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

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ABSTRACT SUMMARY
Supercritical carbon dioxide (sCO2) is commonly injected into twin screw extruders (TSEs) in the plastics and food industries to facilitate foaming of high-rate, mass produced products. The same process has been applied to pharmaceutical processes.

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

These TSE unit operations are typical:

**Metering multiple feed streams to the TSE:** Raw materials are metered 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.

EXPERIMENTAL METHODS
Indomethacin (INM) was used as a poorly-water soluble (BSC II) model drug. PVCap-PVAc-PEG was used a model hydrophilic polymer. The experiments used a Leistritz ZSE-18 mm, 40 L/D, co-rotating TSE using sCO2 as a physical blowing agent. Foamed and un-foamed 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. It is evident that the bulk density of the pre-milled foamed extrudates leads to smaller size and narrow size distribution of particles upon milling. Therefore in this case, the smallest particles with the narrowest size distribution were produced by milling the low density foamed extrudate LD-fHME (Figure 1).

<table>
<thead>
<tr>
<th>Property</th>
<th>Sample</th>
<th>HME</th>
<th>HD-fHME</th>
<th>LD-fHME</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂ concentration [wt%]</td>
<td>0</td>
<td>12</td>
<td>4</td>
<td></td>
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<tr>
<td>Bulk density [g/cm³]</td>
<td>0.69 ± 0.55</td>
<td>0.21 ±</td>
<td>0.01</td>
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<tr>
<td>d10 [µm]</td>
<td>72 ± 1</td>
<td>50 ± 6</td>
<td>16.4 ± 0.2</td>
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<tr>
<td>d50 [µm]</td>
<td>296 ± 7</td>
<td>206 ± 10</td>
<td>67 ± 1</td>
<td></td>
</tr>
<tr>
<td>d90 [µm]</td>
<td>864 ± 4</td>
<td>574 ± 56</td>
<td>256 ± 13</td>
<td></td>
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</tbody>
</table>
The release profiles of INM from HPMC capsules containing an average of 25 mg of drug are presented in Figure 2. While the API in the capsules containing pure INM is in its crystalline γ-form, in the ones containing the milled extrudates INM is amorphous having formed a solid solution with the excipient during extrusion. The *in vitro* dissolution tests are conducted in a phosphate buffer solution with pH 7.4. The release profiles in Figure 2 clearly indicate that INM is released faster from the milled extrudates in capsules, than from capsules containing pure crystalline INM. In 30 minutes the amount of INM released from capsules containing pure γ- INM is 50±5 %, while from the milled extrudates it is 95±3 % for ground HME sample, 97±1 % for ground HD-fHME and 96±2 % for ground LD-fHME. Since INM is amorphous in the milled extrudates its release is faster compared to the crystalline samples. 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 2 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 sample is 51±5 % and from ground HME sample 42±2 %. These results suggest that there is a direct correlation between release rate and particle size. Other reports found in the literature show similar results. (Lyons et al. 2007; Verreck et al. 2007; Nagy et al. 2012), the same results have also been reported for placebo formulations (Verreck et al. 2006b).

**CONCLUSION**

We have demonstrated that foam extrusion can be used for improving a) the grind-ability b) 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 particle 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.

**REFERENCES**