# Hot Melt Extrusion of Ketoprofen: Effect of Polymeric Excipient Selection

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## Introduction

Excipient selection is anticipated to have a significant impact on the characteristics of dosage forms produced via hot melt extrusion (HME). The purpose of this study was to investigate this effect on dosage forms produced using ketoprofen as a model drug. Specifically, various grades of ethylcellulose (EC), hypromellose (HPMC), and polyethylene oxide (PEO) were used to generate ketoprofen containing formulations via HME. Ketoprofen morphology, dissolution profiles and accelerated stability analyses were performed on the dosage forms produced.

## Materials and Methods

Materials:

The excipients used were provided by the Dow Chemical Company. Specific grades were ETHOCEL* STD 10 (ethyl cellulose), METHOCEL* E5 (hypromellose), and POLYOX™ WSR N-10, 1105 (PEO). In addition, some proprietary materials were included in the study and are noted as Material A, Material B, etc.

Ketoprofen is USP classified as very slightly soluble (aqueous solubility = 0.1436 mg/ml)[1]. Material was obtained from Spectrum Chemical and Laboratory Products.

Acetaminophen is USP classified as sparingly soluble (aqueous solubility = 14.10 mg/ml)[1]. Material was obtained from Spectrum Chemical and Laboratory Products.

Methods:

Each formulation was pre-blended by adding the appropriate amounts of each raw material to a laboratory scale V-Blender and mixing for 10 minutes.

Single screw extrusion studies were performed on a Haake Rheocord system 90 single-screw extrusion system. The extruder was a 0.75-inch diameter, 28:1 L/D single-screw Rheomex extruder attachment controlled by three heating/cooling zones. A 0.325" diameter rod die was used to shape the extrudate. The extruded rod was cut immediately to produce 300 – 500 mg tablets.

Twin screw extrusion studies were performed using a C.W. Brabender Conical Twin Screw Extruder (model PL2000) equipped with a 5 mm rod die. The pre-blended formulation was fed via a K-Tron volumetric feeder at a rate of 20 g/min. Various temperature profiles and screw rpm were used. The extruded rod was cut immediately to produce 300 – 500 mg tablets.

Dissolution testing was performed with a Distek TCS0200B dissolution system equipped with a Hewlett-Packard 8452A Diode Array Spectrophotometer. The wavelength used for detection was 258 to 262 nm. The testing was performed in 900 mL deaerated (Distek MD-1 De-Gasser) simulated intestinal fluid (pH 7.4). The media temperature was 37 ± 0.5°C. USP Apparatus II was used (paddles) with a rotation speed of 50 rpm. Six replicate samples were run for each test.

X-Ray Crystallography data were generated as follows. Thin sections were sliced from each sample and mounted on zero background holders and held in place using Kapton film. The XRPD patterns were collected using a Bruker D-8 automated powder diffractometer equipped with a Cobalt x-ray tube source, primary beam monochromator and a Vantec detector. The incident beam was collimated using a 3° divergence slit. The active area of the Vantec subtended approximately 10° 2θ. The tube was operated at 30 kV and 50 mA and the samples were illuminated with Cobalt K-α radiation, λ=1.7889Å. XRPD data were collected from 5.0 to 90.0° 2θ using a step width of 0.017° and a scan rate of 1.02°/min. The XRPD patterns were graphically evaluated using JADE XRD pattern processing software.

Differential Scanning Calorimetry (DSC) was performed using a TA Instruments Model Q100 Modulated Differential Scanning Calorimeter. Scans were performed from -40 to 250°C at a rate of 10°C/min.

Thermogravimetric analyses (TGA) were performed using a TA Instruments Model Q500 Thermogravimetric analyzer. Scans were performed at 10°C/min from 20 to 250°C.

Accelerated stability testing was performed in a Lab-Line environmental chamber maintained at 40°C and 75% RH. Tablets were packaged in HDPE containers with foil lined plastic lids. The duration of the study was 6 months. Dissolution testing was performed on interim samples (1 and 3 months). Final samples were analyzed via DSC and X-ray crystallography, in addition to dissolution testing.

