Metformin HCl 1000 mg ER – Formulation Approaches to Improve Patient Acceptability

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Introduction

Metformin HCl extended release formulation is one of the most successful and popular ways to control hyperglycemia through maintaining effective drug plasma concentration over a long period thus reducing frequency of dosing.[1] Extended release (ER) formulation of 1000 mg doses of metformin HCl often have higher tablet weight (1500 mg) which may impact patient compliance. Reducing the weight, and subsequently, the size of such tablets could enhance patient acceptability, increase manufacturing productivity and reduce cost. The purpose of this work was to investigate the feasibility of formulating metformin HCl 1000 mg, using direct compression, with reduced tablet weight and application of an easy swallow film coating to improve swallowing, still achieving desired ER profiles.

Methods

Metformin HCl (1000 mg) ER hydrophilic matrices were manufactured according to the formulation in Table 1 using direct compression. A directly compressible grade of metformin HCl (Compresso MF 95P, Granules India), was screened through ASTM #18 mesh sieve. Separately, directly compressible grades of other ingredients, METHOCEL™ K100M DC2, METHOCEL™ K4M DC2 and MCC (90 µm), were screened through ASTM #40 sieve. The sieved material was blended for 10 minutes in a double cone blender and then lubricated with magnesium stearate (previously screened through ASTM 60# sieve) for an additional 2 minutes. The final blend was compressed on a single rotary tablet press (Rimek, Mini Press II) fitted with 19 x 9 mm oval standard concave tablet tooling at a target tablet weight of 1290 mg. The matrix tablets were then barrier membrane (BM) coated (Table 1) to 9% theoretical weight gain (WG), using a fully perforated side-vented pan coater (Lab Coat, O'Hara). Coated tablets were sampled at intermediate weight gains and evaluated for their drug release profiles. Final BM coated tablets (9% WG) were top-coated with Opadry® EZ clear at 2% WG (BM + EZ Clear). Process parameters for BM coating and Opadry EZ film coating are shown in Table 2.

Dissolution testing

Metformin HCl ER tablets were tested using 900 mL phosphate buffer pH 6.8 at 37ºC, in a USP I (basket) apparatus at 100 rpm. Drug release was analysed spectrophotometrically at 250 nm. The dissolution test results were compared with USP 40 monograph test #5 specification for compliance.[2]

Table 1. Composition of Metformin HCl ER Tablets, 1000 mg

Ingredients	% w/w	mg / tablet
Hydrophilic matrix core tablet		
Metformin HCl, DC grade (Granules)	81.60	1052.64
METHOCEL™ K100M DC2 (DuPont)	8.28	106.81
METHOCEL™ K4M DC2 (DuPont)	4.66	60.12
Avicel PH 102, MCC (DuPont)	4.96	63.98
Magnesium stearate (Ackros)	.50	6.45
Core Tablet Weight	100.00	*1290.00*
Barrier membrane (BM) coating		
Surelease E-7-19040 (Colorcon)	6.75	87.07
Opadry (Colorcon)	2.25	29.02
Purified water to make 10% w/w solids content	Q.S.	
BM coated tablet weight	109.00	1406.10

Note: ^ 1052 mg of Compresso MF95P was equivalent to 1000 mg of metformin HCl (based on 95% assay).

Table 2. Barrier Membrane (BM) and Film Coating Process Conditions

Process Parameter	BM Coating (Surelease + Opadry Pore-former)	Film Coating (Opadry EZ Clear)
Pan size (inch)	12	8.5
Spray equipment	970/& - 1S75, 1.2 mm nozzle, ABC cap (Schlick)	970/& - 1S75, 0.9 mm nozzle, ABC cap (Schlick)
Total dispersion solid content (% w/w)	10	08
Theoretical coating weight gain (%)	3 to 9	2
Pan charge (kg)	0.7	0.3
Pan speed (rpm)	11 – 12	10
Inlet air temperature (ºC)	56 – 59	58 – 62
Pattern air pressure (psi)	20 – 25	18 – 20
Air volume (m3/hr)	125 – 150	90 – 110
Atomizing air pressure (psi)	20 – 25	18 – 20
Gun to bed distance (cm)	8	5
Product bed temperature (ºC)	43 – 45	43 – 44
Spray rate (g/min)	5 – 6	1 – 2

Results

Direct compression using Methocel DC2

For a low tablet weight formulation, using the powder form of metformin HCl often requires a wet granulation process.[3] However, in this work, directly compressible grades of metformin HCl and hypromellose (METHOCEL™ K4M DC2 and K100M DC2) were utilized. The lubricated formulation blend showed good powder flow (Table 3) and easily flowed on the rotary tablet press using gravity feeder with very low variation in tablet weight, hardness and thickness (Table 4). Tablet cores of around 1290 mg were achieved without any defects and with suitable mechanical strength for coating. Uncoated core tablets of metformin HCl exhibited an initial burst of drug due to high solubility of the API (Figure 1).

