Development of High Dose Metformin ER and Low Dose Glimepiride IR as a Bilayer Tablets

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Introduction

Bilayer tablets comprising of two or more actives provide the ability to combine extended and immediate release formulations into a single dosage which helps to improve patient compliance. However, designing this type of formulation involves technical challenges with powder flow, compressibility, and content uniformity for the low dose layer as well as adhesion between the two layers. The purpose of this study was to develop a bilayer tablet containing two APIs: a high dose water-soluble drug (metformin HCl) in an extended release (ER) layer and a model low dose water-insoluble drug (glimepiride) in an immediate release (IR) layer. Tablets were prepared using direct compression of the colored IR layer and a "partial" aqueous granulation of the ER layer. Bilayer tablets were evaluated for their physical attributes, content uniformity, and drug release profiles.

Methods

For the bilayer tablets, the ER layer of metformin HCl (500 mg) used a partial granulation method to hydrate the microcrystalline cellulose (MCC) with the correct amount of moisture content to help increase compressibility, without employing a granulation technique. The IR layer of low dose glimepiride (1 mg) was formulated using a direct compression method. The composition of the individual layers is shown in Table 1.

Table 1. Composition of Bilayer Tablets

Ingredients	% w/w	mg/tablet
Metformin ER Layer (Partial Aqueous Granulation)		
Metformin HCl	71.40	499.80
METHOCEL K100M Premium	23.30	163.10
MCC PH101	4.00	28.00
Colloidal silicon dioxide	0.90	6.30
Magnesium stearate	0.40	2.80
Total ER Layer	100.00	700.00
Glimepiride IR Layer (Direct Compression)		
Glimepiride	0.50	1.00
StarTab, directly compressible starch	33.08	66.16
Lactose monohydrate	65.67	131.34
Iron oxide yellow	0.50	1.00
Magnesium stearate	0.25	0.50
Total IR Layer	100.00	200.00
Total Tablet Weight	--	900.00

Manufacturing of ER layer by partial aqueous granulation: A sufficient quantity of water (~ 3% of the total batch size) was added to MCC during constant mixing. This wetted MCC was then passed through an ASTM # 18 sieve to obtain consistent sizing. The wetted MCC (without drying) was then mixed with metformin, METHOCEL™ K100M and colloidal silicon dioxide.

Manufacturing of IR layer by direct compression. Glimepiride and StarTab®, Directly Compressible Starch were pre-mixed and passed through an ASTM # 40 sieve. Lactose monohydrate and iron oxide yellow were also passed through an ASTM # 40 sieve and mixed with the glimepiride blend.

ER and IR layer components were individually blended for 10 and 20 minutes, respectively in a V-blender and subsequently lubricated for an additional 2 minutes with magnesium stearate (pre-screened through 60 mesh screen).

Compression of bilayer tablets: Tablets were compressed on a rotary bilayer tablet press (Rimek Mini II DL, India) fitted with 2 stations of 16.5 x 8 mm caplet D-tooling. The powder blends and compressed tablets were tested for physical attributes. Tablets were coated in a perforated coating pan (O'Hara Labcoat LCM) using Opadry® QX, Quick and FleXible Film Coating at 3% weight gain using recommended process parameters.

Table 2. Coating Process Parameters

Parameters	Settings
Pan diameter (inches)	8.5
Spray nozzle bore diameter (0.8mm)	0.8
Batch size (g)	300
Solid content (%w/w)	30
Inlet air temperature (°C)	49 – 51
Product bed temperature (°C)	39 – 41
Exhaust air temperature (°C)	39 – 41
Atomization air pressure (bar)	1.2
Pattern air pressure (bar)	1.2
Airflow (m3/hr)	115 – 120
Spray rate (g/min)	3 – 4
Pan speed (rpm)	12 – 15

Release profiles of uncoated and coated bilayer tablets were measured using USP Apparatus II at 100 rpm using 1000 mL of phosphate buffer pH 6.8 for the metformin layer, and USP Apparatus I, 900 mL of phosphate buffer pH 7.8 with 10% sodium lauryl sulfate for the glimepiride layer at 37.0 ± 0.5/1.0°C. Metformin and glimepiride were analyzed spectrophotometrically (233nm) and by high performance chromatography (228 nm), respectively.

