Discover the quality of Frewitt's expertise in the milling of hard to treat materials, such as polymers

Veterans of 75 plus years in the domain of grinding and milling of powders, Frewitt has established itself over time as a leader in this field by constantly anticipating the needs of its markets, and developing tools for processes accordingly. Frewitt's wide range of applications in terms of high-tech solutions for grinding, homogenizing, de-agglomerating, conveying, dosing and filling of all kinds of powders and granulates makes Frewitt the ideal partner for your most complex projects.

One of our customers, Shin Etsu (USA, NJ) has recently acquired Frewitt machinery. After various tests were carried out on Frewitt equipment, discover below the conclusions they reached in their publication.

Introduction

Amorphous solid dispersion (ASD), where the drug is dispersed in polymers either molecularly or in the amorphous state, has extensively been researched to increase dissolution rate and bioavailability of poorly water- soluble drugs. The most commonly used methods of preparing ASDs are spray drying and hot-melt extrusion (HME). In the recent years, HME has become a popular alternative as a solvent-free method of preparing ASDs. However, the downstream processing of HME extrudates such as milling and further development of a tablet dosage form has always been a challenge due to simultaneous processing of melting and solidification of drug polymer mixture.[1] Because of this, a significant micro and macro level of change in mechanical properties such as loss of compressibility as well as fracture propensity occurs.[2] We present the preparation and downstream processing of an amorphous solid dispersion with itraconazole(ITZ) and Shin-Etsu AQOAT® HPMCAS using HME and different milling technologies. Tablets were prepared from milled extrudates and analyzed.

Experiment

Preparation of amorphous solid dispersion

ITZ was purchased from Fisher Scientific. Shin-Etsu AQOAT® AS-MMP, a recently introduced grade of HPMCAS of mid particle size range for hot melt extrusion (HME) applications, and low-substituted hydroxypropyl cellulose (L-HPC NBD-021) was supplied from Shin-Etsu Chemicals Co. Ltd, Japan. The drug and polymer in the ratio of 15:85 was blended and extruded through 1 mm die using twin screw extruder (Pharma11, Thermofisher Scientific) at constant temperature of 165°C rotating at 150 rpm. Once the extrudates was formed, it was immediately cooled at the conveyor belt and was hand cut into filaments.

Milling of extruded filaments

The extruded amorphous solid dispersions filaments were milled using cryo milling technique on the Frewitt FlexMill- ab system (located at Frewitt USA) equipped with two different technologies, hammer mill (model FlexMill-Lab HM-1) and pin mill (model FlexMill-Lab PM-160) (Frewitt USA). For processing in the pin mill,

the filaments were soaked into liquid nitrogen and passed through the pin mill at dosing valve rpm of 10 as well as rotor rpm of 15000. Whereas, for milling processing through hammer mill, the filaments were milled in two steps. In the first step, filaments were milled to granules using 4 mm screen. The granules were soaked into liquid nitrogen and were further processed through hammer mill at dosing valve rate of 4 RPM and rotor speed of 15000 rpm using 2 mm screen. After the milling process, the particle size distribution of milled extrudates was analyzed using Master Sizer (Malvern Instruments Inc.) and morphological characteristics were examined by SEM (Hitachi TM 3000) at two different magnification of x100 and x500.

Development of tablets

Three different tablet formulation of ITZ: HPMCAS ASD from both milling techniques with varying concentration of milled extrudates was prepared (Table 1). All powder materials except magnesium stearate was blended in Turbula mixer for 15 minutes and further mixed with magnesium stearate for additional 5 minutes. The blend (400 mg) was compressed using a set of 10 mm flat-faced tooling (Natoli Engineering Co. Inc.) using a single press HANDTAP-200 (Ichihashi Seiki) at 12 kN (~153 MPa). Tablets were stored for 24 hours before subject to further evaluation of mechanical properties. Hardness of tablets and dimensions (thickness and diameter) were determined with a hardness tester (Erweka TB125) and tensile strength was calculated (n=6). Disintegration time of tablets was determined using a disintegration apparatus (Erweka ZT72) as per USP specifications at 37±0.5°C (n=6).

Table 1: Itraconazole: HPMCAS ASD formulations.

