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Klucel™ HPC in Hot Melt Extrusion Applications

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Hot-melt extrusion (HME) is increasingly being used as an alternate commercially viable method to prepare immediate- and sustained-release tablets. In this application, molten thermoplastic polymers function as thermal binders during extrusion and upon cooling and solidification. Klucel HPC is a family of products that are fully approved for pharmaceutical and food use and can be processed without plasticizers at significantly lower temperatures than other frequently used polymers.

Enhanced Solubility of Low Solubility Drugs

In the case of lipophilic drugs, HME can be used to enhance the solubility of the drug by using the molten HPC polymer as a water soluble matrix in which drug molecules are immobilized and dispersed in a nanocrystalline or amorphous state⁽¹⁾. An immediate release formulation with nifedipine (NIF, aqueous solubility of 6 µg/ml), Klucel HPC EF (Ashland, Wilmington, DE) and Avicel* 102 MCC (FCC, Newark, DE) was hot melt extruded using the following blend composition and conditions.

Table 1. Extruder Barrel Zone Temperature Settings.

Extrudate Blend	Temperature (°C)					
	1	2	3	4, 5	6	7, 8
33% NIF, 33% HPC, 33% MCC	80	100	120	140	140	140
33% NIF, 33% HPC, 33% MCC	80	110	140	180	160	140
33% NIF, 66% HPC	80	100	120	120	120	120
25% NIF, 50% HPC, 25% MCC	80	100	120	140	140	140

The extrudates were milled and compressed into 300 mg tablets containing 30 mg nifedipine with a final composition of:

Table 2. Formulation composition of 30 mg Nifedipine tablets

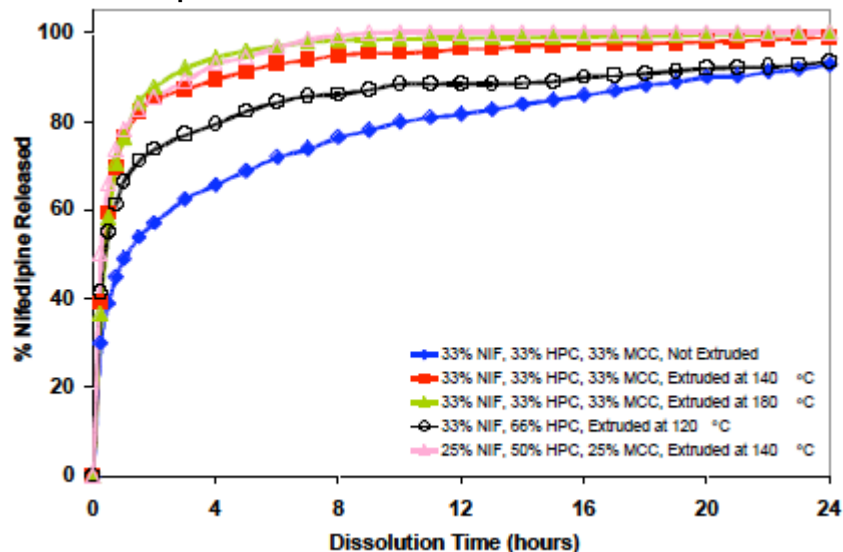
Sample	Extrudate Blend	Final Tablet Composition				
		% NF	% HPC	% MCC	% Ac-Di-Sol	% Mg St.
C ^(a)	33% NIF, 33% HPC, 33% MCC	10	10	77.5	2	0.5
1	33% NIF, 33% HPC, 33% MCC	10	10	77.5	2	0.5
2	33% NIF, 33% HPC, 33% MCC	10	10	77.5	2	0.5
3	33% NIF, 66% HPC	10	20	67.5	2	0.5
4	25% NIF, 50% HPC, 25% MCC	10	20	67.5	2	0.5

^(a)C is the control that was not hot melt extruded. The blend was prepared by direct compression.

All tablet formulations comprising the extrudate blends dissolved much faster than the non extruded reference formulation, with 80% of dose dissolved in 1 hour, as compared to 12 hours for the reference (Figure 1). The only exception was the formulation comprising 66% HPC which dissolved slightly slower (80% dissolved in 4 hours) due to the higher polymer concentration, which resulted in a sustained release matrix.

Figure 1

Dissolution profiles comparing extruded nifedipine formulations of varying compositions made at various extrusion temperatures with a non extruded reference formulation.



