Ashland Specialty Ingredients
ashland.com

PTR-072

Melt Flow Properties of Hydroxypropyl Cellulose for Solubilization of Lipophilic Actives

*E. Pinto, H. Yang, A.J. Sosnowik, W. W. Harcum, A. Pittman, T. Dürig**

Introduction

Hot-melt extrusion (HME) is increasingly being used as an alternate commercially viable method to prepare immediate and sustained release tablets. Select thermoplastic polymers can function as "thermal binders" during extrusion and upon cooling and solidification. In the case of lipophilic drugs, HME can be used to enhance the solubility of the drug by using the molten polymer as a water-soluble matrix in which drug molecules are immobilized and dispersed in a nanocrystalline or amorphous state (1). This project investigates the effectiveness of Klucel™ hydroxypropylcellulose (HPC) to enhance the solubility of nifedipine, a poorly soluble drug, using HME.

Experimental methods

Drug/Polymer Blends were prepared by blending nifedipine, Klucel HPC EF or ELF Pharm, and MCC where needed, in a V-blender (Patterson-Kelley Co. Liquid-Solid Blender, East Stroudsburg, PA) for 15 minutes.

Diffrential Scanning Calorimetry (DSC) Analysis: was performed with a 2920 DSC from TA Instruments (New Castle, DE) using the following conditions: Sampling interval 2.00 sec/pt, heat cycle 1: Ramp 0.50°C/min from 20.00°C to 185.00°C, cooling cycle: Ramp 0.50°C/min to 20.00°C, heat cycle 2: Ramp 0.50°C/min to 185.00°C.

The samples were analyzed in crimped aluminum pans, under a nitrogen purge. For the stability test, the tablets were stored in an oven at 40°C and 75% relative humidity (RH). DSC (1st heat only) was performed at 10°C per minute on tablets at week 0, week 1, and week 4 in order to detect presence or absence of crystallinity as measured by presence or absence of nifedipine melting enthalpies.

Melt flow indices were measured with Tinius Olsen Thermodyne apparatus (Willow Grove, PA) using the ASTM D1238 as a guide. The die had a bore diameter of 0.0823 inches and length of 8.0 inches. The samples were analyzed at 125°C with a load of 2.16 kg.

Melt viscosity was measured on an AR-G2 stress controlled rheometer from TA Instruments. A parallel plates geometry at 25mm in diameter was used. The dynamic viscosity was measured from 160 to 220°C using the oscillatory method at 0.03% of strain and frequencies of 0.1 to 100 rad/sec. The samples were measured as received.

Hot Melt Extrusion was performed on an 18 mm diameter twin-screw, co-rotating Leistritz ZSE 18HP (Somerville, NJ) extruder equipped with a double strand die under the following conditions:

Note: This work was presented at the Annual Meeting of the American Association of Pharmaceutical Scientists, November 8-12, 2009, Los Angeles, California.

Table 1. Barrel zone temperature settings.

		Temperature (^{O}C) at different zones					
Sample	**Extrudate Blend**	**1**	**2**	**3**	**4 & 5**	**6**	**7 & 8**
1	33% NF, 33% HPC, 33% MCC	80	100	120	140	140	140
2	33% NF, 33% HPC, 33% MCC	80	110	140	180	160	140
3	33% NF, 66% HPC	80	100	120	120	120	120
4	25% NF, 50% HPC, 25% MCC	80	100	120	140	140	140

The material blend was added to the hopper and fed into the extruder at 150 rpm. The extruder screw speed was set at 150 rpm. The extruded strands were cut at 2ft in length. The 2ft strands containing MCC were stored at room temperature in a sealed plastic bag. The 2ft strands not containing MCC (Sample 3) were stored at -40°C overnight in a sealed plastic bag to render them brittle for milling.

Milling and Tabletting

The strands were milled using the Fitzmill Model M (The FitzPatrick Company, Elmhurst, IL) knives forward, medium speed with 0.065" screen. The formulations were blended with MCC so that the final composition was as follows:

Table 2. Formulation composition of 30 mg Nifedipine tablets

			Final Tablet Composition				
Sample	**Extrudate Blend**	**Extrusion Temp. (^{O}C)**	**% NIF**	**% HPC**	**% MCC**	**% Ac-Di-Sol**	**% Mg St.**
Control	33% NF, 33% HPC, 33% MCC	N/A	10	10	77.5	2	0.5
1	33% NF, 33% HPC, 33% MCC	140	10	10	77.5	2	0.5
2	33% NF, 33% HPC, 33% MCC	180	10	10	77.5	2	0.5
3	33% NF, 66% HPC	120	10	20	67.5	2	0.5
4	25% NF, 50% HPC, 25% MCC	140	10	20	67.5	2	0.5