Stability Testing – Coated tablets were packaged in 75 cc HDPE bottles, induction sealed and screw-capped. The packed tablets were subjected to stability evaluation for 3 months, at 40°C/75% RH storage condition. The stability of coated tablets was monitored by testing the drug release profile for both metformin ER and the glimepiride IR layer.

Results

Powder blends showed satisfactory powder flow properties for rotary compression (Table 3). Compressed tablets were robust with good hardness (~24 kP), low friability (0.14% at 100 rotations), and good adhesion between the two layers of bilayer tablets (Table 4).

Table 3. Physical Properties of Powder Blend

Parameters	Metformin Blend	Glimepiride Blend
Bulk density (g/ml)	0.47	0.58
Tapped density (g/ml)	0.64	0.71
Compressibility index (%)	26.4	18.61
Hausner ratio	1.36	1.23
LOD (%)	3.70	7.47

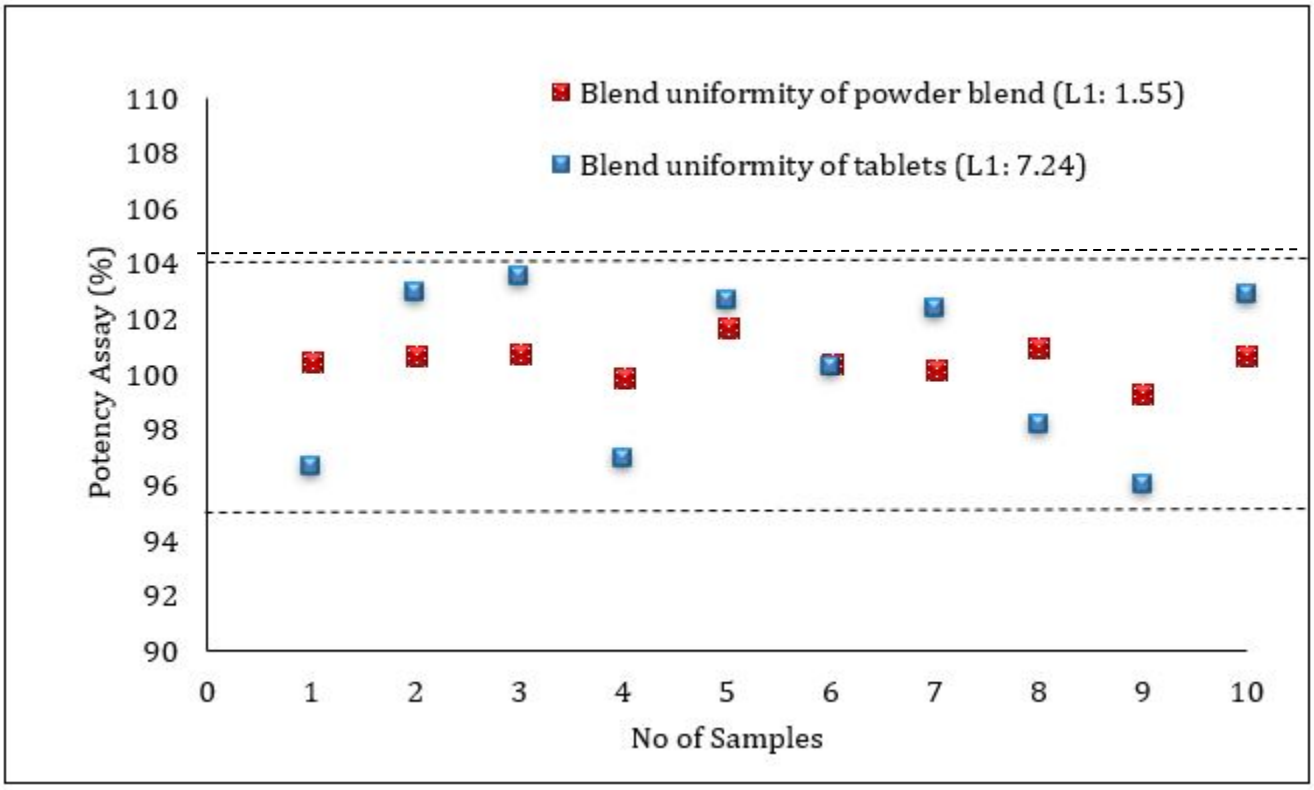
Table 4. Physical Properties of Bilayer Tablets

