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# Hot Melt Extrusion with Klucel™ hydroxypropylcellulose HPC for the Controlled Release of High Doses of a Highly Soluble Active

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## 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. This study investigates the feasibility of using hot melt extrusion (HME) as an alternative to wet granulation (WG) for the preparation of controlled release formulations of a highly soluble drug at high drug loads (75%).

High molecular weight grades of Klucel™ hydroxypropylcellulose (HPC) were used as a thermoplastic, water soluble carrier and release controlling polymer. The efficacy of hot melt extrusion was assessed by comparing similar formulations prepared by wet granulation and direct compression.

## Experimental Methods

*Wet granulation*. 1 kg batches comprising 75% Metformin (METF) and 25% Klucel HPC HF Pharm were wet granulated in a high shear mixer. After drying, milling, and lubrication, 1000 mg tablets were precompressed at 3kN and compressed at 15kN on an instrumented Manesty Beta Press equipped with 0.750 x 0.343" caplet tooling. The press speed was 33 rpm. 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 granules before compression was measured by Helium pycnometry. Tablet dissolution was tested in USP apparatus I with 6.8 pH phosphate buffer.

*Direct Compression*. 1 kg batches comprising 75% Metformin (METF) and 25% Klucel HPC HF Pharm were mixed in a V-blender for 15 minutes. Tabletting and dissolution studies were performed using the same conditions mentioned above.

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*Hot Melt Extrusion*. 1 kg batches of the above mentioned blend was hot melt extruded at a processing temperature of 165°C and screw speed of 150 rpm using the Leistritz ZSE 18HP counter-rotating twin screw extruder without a die (Figure 1). Extrudrate was hammer milled and lubricated. Tabletting and dissolution studies were performed using the same conditions mentioned above.

**Figure 1. Extruder setup. The drug/polymer blend consisting of 75% Metformin HCl and 25% Klucel™ HPC HF was extruded without the use of a die and at the temperature settings and extruder settings mentioned below.**


| | Extrusion Temperature Settings (°C) | | | | | | | | Screw Speed (rpm) | Feed Speed (rpm) | % Loading | Melt Pressure (psi) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Zone 1 | Zone 2 | Zone 3 | Zone 4 | Zone 5 | Zone 6 | Zone 7/8 | Melt | | | | |
| **With Die** | 120 | 150 | 170 | 185 | 185 | 185 | 185 | 145 | 225 | 225 | 21 | 790 |
| **Without Die** | 110 | 140 | 145 | 160 | 165 | 160 | 155 | - | 150 | 150 | 40 | - |