The additional MCC and croscarmellose (prescreened through a 20 mesh sieve) were mixed with the extruded blend in an 8 qt V-blender for 10 minutes. Lastly magnesium stearate (prescreened through a 20 mesh sieve) was added for the final 2 minute blending time. The final blend was tabletted on a Manesty Betapress 16 Station rotary press (Thomas Engineering Inc., Hoffman Estates, IL) using 7/16" SC shaped tooling at a 15 kN compaction force to make 300 mg tablets (Figure 1).

Dissolution Testing was performed with the USP apparatus II (Distek Dissolution System 2100 C,North Brunswick, NJ) at 50 rpm in amber dissolution flasks. The dissolution media (900 ml each) comprised of pH 4.6 buffer with 1% sodium lauryl sulfate. For the stability tests, the tablets were packaged in sealed HDPE bottles and stored in an oven at 40°C and 75% relative humidity (RH). Dissolution testing was performed on week 0, week 1, and week 4.

Materials

1. Klucel hydroxypropylcellulose EF and ELF Pharm, marketed by Ashland Specialty Ingredients, Ashland Inc., Wilmington, DE.
2. Nifedipine, USP, marketed by RIA International, Whippany, NJ
3. Avicel* PH-102 Microcrystalline cellulose, NF, marketed by FMC Corporation, Philadelphia, PA.
4. Ac-Di-Sol* croscarmellose sodium, NF, marketed by FMC Corporation, Philadelphia, PA.
5. HyQual* magnesium stearate, NF, marketed by Mallinckrodt Inc., a Division of Tyco International, St. Louis, MO.

Results and Discussion

Solubility of Nifedipine in Klucel HPC
Binary blends of Klucel HPC ELF and 10, 20, 30, 40, or 50% nifedipine were prepared. Figure 2 shows the thermograms of the binary blends after the second heating cycle. The first heating cycle was performed to yield a fused blend of the drug and polymer, thus mimicking the phase transitions that would occur in an extruder. The molten blend was then cooled and reheated to test for residual drug crystallinity as measured by residual melting enthalpy peaks. It can be seen that the pure drug has a melting temperature (T_m) at approximately 172°C. However, with the binary blends comprising less than 50% nifedipine (10 to 40%), no peak is observed at 172°C indicating spontaneous formation of amorphous dispersions.

Drug loading also has a significant impact on the melt flow behavior of the drug-polymer blends. As shown in Figure 3, the drug exerts a plasticizing effect when drug loadings are increased from 0 to 30%. Above this drug level, melt flow rapidly decreases. The melt viscosity results in Figure 4 support these findings. Increasing the drug composition from 0 to 20% lowers the oscillatory viscosity at a given oscillatory shear rate, indicating that at a 20% drug level, the binary blend is more fluid-like and can flow better. This can be attributed to disruption of inter polymer hydrogen bonding in the fluid state. However, at higher drug levels, the binary blend becomes more viscous and rigid as the non-thermoplastic drug begins to dominate the mixture characteristics and essentially acts as a filler or extender.

Physical Characterization and Stability of the Extrudate Blends
As shown in Figure 5, the extent of residual nifedipine crystallinity (as measured by melting enthalpy) in the extrudate blends was dependent on composition and extrusion temperature. Consistent with the findings for the binary drug-polymer blends, no drug crystallinity was detected for formulations with drug to polymer ratios of 1:2. Extrusion temperatures as low as 120°C were sufficient to achieve amorphous nifedipine dispersions. On the other hand, some crystallinity was detected when equal amounts of drug and HPC were used, indicating a partially crystalline or nano crystalline system. The presence of MCC did not appear to affect the physical state of the drug/polymer dispersions.

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

Dissolutions Rate Enhancement
As shown in Figure 6, 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. 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. Dissolution profiles remained relatively stable over 4 weeks storage at 40°C and 75% RH (Figure 7).

Conclusions

Klucel HPC 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. Drug levels below 30% have a plasticizing effect. Additionally, drug levels at 40% and lower yield amorphous drug dispersions stabilized by the polymer matrix. At 50% drug levels, the extrudate was partially crystalline, but remained stable under accelerated conditions. The amorphous and partially crystalline extrudates were equally capable of enhancing nifedipine dissolution rates.

