Approaches to Reduce the Weight of Extended Release Tablets: Metformin HCl

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Purpose

Extended release (ER) matrix formulations of high dose drugs result in large tablets, which may affect patient acceptability and compliance. For example, metformin HCl ER formulations comprise a high dose (500-1000 mg) with high tablet weights (1000-1500 mg). Reducing the weight of such tablets can improve patient compliance, increase productivity and reduce overall cost to pharmaceutical manufacturers. Reduction in tablet weight and size may cause issues in powder flow and compressibility as well as change in the release profile that no longer complies with dissolution test specifications. The purpose of this study was to identify formulation approaches for reducing the weight of 500 mg dose metformin HCl ER tablets, as a model drug, and understand practical options to maintain ER performance while reducing the weight of the tablets. An evaluation was made into primary compliance of the release profiles for the different formulation options to various dissolution test specifications in the USP 39.[1]

Methods

Tablet Production – Polymer Blends

Metformin 500 mg hydrophilic matrices were manufactured by dry blending metformin HCl powder with other components, including 300 mg of polymer, in 20 g batches as shown in Table 1. Tablets were produced using 14.2 mm round standard concave tooling using a manual tablet press (MTCM-1, Globe Pharma, USA) at a target piston force of 4000 psi.

Table 1: Tablet Composition (mg per tablet) of Metformin HCl Matrices

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Metformin HCl (Medilom, Belgium)	500	500	500	500	500	500	500	500	500
Hypromellose (METHOCEL™ K100M Premium CR, Dow)	300	---	---	---	---	---	---	---	---
Hypromellose (METHOCEL™ K200M Premium CR, Dow)	---	300	300	150	150	150	225	150	225
Various polymers*	---	---	---	---	150	---	---	---	---
Ion Exchange Resin (AMBERLITE™ IRP69 or AMBERLITE™ IRP 88, Dow)	---	---	---	---	---	150	75	---	---
Carbomer polymer (Carbopol 971P or Carbopol 974P, Lubrizol)	---	---	---	---	---	---	---	150	75
MCC (90 Microns)	200	200	---	---	---	---	---	---	---
Total tablet weight	**1000**	**1000**	**800**	**650**	**800**	**800**	**800**	**800**	**800**
Total polymer concentration (%)	30.0	30.0	37.5	23.1	37.5	37.5	37.5	37.5	37.5

Tablet Production and Coating – Barrier Membrane Coated Matrices

Metformin 500 mg hydrophilic matrices were manufactured at 18.4% w/w polymer level blending a directly compressible, granular grade of metformin HCl with a high molecular weight grade of HPMC in 1.0 kg batches as shown in Table 2. Tablets were produced using 11.1 mm round concave tooling on an instrumented rotary tablet press (Piccola, Riva, Argentina) at a turret speed of 30 rpm, targeting a tablet breaking force of 15 kN. The tablets were then coated using process parameters shown in Table 3 with a barrier membrane formulation comprising 75% of a fully formulated ethylcellulose film coating (Surelease®, Ethylcellulose Dispersion Type B NF) and 25% of a water-soluble film coating (Opadry®, Complete Film Coating System) as a pore-former.

Table 2: Tablet Composition (mg per tablet) of Barrier Membrane Coated Matrices

Ingredients: Hydrophilic Matrix Core Tablet	F10
Metformin HCl DC Grade (Granules USA)	530
Hypromellose (METHOCEL™ K200M Premium CR, Dow)	120
Total tablet weight	**650**
Hydrophilic polymer concentration (%)	*18.4*
Barrier membrane coating*	
Surelease (aqueous ethylcellulose dispersion, 25% solid content)	195.0
Opadry	16.3
Purified Water#	222.1

Table 3: Barrier Membrane Coating Process Conditions

Coating equipment	Labcoat 1 (O'Hara, Canada)
Pan size (inch)	12
Total dispersion solid content	15% w/w
Theoretical coating weight gain (%)	2, 4, 6, 8, 10
Spray equipment	1/8 VAU, 1.2 mm nozzle (Spraying Systems, USA)
Pan charge (kg)	1.0
Pan speed (rpm)	20
Inlet air temperature (°C)	54 – 56
Exhaust air temperature (°C)	45 – 48
Pattern air pressure (psi / bar)	20 / 1.4
Air volume [CFM / (m3/hr)]	170 / 289
Atomizing air pressure (psi / bar)	20 / 1.4
Product temperature (°C)	43 – 45
Fluid delivery rate (g/min)	6.8

Dissolution Testing

Dissolution testing was conducted using USP Apparatus II (paddle) at 100 rpm with sinkers in 1000 mL of either deionized water or phosphate buffer pH 6.8 at 37°C. Release profiles were measured spectrophotometrically at a wavelength of 233 nm. The release profiles were also checked for initial compliance to various dissolution test specifications as per USP 39 monograph on metformin HCl ER tablets (Table 4).