## Materials

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

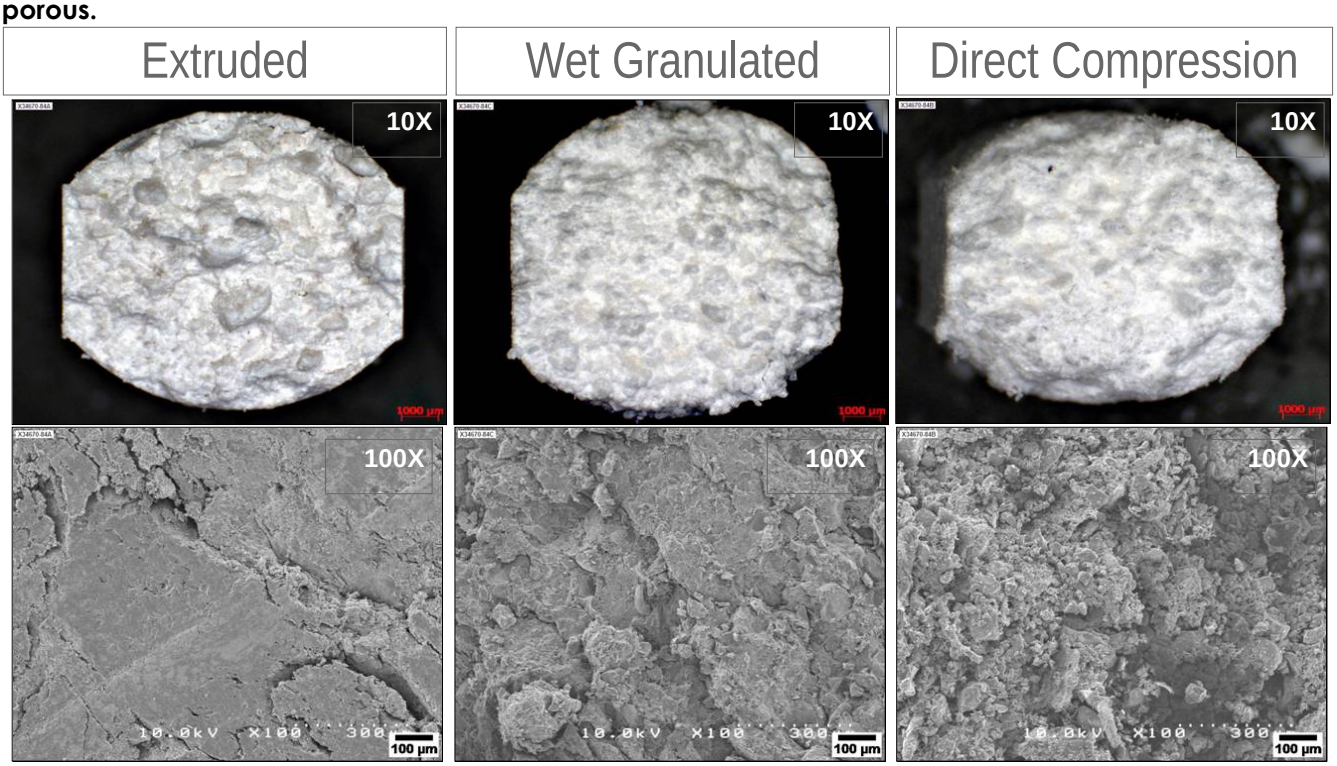
## Results and Discussion

The METF tablets made by hot melt extrusion were more than two times stronger, smaller, and consequently less porous as compared to the analogous tablets made by wet granulation and direct compression (Table 1). The lower porosity of the extruded tablets is also readily seen from the tablet cross-section (Figure 2). 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 and final tablet. In addition, the extrusion process also resulted in improved compactability and reduced elastic recovery as evidenced by the enhanced tablet strength and reduced friability.

**Table 1. Tablet physicals. Extrusion results in marked reduction of tablet porosity, increasing strength, and decreased drug release (burst) in early time phase.**

| Unit Process | Granule Density (g/ml) | Tablet Volume (ml) | Porosity (%) | Tablet Strength (Kp) 3kN Pre-compression 15kN Main compression |
|---|---|---|---|---|
| Extrusion | 1.30 | 0.8 | 3.4 | 14.2 |
| Wet Granulation | 1.35 | 0.9 | 12.7 | 4.0 |
| Direct Compression | 1.35 | 0.9 | 15.3 | 5.0 |

**Figure 2. Porosity of Metformin HCl tablets. The Scanning Electron Microscope (SEM) pictures of the cross-section of the tablets show that the tablets made by hot melt extrusion were a lot more dense and less porous.**




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 (Figure 3). The differences can be attributed to the lower porosity of the hot melt extruded tablets resulting in slower ingress of media into the tablet (Figures 4 and 5) 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.

**Figure 3. Dissolution profile of Metformin HCl tablets. The extruded tablets resulted in greater drug release retardation (USP apparatus I, 6.8 pH phosphate buffer, 100 rpm).**

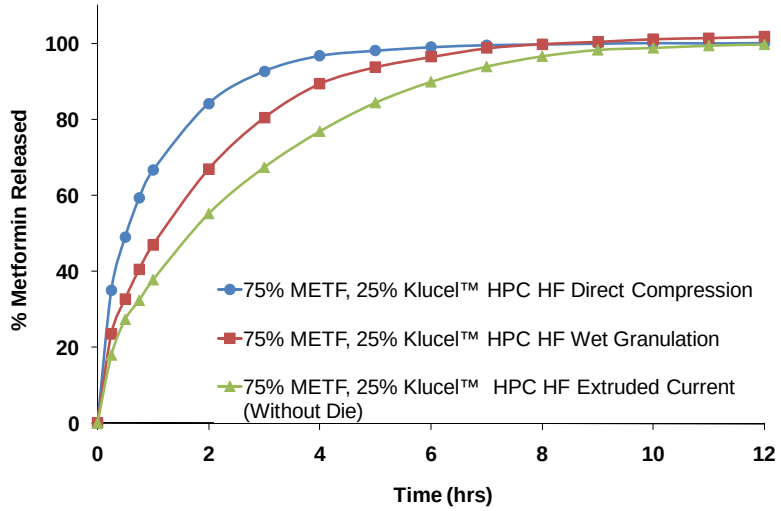


**Figure 4. Media uptake of Metformin HCl tablets. Tablets made by hot melt extrusion were the least porous of the three and hence had slower dissolution media penetration rate. The porosity of the porous surfaces were further illustrated by the rapidly changing and much lower contact angle for the wet granulated and direct compression tablets.**

