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Advantages of Hot Melt Extrusion for the Controlled Release of High Doses of Highly Soluble Actives

E. Pinto, H. Yang, A. Pittman, D. Tewari and T. Dürig

Introduction

Delivering high doses of highly soluble actives in matrix tablets is challenging as it necessitates the minimum addition of release controlling excipients and other process and formulation aids in order to limit tablet size for ease of swallowing. Typically maximum weights for swallowable tablets range from 800 to 1000 mg. The granule and final tablet density also have to be considered when attempting to minimize unit dose volume. In this study, highly soluble metformin hydrochloride (METF) was chosen as a typical high dose compound (1500 to 3000 mg daily in a 12 hour dosing period). Since METF is typically administered with food and is mainly absorbed from the proximal small intestine [1], the aim of the study was to deliver a 600 to 750 mg dose over a period of 6-8 hours, with 60% released between 2 to 4 hours.

Hydroxpropylcellulose (HPC) is a commonly used thermoplastic, water soluble carrier and release controlling polymer. The efficacy of hot melt extrusion was assessed by comparing similar formulations prepared by wet granulation.

Experimental Methods

Wet granulation. 1 kg batches comprising 75% Metformin (METF) and 25% Klucel™ MF Pharm HPC were wet granulated in a high shear mixer. After drying, milling, and lubrication, 1000 mg tablets were compressed at 30 kN on an instrumented Manesty Beta Press equipped with 0.750 x 0.343" caplet tooling. Tablet porosity (ε) was calculated as follows:

$\varepsilon = 1 - \text{Tablet Density} / \text{True density}$

Tablet density was calculated from the tablet volume and mass. The True density of the granule before compression was measured by Helium pycnometry. Tablet dissolution was tested in USP apparatus I with 6.8 pH phosphate buffer. Additional studies simulating fed state hydrodymanics were done in Apparatus III.

Hot Melt Extrusion. 1 kg batches of the above mentioned blend was hot melt extruded at a processing temperature of 185°C and screw speed of 225 rpm using the Leistritz ZSE 18HP counter-rotating twin screw extruder without a die. The extrudrate was milled and lubricated. The tabletting and dissolution studies were performed using the same conditions mentioned above.

Note: This work was presented at the Controlled Release Society Annual Meeting, July 11- July 15, 2010, Portland, Oregon.

Materials

1. Metformin HCl, marketed by Ria International, East Hanover, NJ.
2. Klucel™ HPC hydroxypropylcellulose, marketed by Ashland Incorporated, Wilmington, DE
3. HyQual* magnesium stearate, NF, marketed by Mallinckrodt Inc., a Division of Tyco International, St. Louis, MO.

Results and Discussion

The METF tablets made by hot melt extrusion were two times stronger, smaller, and consequently less porous as compared with the analogous tablets made by wet granulation and direct compression (Table 1). The improved mechanical properties and smaller tablet size for the same weight of unit dose can be attributed to the intimate mixing of drug with polymer in the molten state and the substantial elimination of air in the extrudate. In addition, the reduction in porosity also resulted in improved compactibility and reduced elastic recovery as evidenced by the enhanced tablet strength and reduced friability.

Unit Process	Granule Density (g/ml)	Tablet Volume (ml)	Tablet Weight (mg)	Porosity (%)	Tablet Strength (kP) 3kN Pre-compression, 15 kN Main Compression
Extrusion	1.2987	0.8	998.6	3.4	14.2
Direct Compression	1.3146	0.9	990.5	16.3	5.1
Wet Granulation	1.3546	0.9	998.8	17.7	4.0

Table 1. Tablet Physical Properties

In Figure 1, the reduced porosity of the hot melt extruded METF tablets resulted in a dramatic improvement in the release retardation of METF as compared to wet granulated and direct compression tablets. The differences can be attributed to the lower porosity of the hot melt extruded tablets resulting in slower ingress of water into the tablet and thus slower diffusion of dissolved drug out of the tablet in the early time phase (first 30 minutes). After this initial period a sufficiently strong gel layer envelops the tablet to control the further ingress of water into the system. For the porous wet granulated tablets, excessive water penetration in the first 30 minutes results in dissolution and diffusion of the majority of the dose before a gel layer could be successfully established. Finally, Figure 2 shows that the tablets made by hot melt extrusion had little susceptibility to hydrodynamic stress and were hence robust. In addition, the extruded MEFT tablets retained the drug in its crystalline form (Figure 3) and were stable (Table 2, Figure 4) under accelerated conditions (40°C and 75% RH).

