Fatty Acids for Controlled Release Applications: A Comparison between Prilling and Solid Lipid Extrusion as Manufacturing Techniques

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Purpose
This study evaluates the impact of 2 continuous processing techniques, prilling and solid lipid extrusion, on the characteristics of multiparticulate fatty acid-based formulations. In contrast to prilling where the entire lipid fraction must be molten to obtain a liquid with adequate viscosity for pumping through narrow prilling nozzles in order to create droplets, solid lipid extrusion operates below the melting point of the lipid component. Via a thermo-mechanical treatment at moderate pressure and temperature, the mass is sufficiently plasticized to mould it through the die of the extruder. As the formulation only partially melts, a solid matrix is formed via the combined action of thermal effects and mechanical compression during screw extrusion. The aim of this study was to evaluate the solid state characteristics, drug release, internal structure and stability of fatty acid-based formulations after processing via prilling and solid lipid extrusion. In addition, process analytical technology (PAT) via in-line Raman spectroscopic monitoring was used to investigate the impact of the extrusion conditions on the physical properties of drug and fatty acid during solid lipid extrusion.

Methods
Myristic acid (MA, Tm: 54.9°C), stearic acid (SA, Tm: 69.5°C) and behenic acid (BA, Tm: 78.0°C) were selected as matrix formers combined with metoprolol tartrate (MPT, Tm: 122.8°C) as model drug (30% w/w). Prilling was performed by means of the PrillDrop® device (Peira, Belgium), equipped with a pneumatic nozzle. Solid spherical particles (± 2.4 mm) were obtained by quench cooling droplets of a homogeneous mixture of drug and molten lipid (100 °C) in liquid nitrogen. Solid lipid extrusion was performed using a Prism Eurolab 16 co-rotating, fully intermeshing twin-screw extruder (Thermo Fisher Scientific, Germany). All mixtures were extruded within a temperature window up to the melting point of the fatty acid using a throughput of 0.3 kg/h and a screw speed of 40 rpm. After cooling to room temperature, the extrudates (diameter: 3 mm) were manually cut into mini-cylinders of 4 mm length. All formulations were characterized by means of in vitro dissolution, MDSC, X-ray diffraction, high resolution X-ray CT-scanning, Raman and FT-IR spectroscopy.

Results
The prilling process allowed complete dissolution of MPT in the molten fatty acid phase, generating semi-crystalline MPT and the formation of hydrogen bonds between drug and fatty acids in the solid prills. In contrast, as solid lipid extrusion induced only limited melting of the fatty acids, molecular interaction with the drug was inhibited, resulting in a crystalline state of the drug. Although the addition of a low melting fatty acid (e.g. 20% MA) to the behenic acid matrix allowed more MPT/fatty acid interaction during extrusion, crystalline MPT was detected after processing. Mathematical modeling using analytical solutions of Fick’s second law of diffusion, revealed that the extrudates exhibited a higher apparent drug/water mobility than prills of the same composition, probably due to differences in the matrix structure of the prills and extrudates. In the extrudates, numerous small pores were distributed all over the systems, whereas the outer matrix of the prills seemed to be much denser. The impact of these differences on drug release was demonstrated by using the apparent diffusion coefficient of MPT (or water) determined with the extrudates to theoretically predict drug release from prills with a diameter of 2.4 mm of the same composition. Comparing this theoretical prediction with the experimental MPT release kinetics from the prills, it became evident that the predicted drug release was substantially overestimated, due to the higher mobility of the drug (or water) in the extrudates compared to the prills.

Irrespective of the processing method, mixed fatty acid systems (e.g. MA/BA matrices (2:5 ratio)) exhibited a lower matrix porosity, resulting in a slower drug release rate. Solid state analysis of these systems revealed a different impact on final matrix crystallinity depending on the processing technique: the extrusion process induced hydrogen bonds between the fatty acids, even though the crystalline structure of the constituent fatty acids was mainly retained, while prilling of mixed fatty acid systems generated a reduced MA crystallinity. Binary MPT/fatty acid systems processed via extrusion showed better stability during storage at 40°C than the corresponding prills. Although mixed fatty acid systems were stable at 25°C, stability problems were encountered during storage at 40°C: a faster release was obtained from the prills, whereas drug release from the extrudates was slower. Further research is recommended to correlate these stability issues with possible aging phenomena of the fatty acid matrices.

Conclusion
This study demonstrated that the processing of fatty acid-based formulations via prilling and solid lipid extrusion created matrices with different drug crystallinity and drug release kinetics. Furthermore, a different impact on final matrix crystallinity of fatty acid mixtures was observed depending on the processing technique.