References

1. Breitenbach, European Journal of Pharmaceutics and Biopharmaceutics, 54(2), pp 107-117 (2002)

Figure 1. Extruded strands (A) containing nifedipine, Klucel HPC EF and MCC were milled into a powder (B) before adding additional MCC, croscarmellose and magnesium stearate and compressing into 300 mg tablets (C).

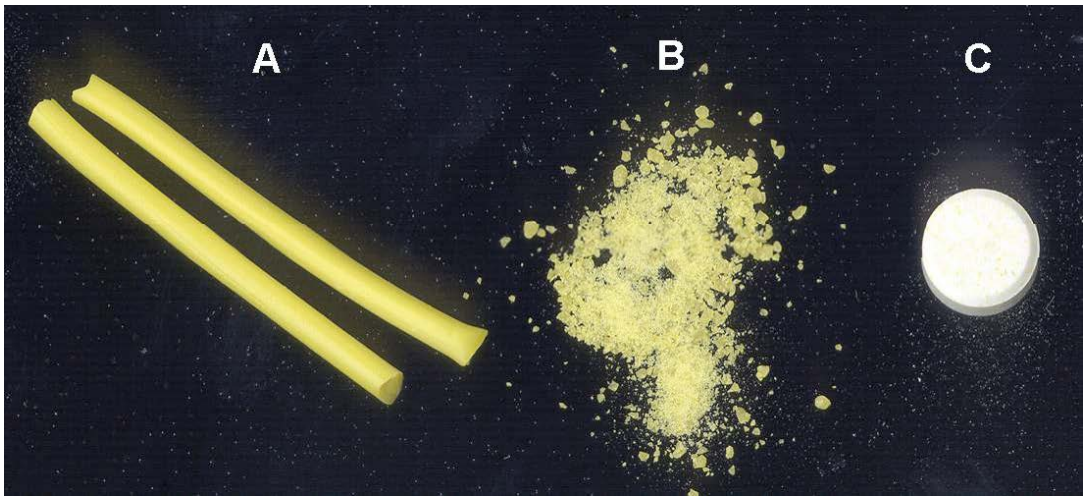


Figure 2. DSC thermograms of binary blends with Nifedipine and Klucel HPC ELF (2nd Heat).