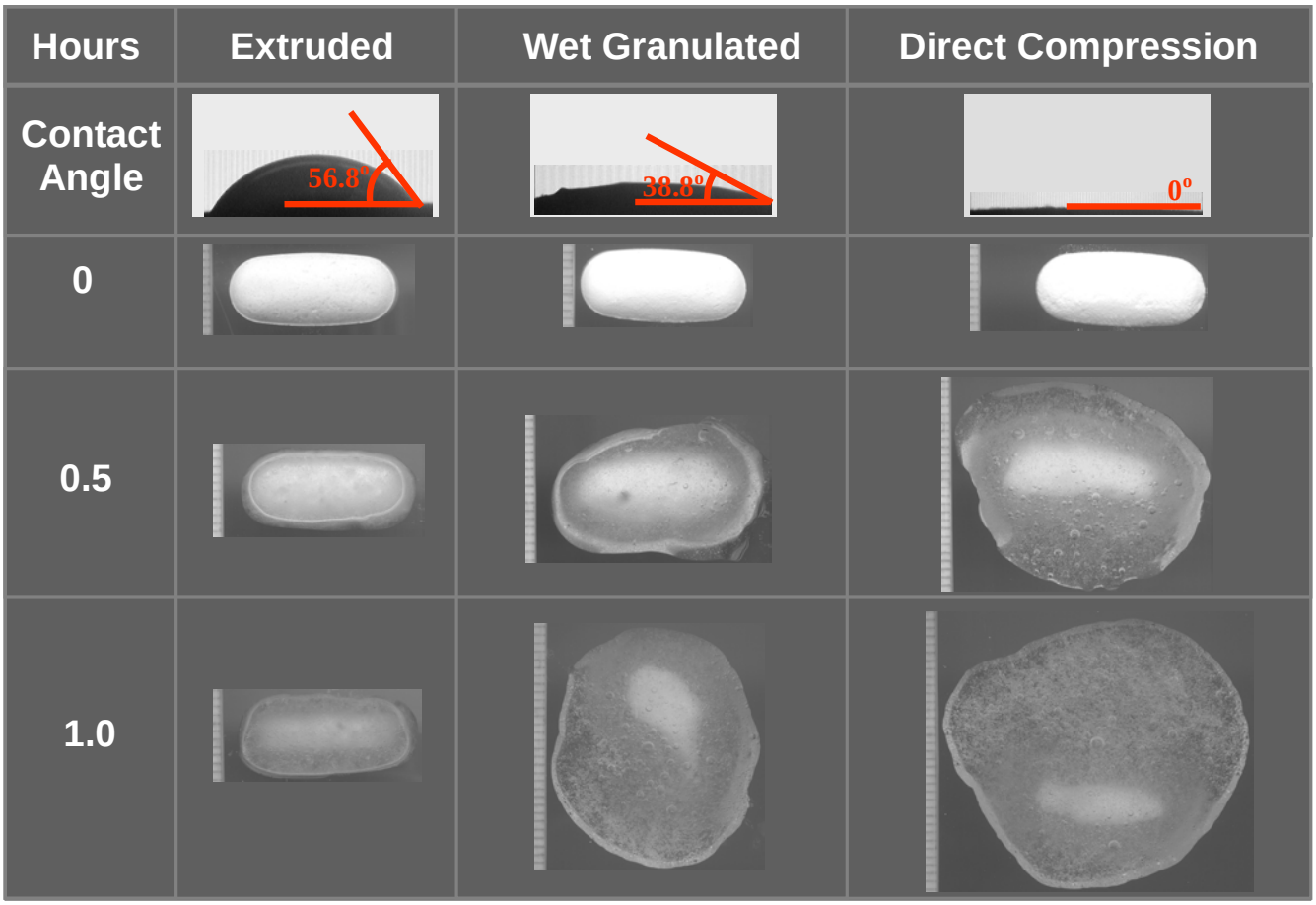
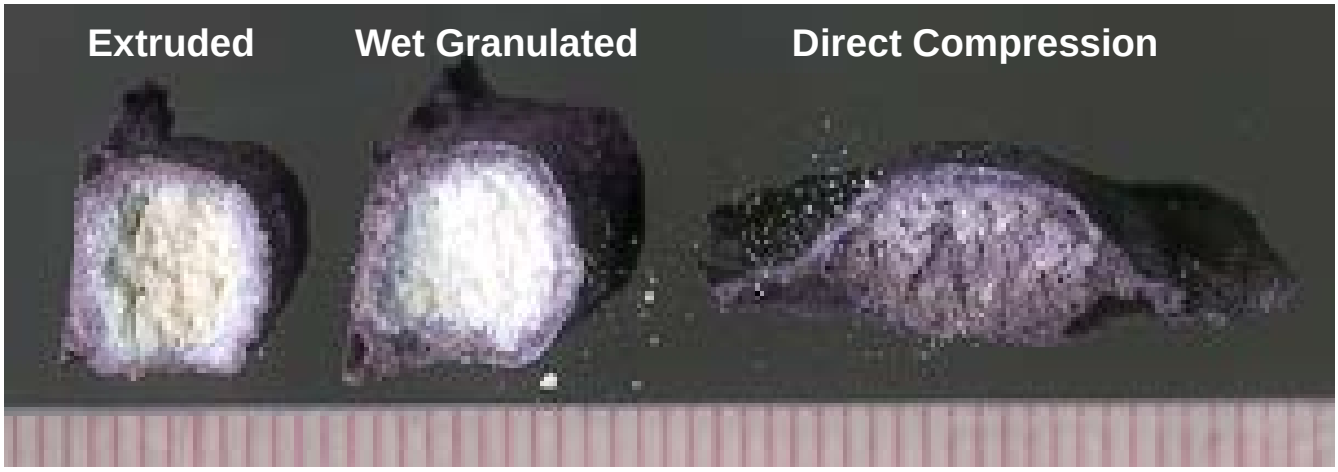