Processing temperatures were selected based on two criteria. First, the minimum processing temperature was established based on previously developed minimum processing temperatures for each excipient included in the study. The maximum processing temperature was established by thermal analysis. DSC and TGA analyses were performed on 50/50 combinations of ketoprofen and excipient. These results collectively identify the temperature at which degradation of ketoprofen and/or excipient occurs. The maximum processing temperature is chosen to be significantly below this degradation temperature. The thermal analyses for these formulations indicated degradation occurring at ca. 165°C. Hence the maximum processing temperature included in the study was 150°C.

## Results and Discussion

The formulations and processing conditions included in the studies are documented in Table I. Formulation variables included the level of excipient and ketoprofen. Processing variables included single screw extrusion, twin screw extrusion, and processing temperature.

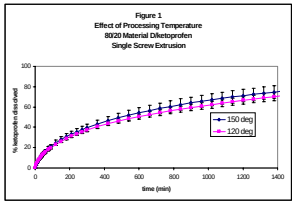
Table 1

| Excipient Type | Excipient Level (%) | Ketoprofen Level (%) | Single Screw Extruder Process Temperature (Deg C) | Twin Screw Extruder Process Temperature (Deg C) |
|---|---|---|---|---|
| EC Std 10 | 95 | 5 | 150 | 150 |
| " | 80 | 20 | 150 | 150 |
| " | 50 | 50 | 150 | 150 |
| PEO N-10 | 95 | 5 | 120 | 120 |
| " | " | " | 100 | 100 |
| " | 80 | 20 | 120 | 120 |
| " | " | " | 100 | 100 |
| " | 50 | 50 | 120 | --- |
| " | " | " | 100 | --- |
| PEO 1105 | 95 | 5 | 150 | --- |
| " | " | " | 120 | --- |
| " | 80 | 20 | 140 | --- |
| " | " | " | 120 | --- |
| " | 50 | 50 | 150 | --- |
| " | " | " | 120 | --- |
| HPMC E5 | 50 | 50 | 150 | --- |
| Material A | 95 | 5 | 160 | --- |
| " | " | " | 150 | --- |
| " | 80 | 20 | --- | 150 |
| " | 50 | 50 | --- | 150 |
| Material B | 95 | 5 | 150 | --- |
| " | 80 | 20 | 150 | --- |
| " | 50 | 50 | 150 | 150 |
| Material C | 95 | 5 | 150 | 150 |
| " | " | " | 120 | 120 |
| " | 80 | 20 | 150 | 150 |
| " | " | " | 120 | 120 |
| " | 50 | 50 | --- | 150 |
| " | " | " | --- | 120 |
| Material D | 95 | 5 | 150 | 150 |
| " | " | " | 120 | --- |
| " | 80 | 20 | 150 | 150 |
| " | " | " | 120 | --- |
| " | 50 | 50 | --- | 150 |
| " | " | " | --- | 120 |
| Material E | 50 | 50 | 150 | 150 |
| " | " | " | 120 | 120 |
| " | 80 | 20 | --- | 150 |

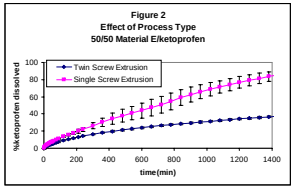
A general observation was that the twin screw extruder allowed processing of some formulations that could not be extruded on the single screw extruder. For example, the 50/50 EC STD 10/ketoprofen formulation could not be extruded on the single screw extruder due to solids conveying issues. This was not unexpected, as twin screw extrusion is known to have excellent solids conveying characteristics.[2]

Processing Variables:

Dissolution testing was used as a means to investigate the impact of processing variables. In general, processing temperature was found to have very little impact. Figure 1 shows typical comparative data.




The mode of extrusion processing was found to have an impact on dissolution behavior. In some cases, dissolution performance was the same. In others, significantly different dissolution profiles were obtained. (Figure 2)

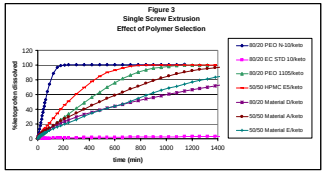



Another general observation was that dissolution data generated with formulations produced via twin screw extrusion often exhibit smaller standard deviations than the same formulation produced via single screw extrusion. This was taken to indicate improved content uniformity for formulations produced via twin screw extrusion.

For the remainder of this paper, the processing mode will be noted for all data presented.

Composition Variables:

Excipient selection was expected to effect ketoprofen dissolution rate. A sampling of these results are shown in Figure 3.




