference in release profile for uncoated, drug layered, and final film coated tablets with f_2 values >60 (Figure 5)

Figure 2. Acceptance Values (AV) for Sitagliptin-Metformin ER tablets

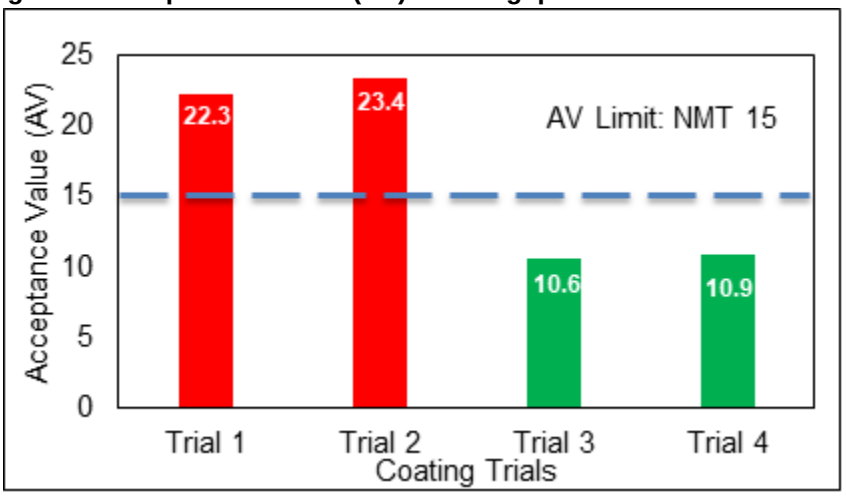


Figure 3. Drug Release Profile of Sitagliptin in Drug Layered vs Film Coated Tablets

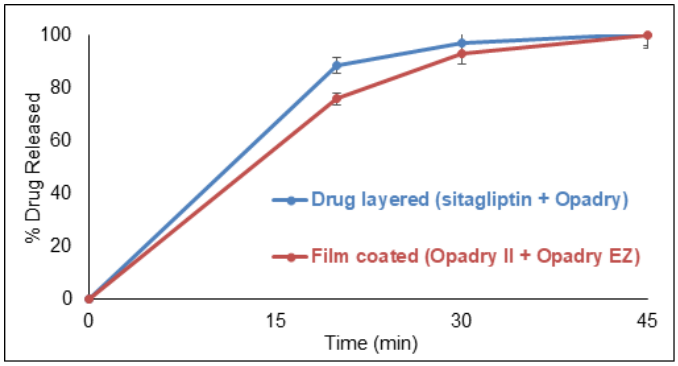
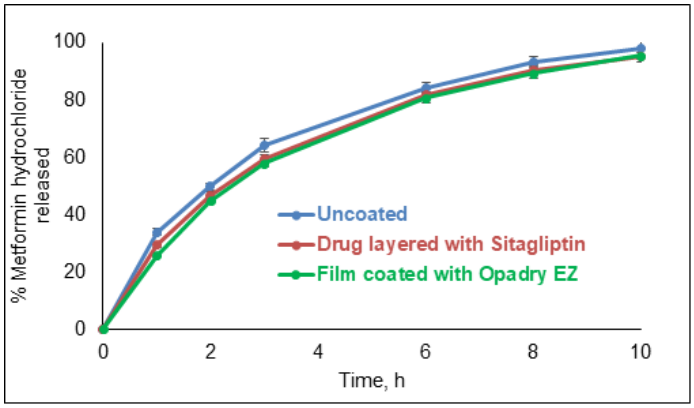


Figure 4. Final Film Coated Sitagliptin-Metformin ER (FDC) Tablets

Figure 5. Release Profiles of Metformin HCl from Uncoated vs Sitagliptin Layered and Coated Tablets



Conclusions

Drug layering of IR sitagliptin (100 mg) over metformin ER core tablets was successfully achieved with the use of an Opadry coating system along with optimization of coating process parameters to achieve a smooth and uniform surface and acceptable CU. Film coating of tablets with Opadry II and Opadry EZ further improved tablet robustness without impacting release profiles of either drug. More than 90% of sitagliptin was released within 45 minutes and the dissolution of metformin remained consistent.

References

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2. Wirges M, Funke A, Serno P, Knop K, Kleinebudde P. Monitoring of an active coating process for two-layer tablets-model development strategies. *J Pharm Sci*. 2013;102(2):556-564. doi:10.1002/jps.23383 https://pubmed.ncbi.nlm.nih.gov/23188659/#:~:text=Monitoring%20of%20an%20active%20coating%20process%20for%20twolayer,a%20method%20mainly%20used%20to%20formulate%20combination%20tablets. Accessed April 21, 2022.

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