Table 4: Dissolution Test Method and Specifications for Metformin HCl ER Tablets, USP 39

USP Test no.	1	2	3	4	5*	6	7	8	9	10	11	12*
	Dissolution Test Methods											
Dose of Metformin HCl	500mg	Not specified	500 mg	Not specified	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg
Apparatus no.	2	2	2	2	1	2	2	2	2	2	2	1
Speed (rpm)	100	100	100	100	100	100	50	100	100	100	100	100
Media volume (mL)	1000	1000	1000	1000	900	1000	1000	1000	1000	1000	1000	1000
pH of media	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8
Time (h)	Dissolution Test specifications (%)											
1	20-40	20-40	20-40	20-40		20-40	20-40	20-40	20-40	25-45	25-45	NMT 15
2	--	35-55	35-55	--	NMT 30	--	--	30-50	--	--	--	--
3	45-65	--	--	45-65	--	45-65	45-65	--	--	50-70	50-70	--
4	--	--	--	--	--	--	--	--	--	--	--	35-65
5	--	--	60-80	--	--	--	--	--	45-65	--	--	--
6	--	65-85	--	65-85	--	--	--	65-85	--	--	--	--
8	--	--	--	--	60-85	--	--	--	--	--	--	--
10	NLT 85	NLT 85	--	NLT 85	--	NLT 85	NLT 80	NLT 85	--	NLT 85	NLT 80	--
12	--	--	NLT 85	--	--	--	--	--	70-90	--	--	NLT 85
16	--	--	--	--	NLT 90	--	--	--	--	--	--	--
20									NLT 85	--	--	--

Results

A) Change of Viscosity Grade of Hypromellose and Change in Tablet Size

Earlier studies have shown that metformin HCl 500 mg ER formulations containing 30% METHOCEL™ K100M, with total tablet weight of 1000 mg, gave release profile similar to a commercially available reference ER product.[2] Similar release profile was obtained from formulation containing 30% METHOCEL™ K15M (data not shown here)[3]. Formula 1, 2 and 3 contained different high viscosity grades of hypromellose and different tablet weights. The polymer content was kept constant, with the total tablet weight altered by changing quantity of filler. Figure 1 shows the release profiles of all these formulations were similar. Table 5 demonstrates that formula 1 and 2 showed compliance to various dissolution test specifications when the tablet weight was 1000 mg. However, when the tablet weight was reduced to 800 mg (formula F3), the dissolution profiles complied with fewer test specifications compared to formula F1 and F2. This was a result of increase in surface area to volume ratio with decreasing tablet weight.[4]

B) Blend of Hypromellose with Various Polymers or Resins

Various formulations were prepared to have a ratio of K200M with different polymers in 50:50 or 75:25 ratios. POLYOX™ (polyethylene oxide), a non-ionic polymer or anionic polymers (e.g. xanthan gum, sodium carboxymethyl cellulose, sodium alginate, locust bean gum, carrageenan, guar gum, acacia or carbomer) or ion exchange resins (e.g. AMBERLITE™ IRP 69, sodium polystyrene sulfonate or IRP 88, polacrilin potassium) were combined with METHOCEL™ K200M to maintain a total tablet weight of 800 mg. Formula F7 (containing Amberlite IRP 69, or IRP 88) and formula F8 (containing Carbomer 971 or 974 grades), gave good release profiles (Figures 2 and 3), complying with various dissolution test specifications (Table 5). All other formulations with various polymer combinations failed to comply with any dissolution test specifications at 800 mg tablet weight.

Figure 1: Metformin HCl Release from Conventional Single Polymer Formulation at Reduced Filler and Polymer Content

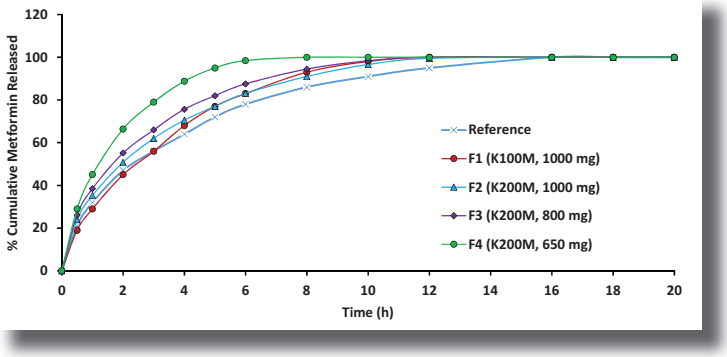


Figure 2: Metformin HCl Release from Formulations Containing Blends of Hypromellose and Ion Exchange Resin