Material	F-1 w/w (%)	F-2 w/w (%)	F-3 w/w (%)
Milled extrudates	33.3	50.0	66.7
MCC PH 102	58.7	42.0	25.3
L-HPC NBD-021	7.5	7.5	7.5
Magnesium stearate [a)]	0.5	0.5	0.5
Total	100.0	100.0	100.0

[a)] Magnesium stearate was added before compression.

Results

Effect of the milling technology on the particle size distribution

The particle size distribution curve and SEM image of HME filaments after milling using pin mill and hammer mill has been represented in Figure 1. The particle size data (D_{50} and D_{90}) has been summarized in Table 2. As evident from Table 2, filaments milled form pin mill has smaller particle size compared to hammer mill.

It can also be confirmed from SEM images of milled HME extrudates (Figure 2) with extrudates milled from pin mill showing smaller particle size compared to hammer mill. This can be attributed to the high-energy impact created by pin breakers hinged at the disc in pin mill compared to the rotating hammers in hammer mill. Although, pin mill works by similar principle as hammer mills (impacts and shearing), the faster tip speed rotor-stator configuration of intermeshing pins, significantly increases the size reduction efficiency by pin mill compared to hammer mill. Moreover, from the particle size data (Table 2), it can be expected that powder achieved by hammer mill is coarser thus would have better flowability compared to the filaments milled from pin mill.

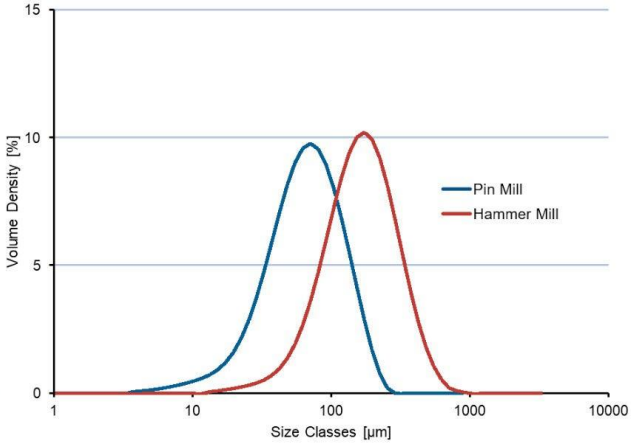

Figure 1: Particle size distribution curve depicting effect of milling techniques on ASD filaments

Table 2: Effect of different milling techniques on particle size distribution of ASD filaments.

Milling head on the FlexMill lab system	Sieve (mm)	Rotor speed (rpm)	Particle size (D_{50}) (µm)	Particle size (D_{90}) (µm)
Pin mill	-	15000	66	137
Hammermill	2	15000	165	341

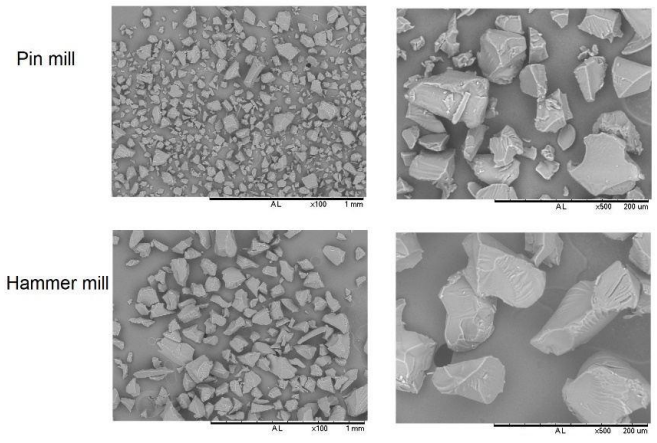

Figure 2: SEM images of HME extrudates milled from pin mill and hammer mill at x100 and x500 magnification

Effect of the milling technology on mechanical properties

The effect of increasing concentration of HME extrudates on mechanical properties is presented in Figure 3. As can be seen from Figure 3, with increase in extrudates concentration, a decrease in tensile strength of tablet can be observed. This is because of poorly compressible properties of extrudates dominating the overall mechanical properties of tablet formulation. A critical evaluation reveals that tensile strength of almost equivalent to 1.7 MPa, suitable for commercial production,[3] can be achieved up to 50 % loading of HME extrudates.