These data demonstrate that the dissolution profiles range from immediate release (e.g. PEO N-10) to controlled release (e.g. Material A) to very slow release (e.g. EC STD 10).

Excipient selection was also anticipated to impact ketoprofen morphology in the extrudate. These determinations were made utilizing DSC and X-Ray crystallography data. Table II documents these data.

Table II.
Effect of Excipient Selection on API Morphology
Formulations Prepared via Single Screw Extrusion

| Excipient | Ketoprofen Level (%) | Crystalline API Present (Yes/No) | Acetaminophen Level (%) | Crystalline API Present (Yes/No) |
|---|---|---|---|---|
| EC STD 10 | 20 | No | --- | --- |
| PEO N-10 | 20 | No | 25 | Yes |
| Material A | 5 | No | 50 | Yes |
| Material B | 20 | No | 50 | Yes |
| Material C | 20 | Yes | 50 | Yes |
| Material D | 20 | Yes | --- | --- |
| Material E | 50 | Yes | 50 | No |

These results indicate that EC STD 10, PEO N-10, Material A and Material B yield compositions that contain no crystalline ketoprofen. Conversely, formulations based on Materials C, D and E all exhibited the presence of crystalline ketoprofen. Similarly produced data is included for formulations incorporating acetaminophen. With this API, only formulations containing material E show the absence of crystalline drug. These data indicate that API morphology in HME produced formulations is very API and excipient specific.

Accelerated Stability Testing Results:

Dissolution testing was performed at 1, 3 and 6 months. Ketoprofen morphology was determined at the conclusion of the accelerated stability test. Table III summarizes these results.

Table III
Impact of Accelerated Stability Testing
Formulations Prepared via Single Screw Extrusion

| Excipient | Ketoprofen Level (%) | Crystalline API Present (Yes/No) Initial | Crystalline API Present (Yes/No) Final | Change in Dissolution Profile (Yes/No) |
|---|---|---|---|---|
| EC STD 10 | 20 | No | No | No |
| PEO N-10 | 20 | No | No | No |
| Material A | 5 | No | No | Yes |
| Material B | 20 | No | No | No |
| Material C | 20 | Yes | No | Yes |
| Material D | 20 | Yes | No | No |
| Material E | 50 | Yes | Yes | Yes |

A number of the formulations exhibited no change in ketoprofen morphology nor change in dissolution profile (e.g. formulations comprising EC STD 10, PEO N-10, Material B). Other formulations showed changes in dissolution profile, with and without changes in the occurrence of crystalline ketoprofen (e.g. Materials A, C and E). A surprising result was the disappearance of crystalline ketoprofen observed with Material D, coupled with no observed change in dissolution profile.

Figures 4 and 5 document the comparative X-ray Crystallography and dissolution results for Material D, respectively.

Figure 4
Accelerated Stability X-Ray Crystallography Results
80/20 Material D/ketoprofen
Single Screw Extrusion

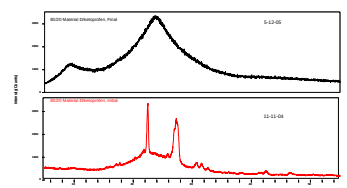
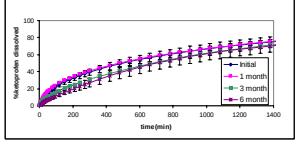



Figure 5
Accelerated Stability Dissolution Results
80/20 Material D/ketoprofen
Single Screw Extrusion




## Conclusions

Excipient selection plays an important role in the characteristics of dosage forms produced by Hot Melt Extrusion. Various dissolution profiles were obtained, depending upon the polymeric excipient used during extrusion. Ketoprofen morphology varied from crystalline to amorphous. Stability performance was found to vary with excipient selection. A number of the excipients included in this study demonstrated no change in dissolution behavior nor ketoprofen morphology over an accelerated stability testing. Notably, PEO N-10, EC STD-10, and Material B proved to be capable of providing stable solid solutions for ketoprofen.

## References:

1. Handbook of Aqueous Solubility Data, S.H. Yalkowsky, Y. He, CRC Press, 2003.
2. TSE Solids conveying reference (David Todd, Ed., *Plastics Compounding*, Hanser/Gardner Publications, Cincinnati (1998).