Table 3. Powder Properties of Metformin HCl Formulation Blend

Powder Property	Lubricated Blend
Bulk density, g/ mL	0.55
Tapped Density, g/ mL	0.69
Compressibility Index, %	20.37
Hausner Ratio	1.25
LOD, %	2.95

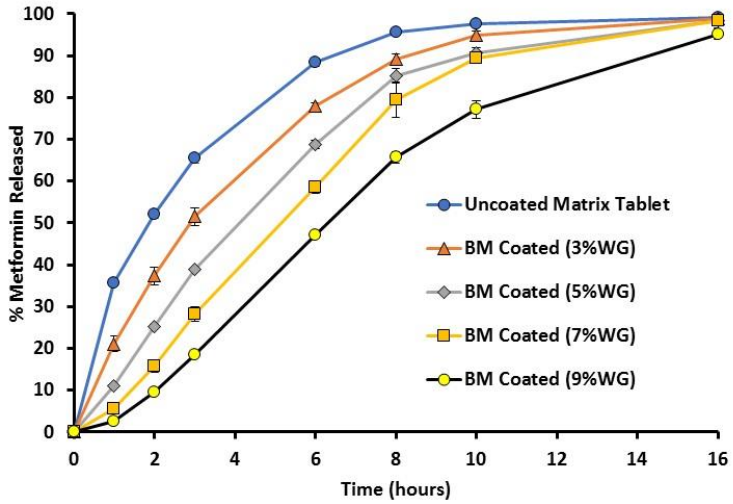
Table 4. Physical Properties of Uncoated Metformin HCl ER Core Tablets

Physical Property	Metformin HCl ER Core Tablet
Tablet weight, mg (n = 10)	1289.3 $\pm$ 2.0
Hardness, kP (n = 6)	17.0 $\pm$ 8.8
Thickness, mm (n=10)	9.5 $\pm$ 0.0
Friability at 100 revolution	0.21%

Barrier membrane coating using Surelease

In earlier work[3], barrier membrane coating of hydrophilic matrix tablets containing highly soluble API successfully resulted in reducing the burst effect. In this study, the matrices were also barrier membrane coated up to 9% WG and inclusion of pore-former at 25% w/w provided flexibility in modulating drug release profile. Higher weight gains ensured uniform coating film thickness, especially at tablet edges. Figure 1 shows dissolution profiles for the matrices, where drug release is slower with increasing weight gain of BM coating. Tablets coated with 9% WG of BM coating complied with USP monograph test # 5 dissolution specification.

Figure 1. Drug Release Profiles from Uncoated and BM- Coated Metformin HCl Hydrophilic Matrix Tablets



Easy swallow film coating using Opadry EZ

BM coated tablets were top-coated with 2% w/w Opadry EZ clear to improve their wet slip and swallowability. Resulting top-coated tablets did not impact dissolution (Figure 3) and were seen to be

smooth, shiny and free of any defects (Figure 2). The top-coating with Opadry EZ provides high slip when the tablets are wet, helping to ease swallowability of tablets.[4-5]

Figure 2. Metformin HCl ER Tablets (A) Uncoated core, (B) BM Coat (9% WG), (C) BM Coat + 2% Opadry EZ Clear

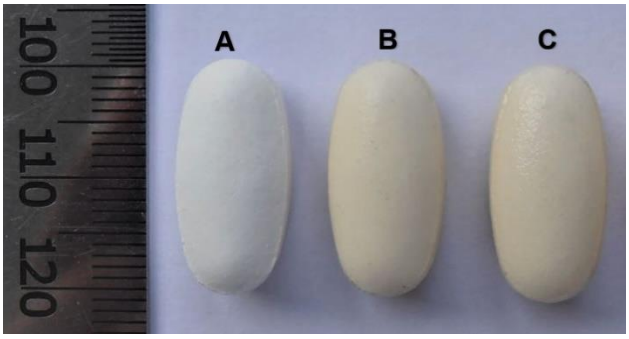
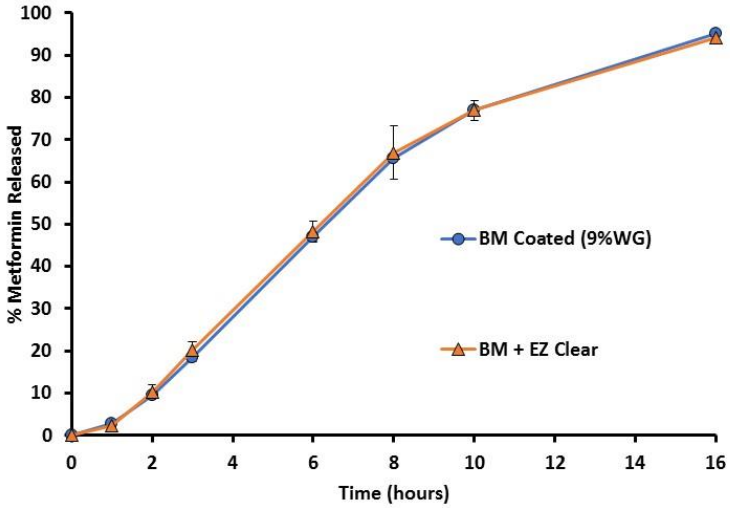


Figure 3. Dissolution Profiles of BM Coat + Opadry EZ Top-coat Metformin HCl ER Tablet



Conclusions

The results demonstrate that two major formulation challenges: poor powder flow and burst release of a highly soluble drug from a reduced weight tablet could be addressed by using directly compressible grades of drug and polymer (METHOCEL™ DC2), along with barrier membrane coating. Reducing tablet weight and applying Opadry EZ as top-coat could collectively enhance patient acceptability.

References

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