Gastro-resistant multiparticles for mesalazine colonic delivery

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PURPOSE

To develop gastro-resistant multiparticles systems for mesalazine colon delivery capable to facilitate the dispersion in water and the intake by children.

METHOD

Mesalazine microparticles, containing stearic acid, carnauba wax and Eudragit L®, were obtained by spray-congealing. "Excipient microparticles" of mannitol/lecithin were prepared by spray-drying. Mesalazine lipid microparticles, non-agglomerating per se, were agglomerated by blending in turbula with mannitol/lecithin spray-dried microparticles in different ratio (2:1, 4:1, 6:1 and 8:1). The lipidic microparticles and agglomerates were characterized by optical microscopy, Scanning Electron Microscopy, Differential Scanning Calorimetry (DSC) and X-ray Powder Diffraction (PXRD) and preliminary study of wettability. Gastro-resistance and drug release were evaluated by dissolution tests at variable pH (2h in HCl 0.1N and 6h in phosphate buffer pH 7.4).

RESULTS

Optical Microscopy

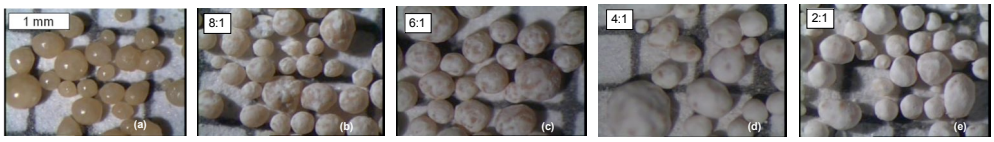

Figure 1. Optical microscopy pictures of lipidic microparticles (a) and the agglomerates in different lipidic microparticles:excipient microparticles ratio (2:1 (b), 4:1 (c), 6.1 (d) and 8:1 (e); (magnification 40X)).

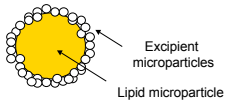

Figure 2. Scheme of agglomerate (lipidic microparticles and "excipient microparticles").

SEM

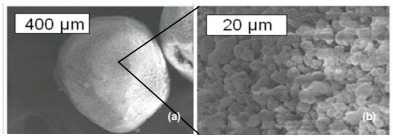

Figure 3. SEM images of agglomerates 2:1.

The lipidic microparticles showed a sticky and smooth surface and quite rounded shape (Figure 1a); the agglomerates presented a less polish surface, but in all cases rounded shape (Figure 1 b-e). In Figure 2 it is reported a scheme of agglomerate. The tumbling process allowed the deposition of lechitin on the wax surface (Figure 3a). In the case of agglomerates 2:1 more layer of "excipient microparticles" were deposited on the lipidic microparticles (Figure 3b).

Dissolution profile

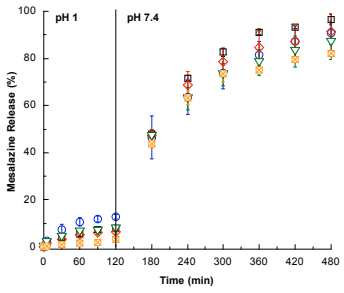

Figure 4. Dissolution profiles of the lipidic microparticles (⊠) and the agglomerates lipidic microparticles/"excipient microparticles" in different ratio (2:1 (○); 4:1 (□); 6:1 (◇) and 8:1 (▽)). (mean ± s.d., n=3).

DSC

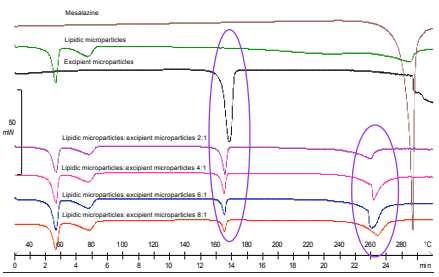

Figure 5. DSC thermograms of mesalazine, lipidic microparticles and agglomerates at different lipidic microparticles/"excipient microparticles" ratio.

PXRD

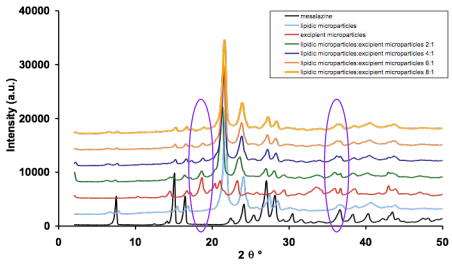

Figure 6. PXRD patterns of mesalazine, lipidic microparticles and agglomerates at different lipidic microparticles/ "excipient microparticles" ratio.

In acid medium less of 10% of drug loaded was released in the first two hours, except for the agglomerates 2:1 where the higher amount of lechitin in the "excipient microparticles" acts as a surfactant, increasing the wettability of the system (Figure 4). In phosphate buffer the release of 5-ASA rose rapidly due to the dissolution of stearic acid and Eudragit S®.

The thermogram of 5-ASA showed a sharp endotherm peak around 285°C (Figure 5). No modification is observed in the lipidic microparticles, while in presence of the "excipient microparticles" the peak shifted to around 262°C. Moreover as the ratio of the "excipient microparticles" decreased, the area of the peak at around 165°C is reduced. This effect, also confirmed from the intensity reduction of the diffraction peaks at around 18.7 and 36.7° (Figure 6), strengthened a lower deposition on the lipidic microparticle surface.

A preliminary study of system wettability, carried out by measuring the water time to pass through a tube filled with agglomerates or lipidic microparticles under a constant speed, showed that the lipidic microparticles had lower retention time, due to their hydrophobic nature (Figure 7).

Wettability study

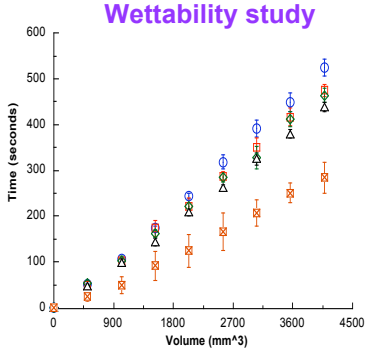

Figure 7. Wettability profiles of lipidic microparticles (⊠) and agglomerates (2:1 (○); 4:1 (□); 6:1 (◇) and 8:1 (△)).

CONCLUSIONS

Lipidic microparticles prepared by spray congealing are gastroresistant; their wettability can be increased by agglomeration with mannitol/lecithin microparticles. The agglomeration technology can make feasible the delivery of gastro-resistant system for extemporaneous oral use in small children.