A comparative evaluation between extrudates milled by two different techniques, reveals that HME filaments milled in the hammer mill gave tablets of higher tensile strength compared to powder milled from pin mill. One of the possible reasons could be that filaments milled from hammer mill have a larger particle size, thus degree of elastic recovery is less compared to smaller particle size achieved by milling extrudates from pin mill.

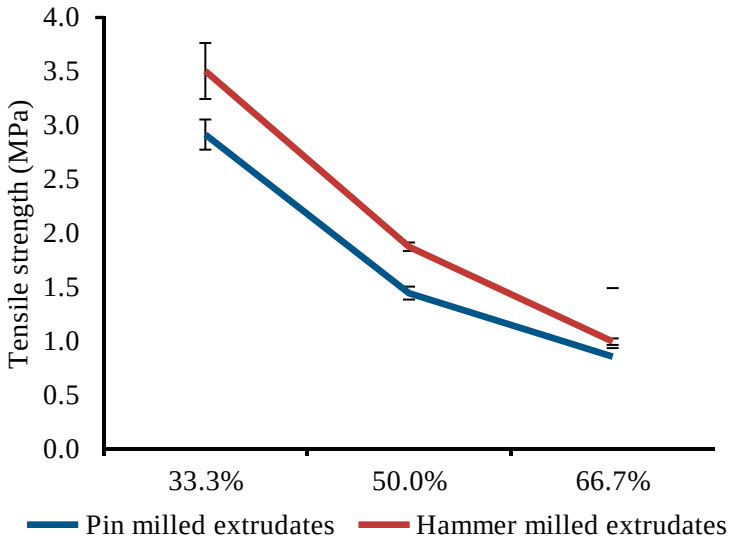

Figure 3: Effect of increasing concentration of milled extrudates on and tensile strength of tablets.

Effect of milled extrudates on disintegration time

The effect of different milling techniques and concentration of HME extrudates on disintegration time is presented in Figure 4. The disintegration time of all the tablet formulation was quick and found to be less than 20 seconds irrespective of tablet milling techniques and concentration of HME extrudates.

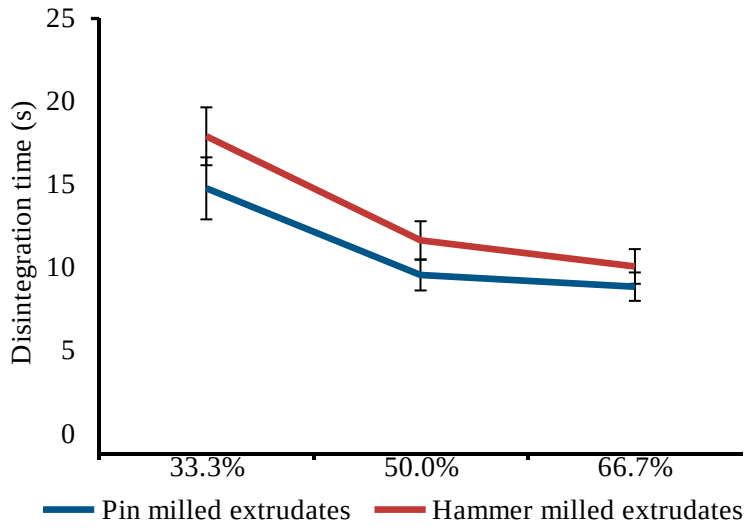

Figure 4: Effect of increasing concentration of HME extrudates on disintegration time of tablets.

Conclusion

An amorphous solid dispersion of itraconazole and Shin-Etsu AQOAT® AS-MMP was prepared by hot melt extrusion. Cryo-milling of extrudates proceeded smoothly on the Frewitt FlexMill-Lab system equipped with a hammer mill or pin mill head. The milled extrudates were successfully compacted into tablets of tensile strength >1.7 MPa at 50 % ASD content regardless of the milling technology used. Increasing concentration of milled extrudates in the formulations decreases tensile strength of the tablets significantly. Additionally, a comparative evaluation indicates that HME extrudates milled on the hammer mill forms tablets of higher strength compared to extrudates milled from pin mill. Thus, based on the present study, it can be concluded that the hammer mill and pin mill are suitable for processing of HME ASD extrudates based on HPMCAS.

References

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