Fixed Dose Combination of Metformin ER and Glipizide IR Bilayer Tablets Using Directly Compressible Excipients

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Introduction

Fixed dose combinations (FDC) are a unique platform that combines two or more actives into a single dosage form. This technology offers benefits such as reducing tablet burden to improve patient adherence while also providing pharmaceutical companies new product patent and market exclusivity opportunities. Bilayer tablets are commonly used for FDC marketed products. Formulation development and manufacturing of FDC products with two distinct active pharmaceutical ingredients (API) that have different solubility, dissolution, dose, powder flow, and/or compressibility, present increased challenges compared to standard formulations containing one API. The purpose of this study was to evaluate various formulation aspects of FDC bilayer tablets containing two model API; a high dose water-soluble drug (metformin HCl) in an extended release (ER) layer and a low dose water-insoluble drug (glipizide) in an immediate release (IR) layer, using direct compression.

Methods

Bilayer tablets containing an ER layer with high dose metformin HCl granules (500 mg) (Compresso MF 95P, Granules USA) and an IR layer with low dose glipizide (5 mg) (Medilom, Belgium) were formulated for direct compression.

Manual Tablet Screening Study

Using a range of excipients, various FDC compositions (Table 1) were separately bottle blended for 10 minutes for each layer, then lubricated for 3 minutes followed by compression using a manual tablet press (MTCM I, Global Pharma) fitted with 19 x 8.3 mm caplet B-tooling. The metformin ER layer was lightly compressed (500 psi), followed by incorporation of the glipizide IR layer; with final compression performed at 4000 psi.

Table 1. Composition of Manually Compressed FDC Tablets

FDC Bilayer Tablet	Effect of IR layer weight			Effect of filler and surfactant on IR Layer			Effect of % of polymer and filler on ER Layer			
Formula	**A**	**B**	**C**	**D**	**E**	**F**	**F'**	**G**	**H**	**I**
Material	% w/w									
Glipizide IR Layer							Glipizide IR Layer was constant			
Glipizide (5mg dose)	5.00	2.50	1.67	1.67	1.67	1.67	1.67			
Sodium Lauryl Sulfate	---	---	---	1.00	1.00	1.00	1.00			
StarTab	94.25	96.75	97.58	96.58	48.29	48.29	48.29			
Avicel PH 102	---	---	---	---	---	48.29	48.29			
Lactose Monohydrate	---	---	---	---	48.29	---	---			
Iron Oxide Red	0.25	0.25	0.25	0.25	0.25	0.25	0.25			
Magnesium Stearate	0.50	0.50	0.50	0.50	0.50	0.50	0.50			
Total IR Layer	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***	***100.00***			
Metformin ER Layer	Metformin ER layer was constant									
Metformin HCl DC Granules*	53.00						53.00	53.00	53.00	53.00
METHOCEL K100M DC2	30.00						30.00	30.00	35.00	40.00
StarTab	16.50						16.50	---	---	---
Avicel PH 102	---						---	16.50	11.50	6.50
Magnesium Stearate	0.50						0.50	0.50	0.50	0.50
Total ER Layer	***100.00***						***100.00***	***100.00***	***100.00***	***100.00***
Weight of IR Layer (mg)	**100**	**200**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**
Weight of ER Layer (mg)	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**	**1000**
Total Tablet Weight	**1100**	**1200**	**1300**	**1300**			**1300**			

*Formulation F and F' are same; *Metformin DC granules has ~95% assay and added at an amount equivalent to 500 mg dose per tablet*

Rotary Bilayer Tablet Compression and Film Coating

Optimal formulations (Table 2) were separately blended for 10 min (ER layer) and 30 min (IR layer) in a V-blender, and then lubricated for an additional 3 minutes with magnesium stearate (pre-screened through 60 mesh sieve). FDC tablets were compressed on a rotary bilayer tablet press (Piccola, Riva) fitted with 2 stations of 19 x 8.3 mm caplet B-tooling, at 15 rpm turret speed, 2.5 kN (pre) and 30 kN (main) compression forces. Tablets were coated in a perforated coating pan (O'Hara Labcoat I) using two different Opadry® complete film coating systems (HPMC and PVA based) at 3% weight gain, using the process parameters listed in Table 3.