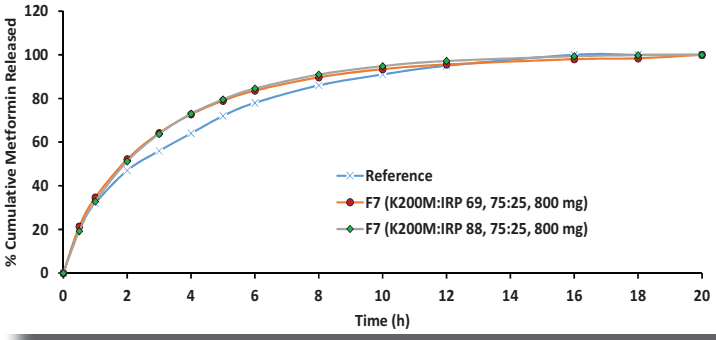
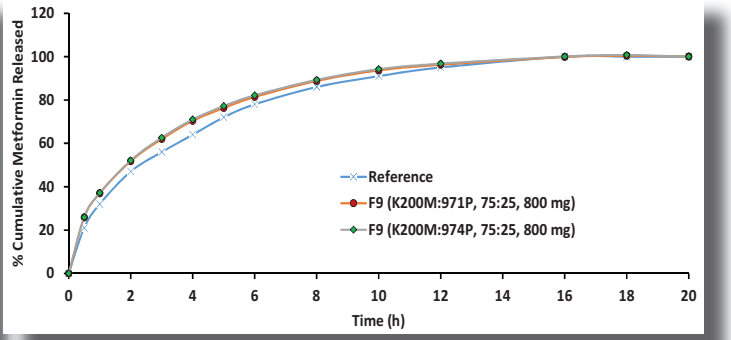


Figure 3: Metformin HCl Release from Formulations Containing Blends of Hypromellose and Carbomer



C) Barrier Membrane Coated Matrices

Previous studies have shown that barrier membrane coated matrices provide effective control over burst release of drugs.[5] Weight gain of barrier membrane coating and tablet shape all have a strong influence in attaining desired drug release.[6] The use of barrier membrane coatings provided effective retardation of drug release from metformin HCl matrix tablets produced at polymer levels and tablet weights far below those used in the single polymer or polymer blend formulations. Reducing polymer content below this range to 18.4% (formula F10) resulted in tablets with uncoated weight of 650 mg. Burst release of drug from these uncoated tablets could be prevented by application of barrier membrane coating. Further drug release modulation was possible by increasing coating weight gain (Figure 4). Drug release from tablets coated with different weight gains complied with different dissolution test specifications (Table 5). It was seen that when the coating weight gain was increased, there was increase in lag time of drug release in initial test condition.

Figure 4: Metformin HCl Release from Matrices Containing 18.4% Hypromellose and Coated with Barrier Membrane at Different Weight Gains

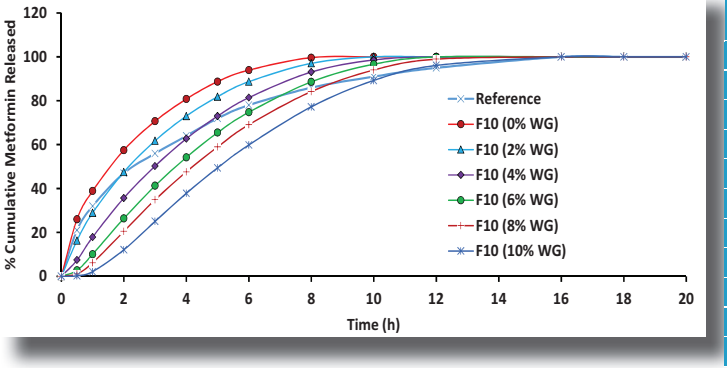


Table 5: Summary of Various Experimental Formulations Showing Primary Compliance to Different Dissolution Test Specification for Metformin HCl ER Tablet Monograph[1]

Formulation	Polymer	% WG BM Coating	Total Hydrophilic Polymer Content (%)	Core Tablet Weight (mg)	Compliance to Test Number for Metformin HCl ER Tablets[2]
Reference	Marketed product (USA)	N/A	~ 30.0	1020	1, 2, 3, 4, 6, 7, 8, 10, 11
F1	K100M CR	N/A	30.0	1000	1, 2, 3, 4, 6, 7, 8, 10, 11
F2	K200M CR	N/A	30.0	1000	1, 2, 3, 4, 6, 7, 10, 11
F3	K200M CR	N/A	37.0	800	10, 11
F7	K200M : AMBERLITE™ IRP69 (75:25)	N/A	37.0	800	1, 2, 3, 4, 6, 7, 10, 11
F7	K200M : AMBERLITE™ IRP88 (75:25)	N/A	37.0	800	1, 2, 3, 4, 6, 7, 10, 11
F9	K200M : Carbopol 971P (75:25)	N/A	37.0	800	1, 2, 3, 4, 6, 7, 10, 11
F9	K200M : Carbopol 974P (75:25)	N/A	37.0	800	1, 2, 3, 4, 6, 7, 10, 11
F10	K200M	2%	18.4	650	1, 3, 4, 11
F10	K200M	8%	18.4	650	9
F10	K200M	10%	18.4	650	9

Conclusions

Reducing weight of ER formulations of metformin HCl is possible. Various formulation strategies: polymer blends of hypromellose with ion exchange resins or carbomer; application of barrier membrane coating onto hydrophilic matrix tablets, resulted in ER profiles of metformin HCl. This poster provides small-scale proof-of-concept formulations that may comply to select USP dissolution test specifications for metformin HCl ER tablet monograph.

References

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