Good physical stability was observed for all the extruded formulations. The amorphous systems (1:2 NIF-HPC ratio) remained stable without any evidence of recrystallization (no melting enthalpy observed) over a four-week period stored at 40°C and 75% RH (Figure 2). Only minor variations in melting enthalpy were evidenced for the partially amorphous systems (1:1 NIF-HPC ratio). Dissolution profiles remained relatively stable over four weeks storage at 40°C and 75% RH (Figure 3).

Figure 2

Melting enthalpies as a measure of residual crystallinity for blends of nifedipine and Klucel HPC EF. The stability tests were performed at 40°C and 75% RH.

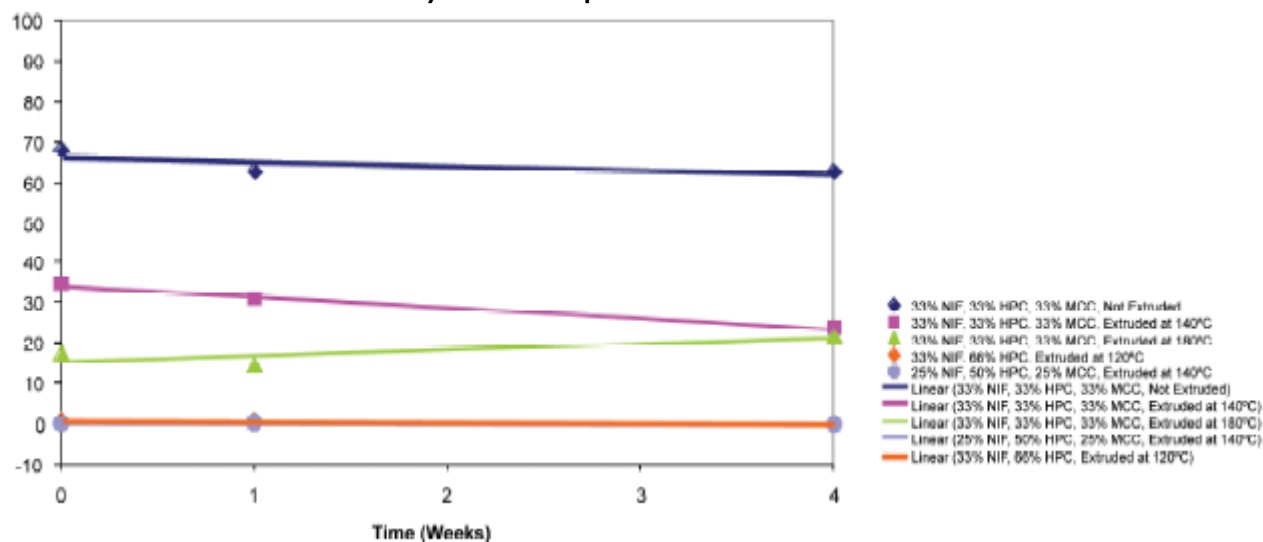
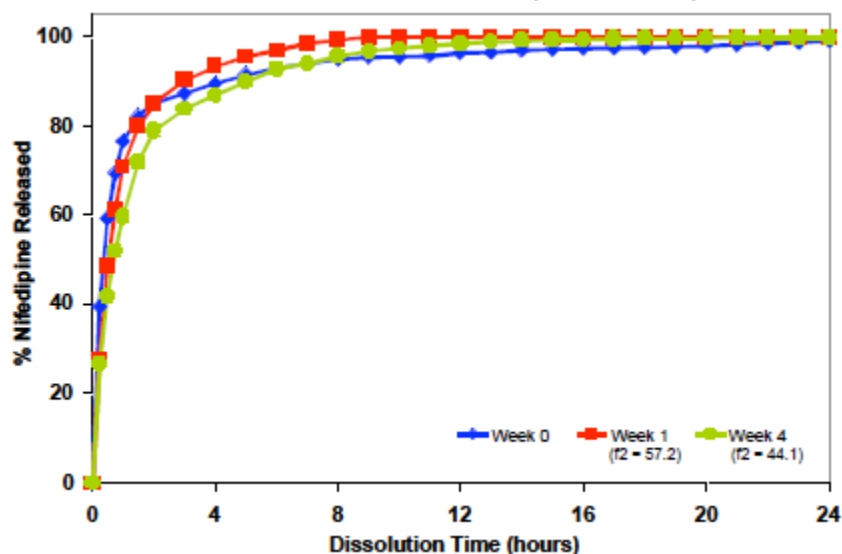


Figure 3

One month dissolution stability profile of extruded nifedipine formulation consisting of 33% nifedipine, 33% Klucel™ HPC EF and 33% MCC extruded at 140°C. The stability tests were performed at 40°C and 75% RH.