Parameters	Test Result
Tablet weight variation (mg)	900.0 ± 5.6
Length (mm)	16.5
Width (mm)	8.0
Hardness (kP)	24.3 ± 1.4
Friability at 100 revolutions (%)	0.14
Friability at 200 revolutions (%)	0.63

The partial granulation technique had several benefits over the wet granulation process, including a reduction in overall tablet weight by elimination of binder and reduction in granulation time as there is no additional drying step of the wet granules. The amount of water (corresponding to ~3% of the total batch size) was sufficient to maintain overall LOD close to 4% resulting in the blend having good flow and compressibility (tablet hardness: ~24 kP). METHOCEL™ K100M as a rate-controlling polymer in the metformin ER layer achieved a consistent drug release profile.

StarTab due to its unique particle morphology and excellent flow properties helped improve the distribution of the low dose drug glimepiride. Typically for such low dose drugs, a granulation step may be required for achieving good content uniformity. With target criteria of acceptance value (AV) less than 15 in the L1 stage, the results showed a very promising 1.55 for powder blend and 7.55 for the tablets indicating very good blend uniformity and content uniformity in tablet for the low dose drug. (Figure 1). The average assay of powder blend was 100.5% and for tablets was 100.3%.

Figure 1: Blend Uniformity of Glimepiride IR Layer for Powder Blend and Tablets

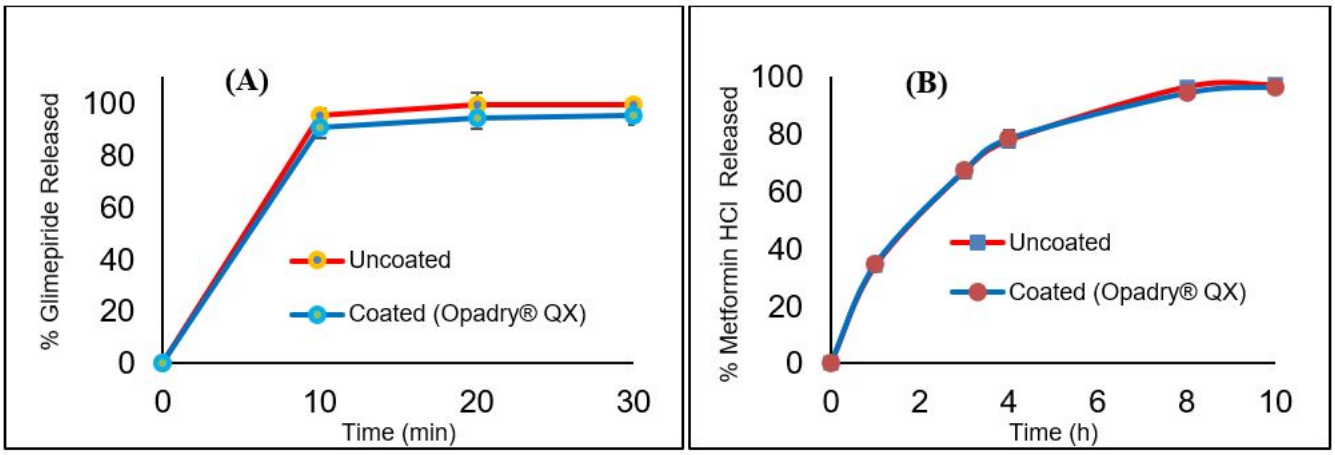


StarTab helped to improve the disintegration of the IR layer, while the presence of lactose in the formulation helped improve the dissolution of the low dose drug glimepiride; with the IR layer providing > 75% drug release in 10 minutes, the tablets coated with Opadry QX showed smooth finish and elegant appearance. (Figure 2). Film coating the bilayer tablets further improved tablet hardness and eliminated friability. The release profiles of metformin ER and glimepiride IR (Figure 3A and 3B) remained unaffected by the coating process (similarity factor f_2 values~90 and ~ 66, respectively).