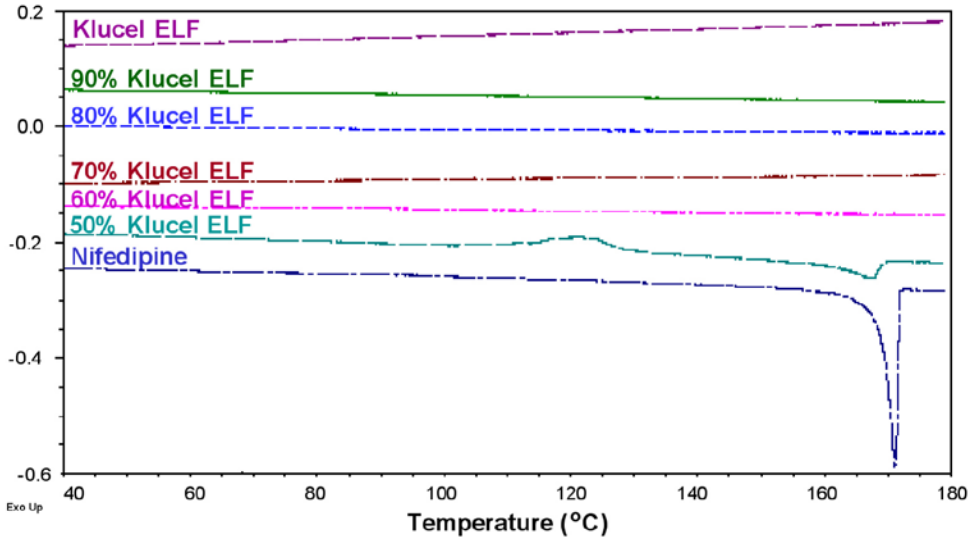
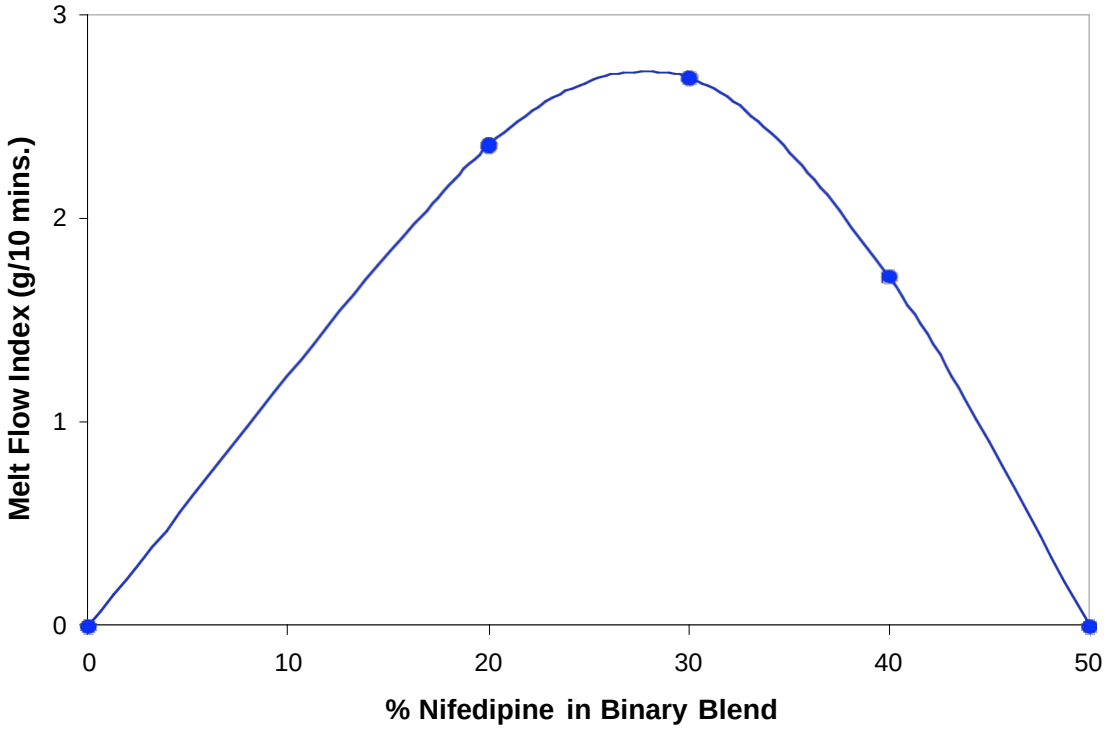


Figure 3. Effect of drug load on Melt Flow Index (g/10 mins.) at 125°C. The drug blends were made with Klucel HPC ELF.



ASHLAND

Figure 4. Effect of drug load on melt viscosity at 120°C. The drug blends were made with Klucel HPC ELF.

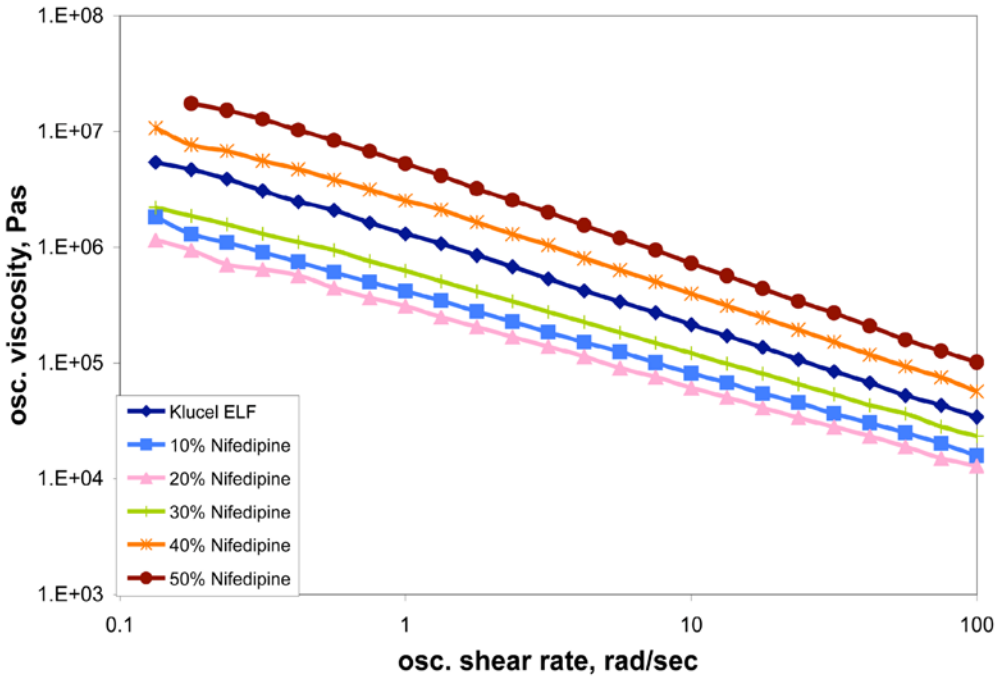


Figure 5. Melting enthalpies as a measure of residual crystallinity for blends of nifedipine and Klucel HPC EF. The stability tests were performed at 40°C and 75% RH.