Klucel EF and ELF were shown to be excellent thermoplastic, water soluble polymeric carriers for hot melt extrusion of nifedipine formulations at temperatures as low as 120°C. The amorphous as well as partially crystalline extrudates were equally capable of enhancing nifedipine dissolution rates.

Improved Retardation of Highly Soluble Drugs

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. The highly soluble metformin hydrochloride (METF, aqueous solubility > 300 mg/ml) 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⁽²⁾, the aim of the study was to deliver a 750 mg dose over a period of 6-8 hours, with 40% released between 4 to 6 hours.

A blend of 75% METF and 25% Klucel MF were hot melt extruded at a processing temperature of 185°C and screw speed of 225 rpm. The extrudates were milled and compressed into 1000 mg tablets containing 750 mg METF. The similar blend was also prepared by wet granulation. The METF tablets made by hot melt extrusion (Table 3) were two times stronger, smaller and consequently less porous (5.7% porosity) as compared to the analogous tablets made by wet granulation (20.6% porosity). 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.

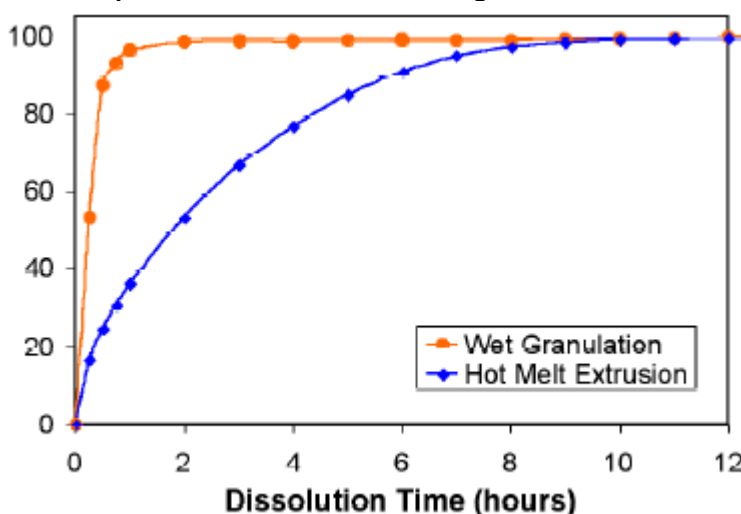
Table 3: Physical properties of granules and 1000 mg tablets compressed at 30kN

	Granule Bulk Density (g/ml)	Tablet Crushing Strength (Kp)	Tablet Thickness (inch)	Tablet Porosity (%)
Wet Granulation	0.533	9.2	0.307	20.6
Hot Melt Extrusion	0.637	17.8	0.286	5.7

The extruded, milled granules were denser and had less internal voids than the wet agglomerated granules, thus allowing the same mass of material to be accommodated in a smaller tablet volume. 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.

The reduced porosity of the hot melt extruded METF tablets resulted in a dramatic improvement in the release retardation of METF (Figure 4) as compared to wet granulated tablets ($t_{80\%}$ 4.5 hrs. vs. 0.5 hrs. for hot melt and wet granulation respectively). In order to achieve similar release retardation from wet granulated tablets the METF dose had to be reduced to 25% (data not shown). The differences can again be explained in terms of significant differences in tablet and granule porosity, with 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.

Figure 4
Dissolution profile of extruded and wet granulated METF tablets.



By using KluCEL™ HPC as a thermoplastic release retarding excipients, 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 to the equivalent composition prepared by wet granulation.

References

- ¹ Breitenbach, European Journal of Pharmaceutics and Biopharmaceutics, 54(2), pp 107-117 (2002).
- ² G. Gusler, J. Gorsline, et. Al., Pharmacokinetics of metformin gastric-retentive tablets in healthy volunteers, *J Clin Pharmacol.* 2001; 41:655-661.