Figure 2: Metformin ER/ Glimepiride IR Bilayer Tablets

Uncoated **Coated with 3% Opadry QX**

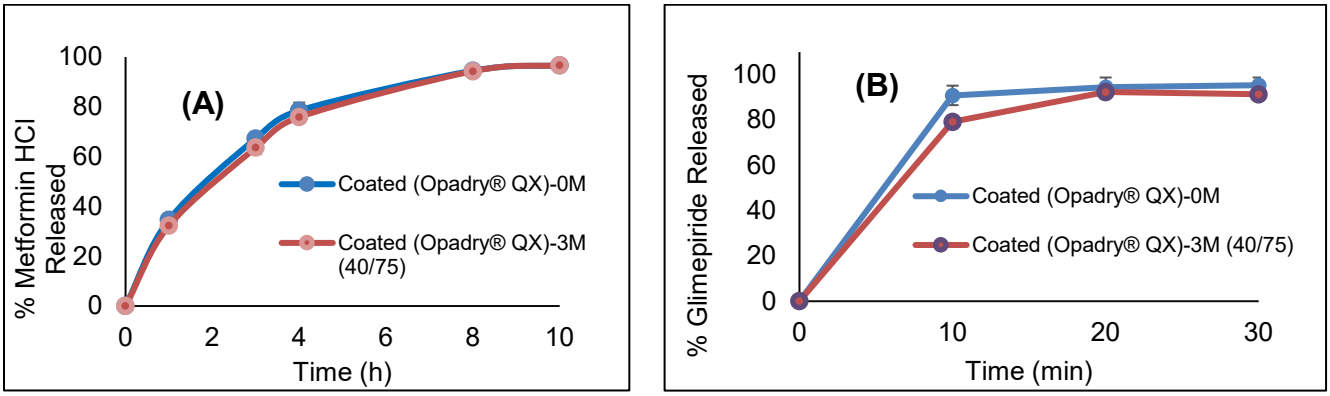
Figure 3: Release Profiles of (A) IR Glimepiride and (B) ER Metformin HCl from Uncoated and Coated Bilayer Tablets



Stability Testing

The results of accelerated stability studies at 3 months showed no significant change in drug release profiles for either metformin ER or glimepiride IR layer (Figure 4a and 4b), confirming that the final dosage forms were stable in accelerated conditions.

Figure 4: Release Profiles of (A) ER Metformin HCl and (B) IR Glimepiride, Coated Bilayer Tablets stored at 40°C/75% RH



Conclusions

The bilayer tablets demonstrating the desired physical attributes and release profiles were successfully developed and coated with Opadry QX. A partial granulation technique was successfully employed for the metformin ER layer, with direct compression formulation for the low dose drug glimepiride providing good blend uniformity. The powder blends for both layers exhibited good flow and compression properties on a rotary bilayer tablet press. The tablets exhibited good hardness and low friability, without layer separation, and demonstrated good content uniformity for the low dose drug glimepiride. Film coating improved the overall robustness of the tablets without impacting the release profiles of both drugs. More than 75% of glimepiride was released in 10 minutes (IR) and more than 90% metformin was released in 8 hours, as anticipated for extended-release profile and the formulation remained stable over the period of 3 months at accelerated storage conditions in all the above quality attributes.

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