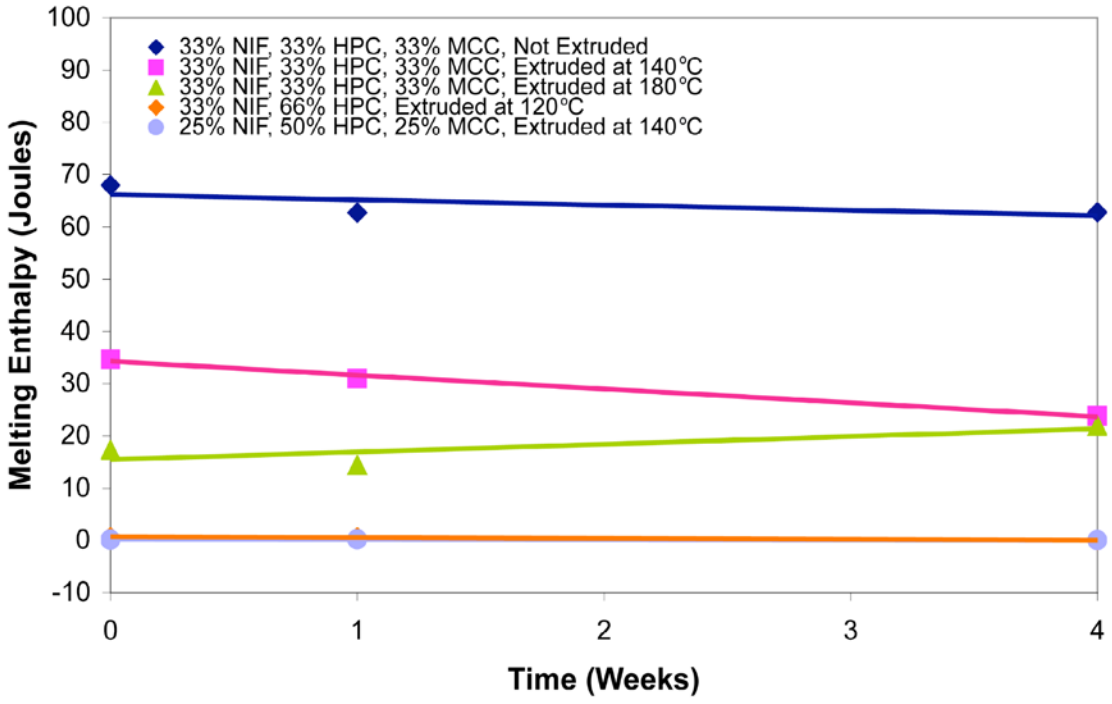


Figure 6. Dissolution profiles comparing extruded nifedipine formulations of varying compositions made at various extrusion temperatures with a non extruded reference formulation.