Table 2. Composition of FDC Formulations Compressed using Rotary Bilayer Tablet Press

FDC Bilayer Tablet	Formulation	
Material	**% w/w**	**mg/ tablet**
Glipizide IR Layer		
Glipizide	1.67	5.00
Sodium Lauryl Sulfate	1.00	3.00
Avicel PH 102	48.29	144.87
StarTab	48.29	144.88
Blue pigment	0.25	0.75
Magnesium Stearate	0.50	1.50
Total IR Layer	***100.00***	***300.00***
Metformin ER Layer		
Metformin HCl DC Granules	53.00	530.00
METHOCEL K100M DC2	30.00	300.00
Avicel PH 102	16.50	165.00
Magnesium Stearate	0.50	5.00
Total ER Layer	***100.00***	***1000.00***
Total Tablet Weight	**---**	**1300.00**

Table 3. Coating Systems and Parameters

Coating System	Opadry Clear HPMC-based	Opadry II 85F Clear PVA-based
Solid Content (% w/w)	10	10
Weight gain (%w/w)	2	3
Pan Speed (rpm)	13	13
Air Volume (CFM)	154	138
Atomizing Air Pressure (psi)	20	20
Pattern Air Pressure (psi)	20	20
Spray Rate (g/min)	10-11	7-8
Inlet Temp (° C)	70	60
Exhaust Temp (° C)	42-43	39
Product Temp (° C)	36-37	33-35

Dissolution

Dissolution testing was performed using USP Apparatus II (Agilent) at 100 rpm in 1000 mL of phosphate buffer pH 6.8 for the metformin layer, and 500 mL of phosphate buffer pH 6.8 for the glipizide layer at 37°C. Metformin and glipizide were analyzed spectrophotometrically at 233 nm and 276 nm, respectively.

Results

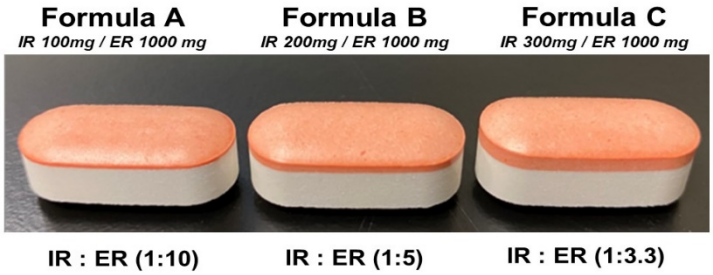
Manual Bilayer Tablet Compression Screening Study

The screening study included fixed compositions of the metformin ER layer and glipizide IR layer while evaluating the effect of formulation variables on the release of metformin or glipizide, respectively.

Effect of IR Layer Weight

The total IR layer weight was set at 100, 200 and 300 mg, while ER layer was constant at 1000 mg. This represented IR: ER ratios of 1: 10 (Formula A), 1: 5 (Formula B) and 1: 3.3 (Formula C), respectively (Figure 1). Formula C was found to provide an optimal IR layer thickness and was selected for further formulation trials. Although Formula C gave the highest glipizide release profile compared to Formula A and B, all three formulations had significantly low dissolution profiles (Figure 2A) due to poor solubility of glipizide. This indicated that the glipizide formulation needs to be modified to improve the dissolution rate. Additionally, metformin ER dissolutions were similar for formula A and B, and slightly slower for formula C (Figure 2B). These results demonstrated that the weight and thickness of the glipizide layer may influence the rate of metformin layer release.

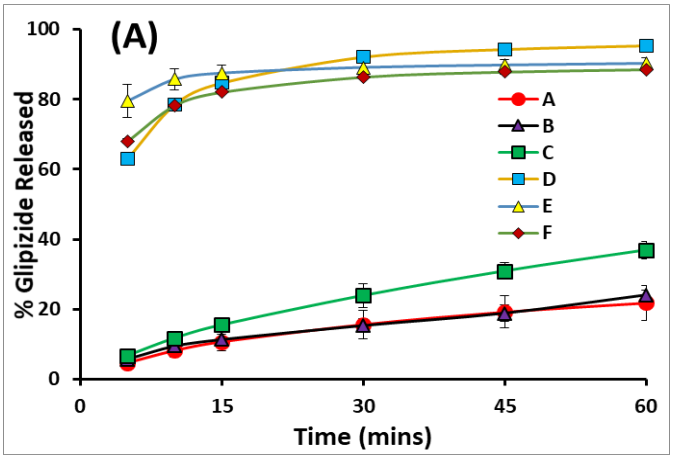
Figure 1. Glipizide IR / Metformin HCl ER FDC Tablets with Different IR Layer Weight

