Foaming via melt extrusion for improving the grindability of extrudates and dissolution rate of oral dosages

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Poster no. 225

INTRODUCTION

Foaming during melt extrusion is used to improve the grindability of extrudates. Oral dosages from foamed extrudates can show faster dissolution characteristics compared to un-foamed extrudates [1, 2].

Typical TSE unit operations during HME include:

- Metering multiple feed streams into the TSE: Raw materials are metered into the TSE by loss-in-weight feeders and TSE screws speed (RPM) is used to optimize melting/mixing efficiencies.
- Conveyance/melting/compounding: Solids conveying, melting and mixing occurs in the early part of the TSE process section. The materials must be thoroughly mixed and conditioned prior to the liquid/gas injection.
- Injection/mixing/seal: After initial melting and mixing, sCO2 is injected into the TSE and mixed, just after a dynamic seal is achieved by the screw and barrels design.
- Cooling/pumping: TSE screws now pump the melt forward. The dissolved sCO2 functions as a plasticizer, which causes a viscosity decrease. Barrel temperature set-points are lowered to cool the melt and raise viscosity in preparation for final conditioning in a die.

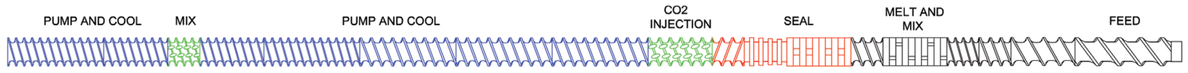

Figure 1: Co-rotating intermeshing twin screw extruder screws design/schematic

EXPERIMENTAL METHODS

Indomethacin (INM) was used as a poorly-water soluble (BSC II) model drug. PVCap-PVAc-PEG was used as a model hydrophilic polymer. Extrusion was performed with a Leistritz ZSE-18 mm, 40 L/D, co-rotating TSE using sCO2 as a physical blowing agent. Foamed and unfoamed extrudates were milled using a laboratory coffee grinder. Dissolution testing in triplicates was performed in a USP apparatus 2 unit. Cell and wall sizes of the foamed extrudates were measured from SEM images.

RESULTS AND DISCUSSION

Table 1 shows the bulk density and particles size/size distribution of the foamed and unfoamed, milled extrudates. The lower the bulk density of the extrudate, the smaller and narrower the resulting particle size and particle size distribution respectively.

Property	*Sample*		
	HME	HD-fHME	LD-fHME
CO_2 concentration [wt%]	**0**	**12**	**4**
Bulk density [g/cm3]	**0.69** ± 0.01	**0.55** ± 0.01	**0.21** ± 0.01
d10 [μm]	**72** ± 1	**50** ± 6	**16.4** ± 0.2
d50 [μm]	**296** ± 7	**206** ± 10	**67** ± 1
d90 [μm]	**864** ± 4	**574** ± 56	**256** ± 13

Table 1: Properties of milled extrudates

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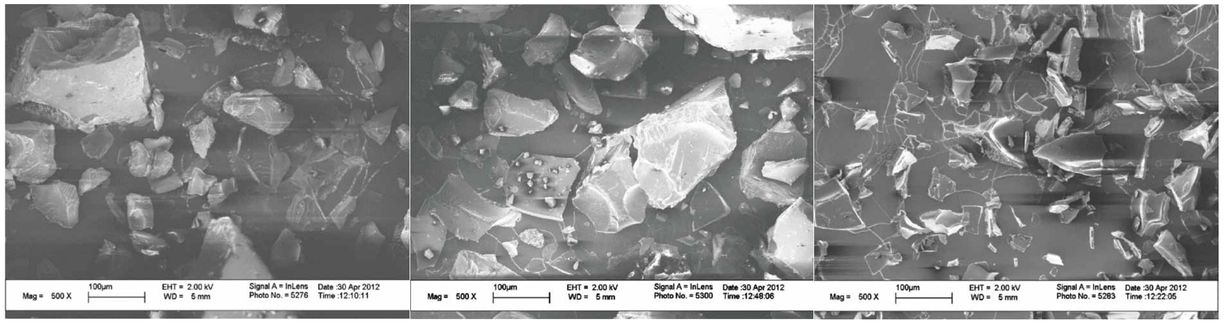

Figure 2: SEM images of a) HME, b) HD-fHME, c) LD-fHM

The release profiles of INM from HPMC capsules containing an average of 25 mg of drug are presented in Figure 3 (dissolution pH = 7). The dissolution of a material in the amorphous state, compared to its crystalline counterpart, is facilitated by the lack of lattice structure and higher free energy. By comparing the release profiles of milled extrudates shown in Figure 3 it is clear that ground LD-fHME leads to the fastest INM release, while the release profiles of ground HME and HD-fHME samples are very similar and their release profiles overlap. The amount of INM released in 10 min from ground LD-fHME sample is 93±4 %, from ground HD-fHME.

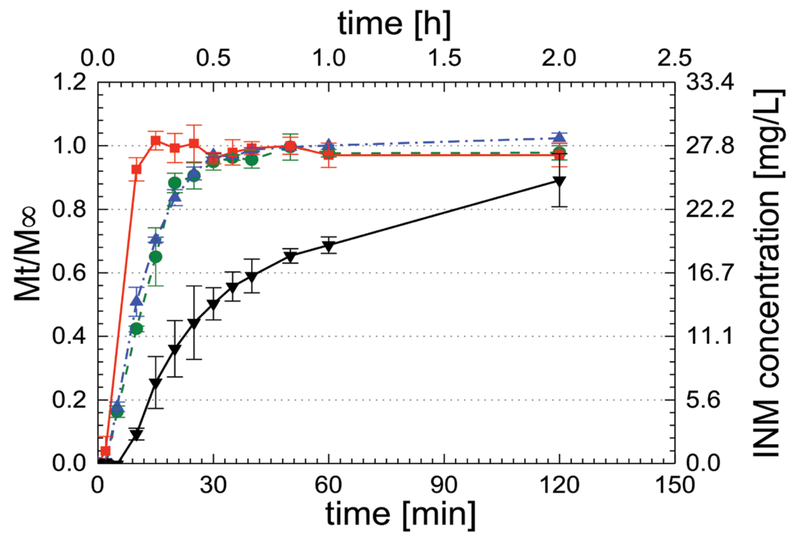

Figure 3:
Release profiles from HPMC capsules of pure INM
(▾), ground HME sample
(●), ground HD-fHME sample
(▲), and ground LD-fHME sample
(■) in phosphate buffer solution with pH 7.4

REFERENCES

1. G. Terife, N. Faridi, C.G. Gogos; SPE ANTEC 2012
2. C.A. McKelvey, C. Brown, L. Schenck, M. Lowinger, J. Moser; SPE ANTEC 2010

CONCLUSION

We have demonstrated that foam extrusion can be used for improving:

- the grindability of extrudates,
- the dissolution rate of oral dosages.

The improvements are directly related to the morphology of the cellular structure developed in the polymer matrix. Smaller cell size and cell wall size results into a smaller parti cle size and particle size distribution during milling. In turn, this increases the total surface area of the oral dosage in contact with the dissolution medium thus improving the dissolution rate.