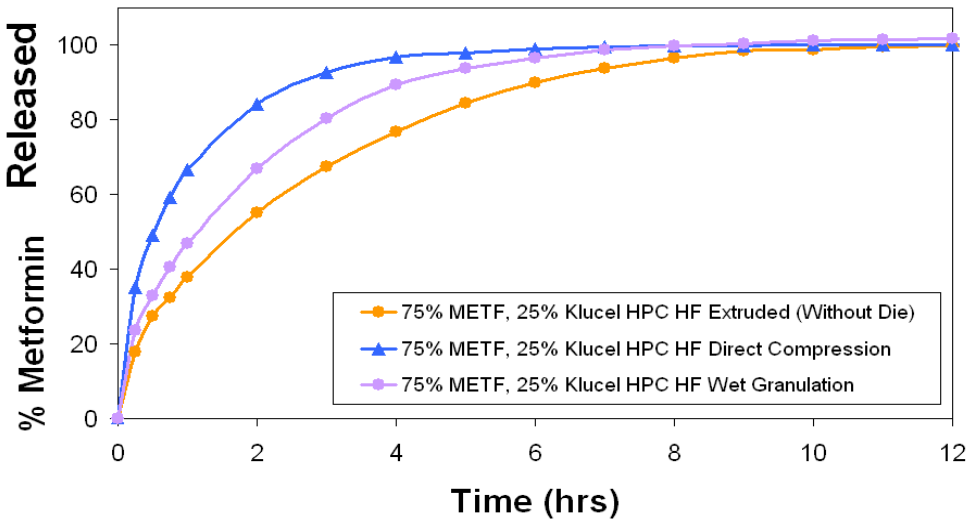

Figure 1. Effect of commonly used tablet manufacturing processes on the release profile of a highly soluble drug Metformin HCl.

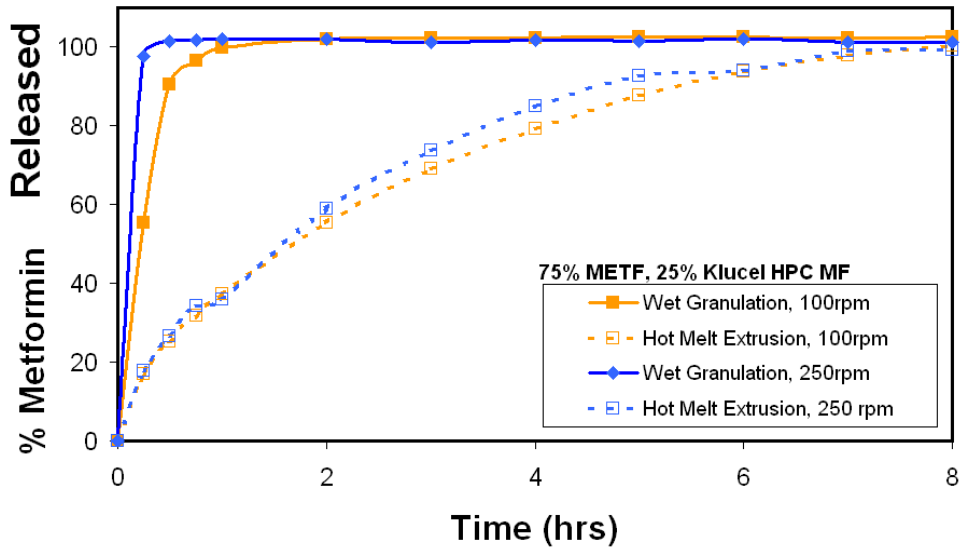

Figure 2. Effect of hydrodynamics on the wet granulated and hot melt extruded Metformin HCl tablets.