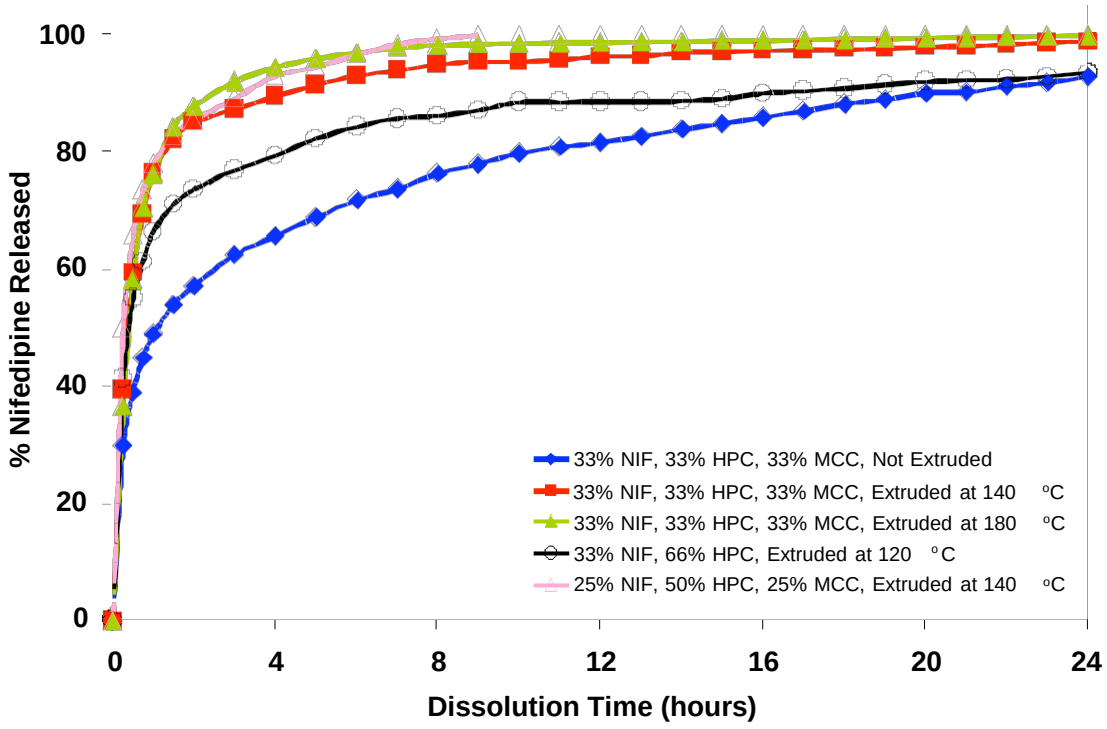
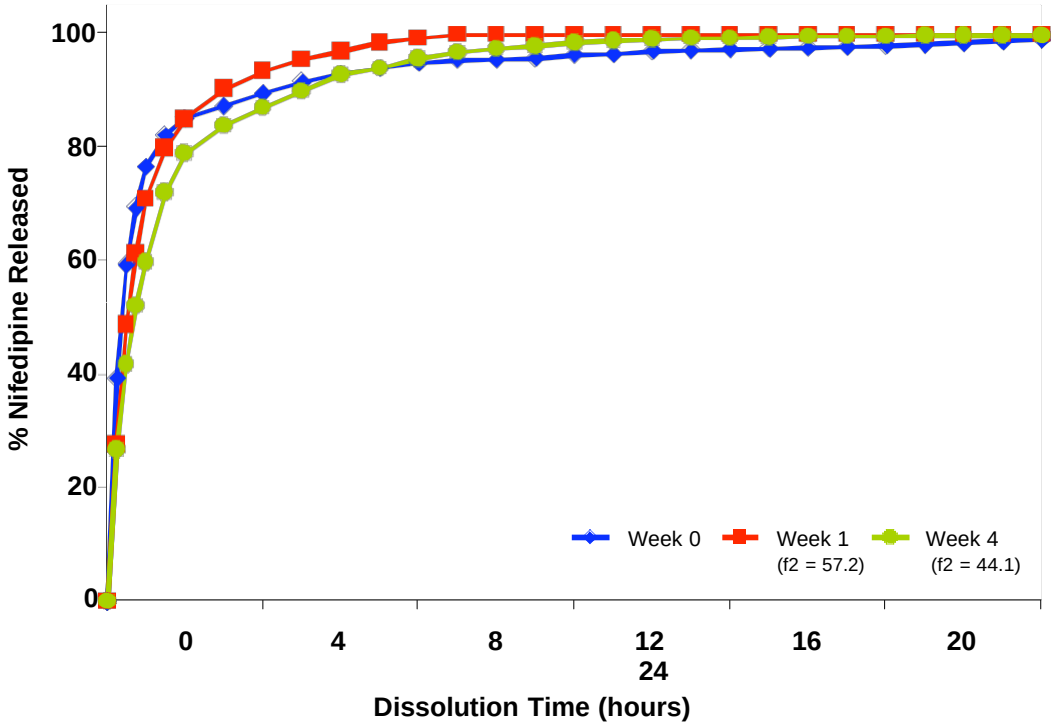


Figure 7. One month dissolution stability profile of extruded nifedipine formulation consisting of 33% nifedipine, 33% Klucel HPC EF, and 33% MCC extruded at 140°C. The stability tests were performed at 40°C and 75% RH.



ASHLAND