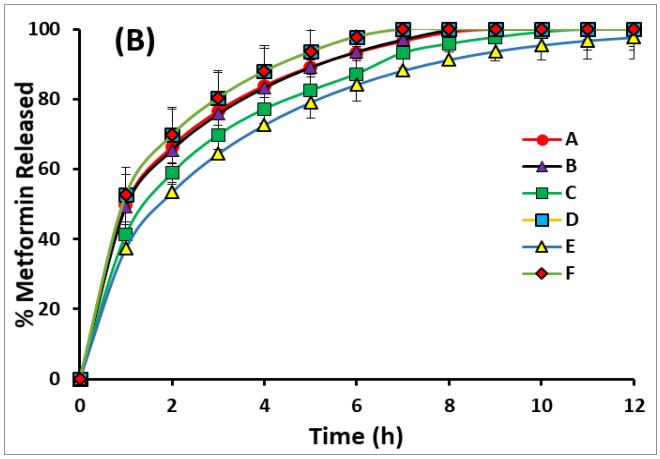


Effect of Fillers and Surfactant in IR Layer

The incorporation of surfactant improved the dissolution of glipizide significantly. Formula D, E and F all gave > 80% release at 45 minutes (Figure 2A) and met USP dissolution specifications. Metformin drug release was significantly affected due to the type of filler used in the IR layer. Formula D and F produced similar release profiles that were faster compared to formula E (Figure 2B). None of the metformin release profiles met USP dissolution specifications.

Figure 2. Effect of IR Layer Formulation Variables on Release Profiles of (A) IR Glipizide and (B) ER Metformin HCl, from Uncoated FDC Formulation

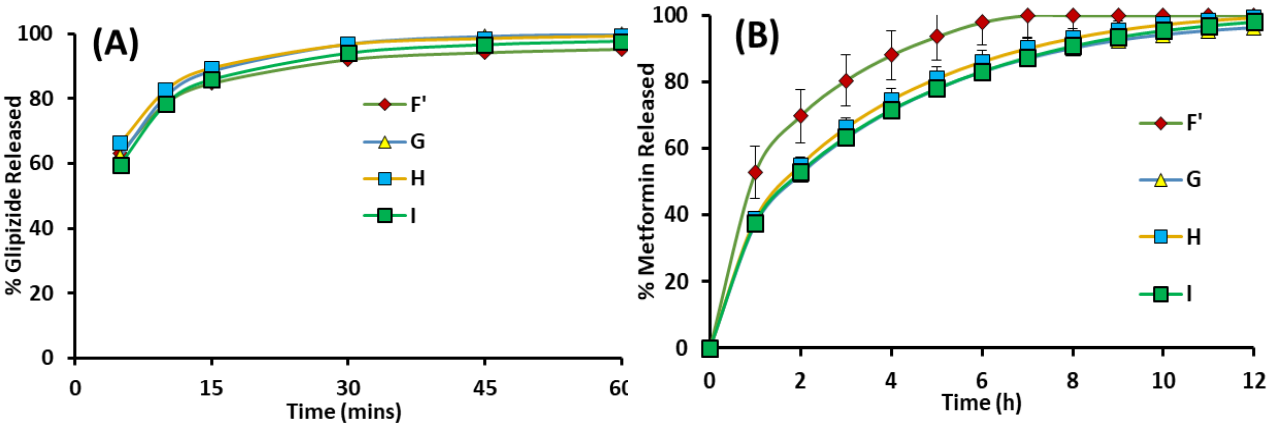




Effect of Filler Type and Polymer Content on ER Layer

In this part of the study, the glipizide IR layer composition was kept constant while the ER layer composition varied. As shown in Figure 3A, changes in the ER layer for filler type and with increasing amounts of METHOCEL™ K100M DC2, the glipizide release profiles did not change and the formulations released > 80% of the drug in 45 minutes. Metformin ER release, however, was affected by the type of filler. The inclusion of MCC (Formula G) in the ER layer gave a lower release profile, whereas the inclusion of StarTab® directly compressible starch (Formula F) in ER layer resulted in faster drug release (Figure 3B). Additionally, increasing levels of METHOCEL™ K100M DC2, in combination with MCC as the filler, did not further reduce the drug release. Hence, Formula G was chosen for the rotary bilayer tableting process.