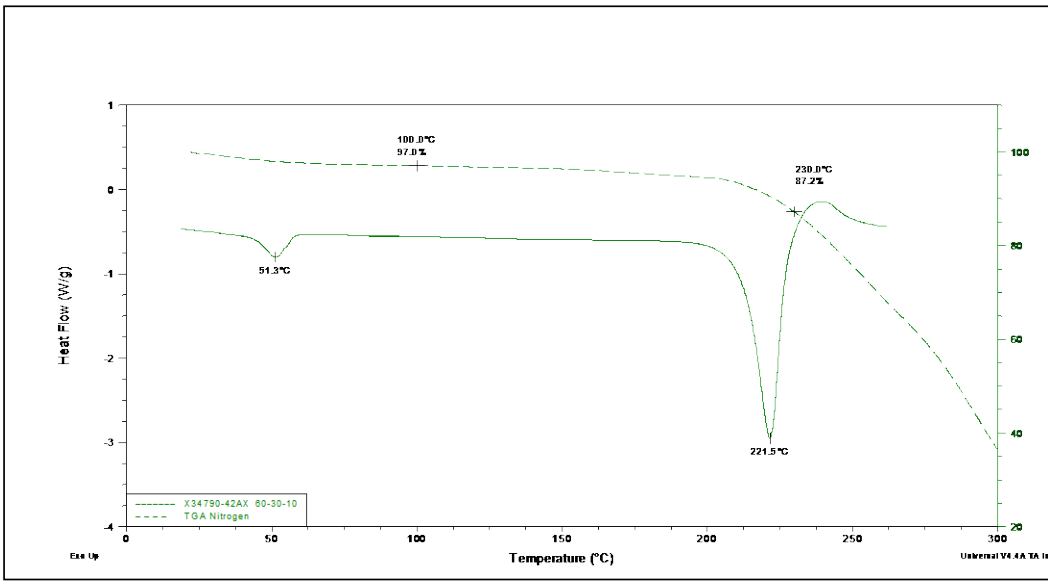

Figure 3. Differential Scanning Calorimetry (DSC) of hot melt extruded Metformin HCl granules.

% Drug by HPLC					
Day 0	Week 1	Week 2	Week 4	Week 8	Week 12
98.8	98.3	97.7	98.4	97.3	96.9

Table 2. Stability of High Dose Extruded Tablets.

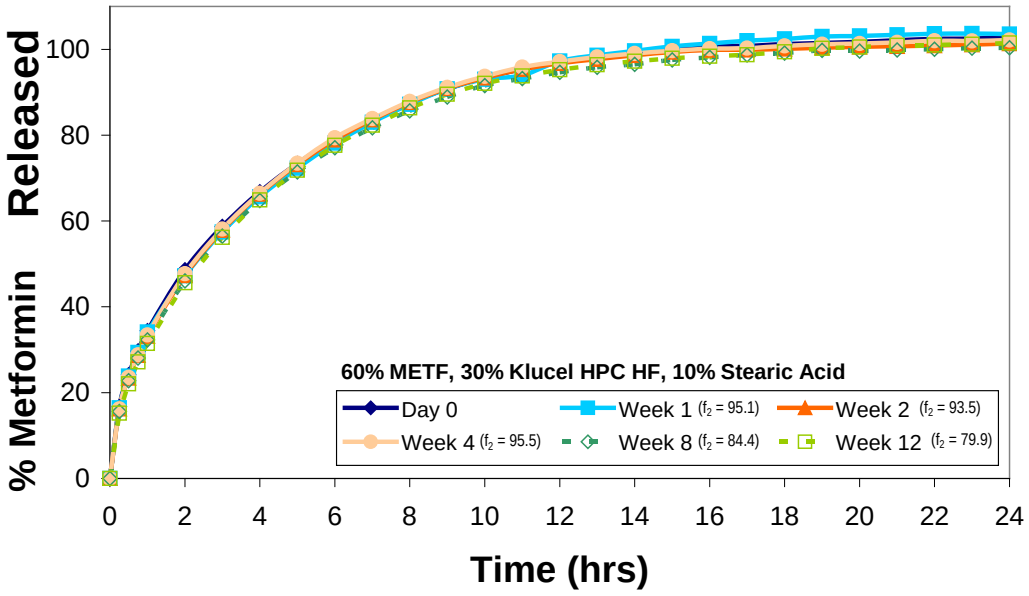

Figure 4. Dissolution profiles of hot melt extruded Metformin HCl tablets under accelerated stability testing (40 °C, 75% RH).

Conclusion

By using Klucel™ HPC as a thermoplastic release retarding excipient, it was possible to produce controlled release METF tablets with very high drug loading (up to 75%). These tablets were superior in their compactibility and mechanical properties, resulting in smaller tablets with significantly enhanced release retardation as compared with the equivalent composition prepared by wet granulation and direct compression.

References

1. G.Gusler, J. Gorsline, et. al., Pharmacokinetics of metformin gastric-retentive tablets in healthy volunteers, *J Clin Pharmacol*. 2001; 41: 655-661