**Figure 5. Media uptake of Metformin HCl tablets. The tablets were submersed in a blue dye solution for 30 minutes and then dried overnight. Pictures of the cross sectional surfaces were then taken.**



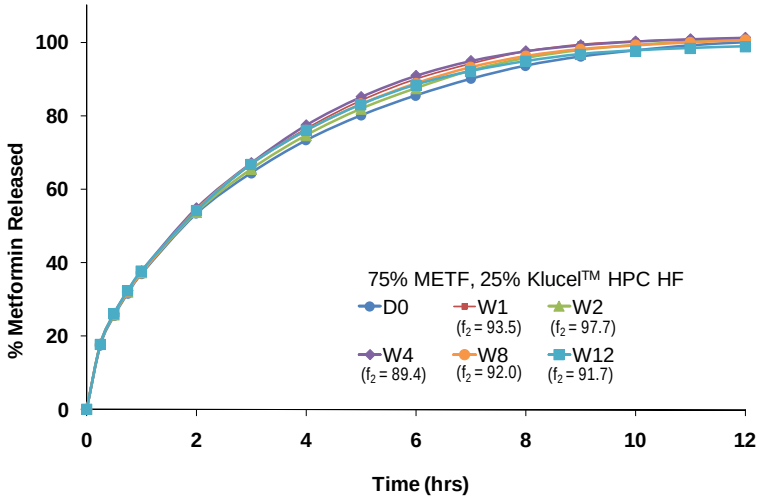
Accelerated stability studies were conducted on the extruded tablets at 40°C and 75% RH. Table 2 shows that the tablets are chemically stable even after 12 weeks of testing.

**Table 2: Drug stability of high dose extruded tablets. Tablets stored in sealed HDPE bottles at 40°C, 75% RH. Tablet formulation comprised of 75% METF and 40% Klucel™ HF HPC.**

| Percent drug by HPLC | | | | | |
|---|---|---|---|---|---|
| Day 0 | Week 1 | Week 2 | Week 4 | Week 8 | Week 12 |
| 96.4 | 96.6 | 96.3 | 96.4 | 96.5 | 96.2 |

In addition, Figure 6 shows that the dissolution profiles remained similar under accelerated storage conditions.

**Figure 6. Dissolution stability of high dose extruded tablets. Tablets stored in sealed HDPE bottles at 40°C, 75% RH. Dissolution was performed using the USP apparatus 1, 6.8 pH phosphate buffer at 100 rpm.**




## 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 had improved compactability and mechanical properties, resulting in smaller tablets with significantly enhanced release retardation as compared to the equivalent composition prepared by wet granulation and direct compression. A further advantage of this processing method is that continuous granulation is possible.

## References

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