Figure 3. Effect of ER Layer Formulation Variables on Release Profiles of (A) IR Glipizide and (B) ER Metformin HCl, from Uncoated FDC Formulation Compressed on Manual Tablet Press



Rotary Bilayer Tablet Compression and Film Coating

All formulation blends demonstrated good powder flow properties for rotary compression (Table 4). The tablets were coated with clear coatings using optimal process conditions to give smooth, shiny and defect-free coated tablets (Figure 4). Bilayer tablets were robust with good hardness, low friability (Table 5) and did not show any visible defects such as uneven interface lining or color bleed through. Release profiles of glipizide IR were slightly affected due to the incorporation of film coating (Figure 5A), however, drug release in all the tablets was more than 80% in 45 minutes. The presence of a film coating did not affect the release profiles for metformin ER (Figure 5B).

Table 4. Powder Properties of the Formulation Blends

Powder Property	Metformin Blend	Glipizide Blend
Bulk density (g/mL)	0.46	0.48
Tapped Density (g/mL)	0.58	0.57
Carr's Index	20.0	16.2
Hausner Ratio	1.25	1.19
LOD%	3.60	9.77

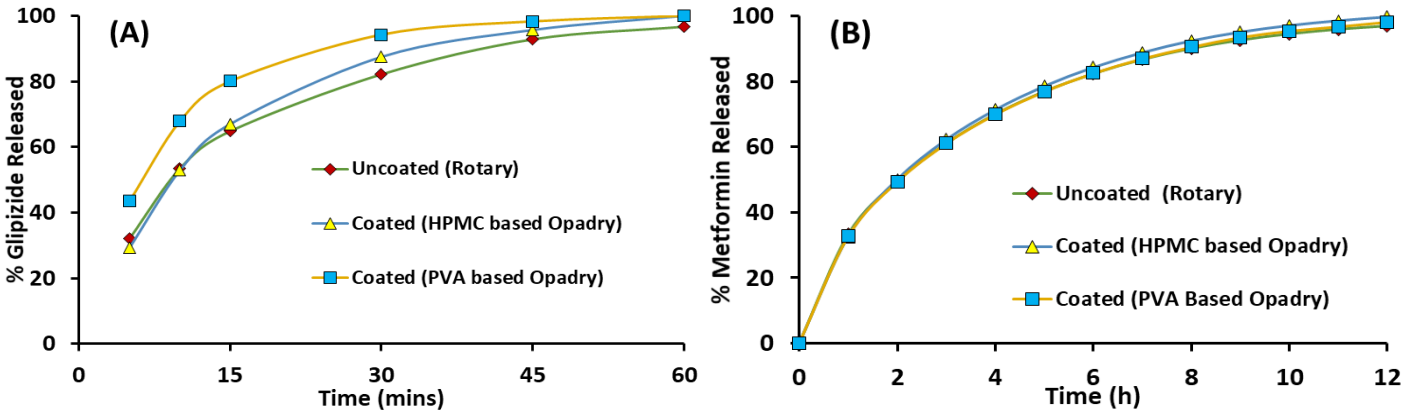
Figure 4. Glipizide IR / Metformin HCl ER FDC Prepared by Rotary Bilayer Tablet Press

Table 5: Physical Properties of Metformin HCl ER and Glipizide IR FDC Tablets

Physical Property N=10 tablets	Uncoated Tablet	Coated w/ Opadry Clear	Coated w/ Opadry 85F Clear
Tablet weight (mg)	1293.6 ± 12.7	1321.4 ± 19.7	1341.8 ±14.6
Hardness (kP)	27.9 ± 1.3	45.0*	38.9 ± 1.3
Thickness (mm)	8.51 ± 0.05	8.70 ± 0.04	8.80 ± 0.05
Friability, 300 rev (%)	0.23%^	0	0

**out of limit for hardness tester; ^300 revolution in a friability tester did not cause any capping or layer separation. All the bilayer tablets were intact.*

Figure 5. Release Profiles of (A) IR Glipizide and (B) ER Metformin HCl, from Uncoated and Coated FDC Formulation Compressed on Rotary Bilayer Tablet Press



Conclusions

Fixed-dose combination bilayer tablets with a high dose ER layer of metformin HCl (500 mg) and a low dose IR layer of glipizide (5 mg) were successfully developed. Powder blends provided good flow and compression properties on a rotary bilayer tablet press. Film coating of tablets further enhanced tablet robustness while not affecting the release profiles of either drug. Glipizide IR release was more than 80% in 45 minutes and the release of metformin ER was consistent for extended release.

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