Enteric-coated spherical granules for dual delivery of orlistat & acarbose with diverging properties

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INTRODUCTION AND AIM

Current immediate-release monotherapy products of **orlistat and acarbose** have limitations, including moderate efficacy and undesirable side effects. Reformulating and combining the two substances into a single **multiple-unit capsule** with a multimodal controlled-release profile has the potential to enhance efficacy while mitigating side effects (1). The target product profile required that the product consisted of three granules (i.e., G1, G2 and G3), of which one is **an enteric coated granule containing both drugs** (Figure 1). The two drugs have different properties regarding solubility, melting point and hygroscopicity.

This study details the preparation of the enteric coated granule and the technical challenges overcome in combining the two drugs.

Granule weight distribution in the EMP16 60/20 mg (orlistat/acarbose) capsule

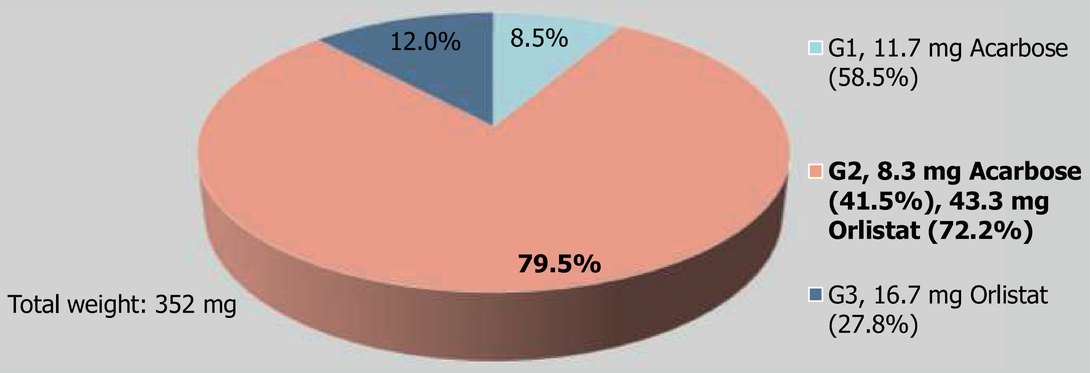

Figure 1. EMP16 60/20 mg (orlistat/acarbose) – granule weight and drug distribution.

METHODS

The particle size of the granules had to be below approximately 1 mm to ensure unrestricted passage through the pylorus (2). Thus, the technology used for G2 preparation was layering the drugs and the enteric polymer on neutral core pellets in a fluid bed coater in three steps:

1. both drugs in a solution of hydroxypropyl cellulose and polysorbate 80,
2. a solution of hydroxypropyl cellulose also containing suspended microcrystalline cellulose and stearic acid particles to form a sub-coat layer,
3. an enteric coating layer composed of the enteric polymer hypromellose acetate succinate, ammoniac and talc.

The appearance and size distribution were assessed and the *in vitro* dissolution (USP 2) of both drugs from both the enteric-coated granules and from the final capsule was determined.

RESULTS

A G2 core granule was selected based on favorable properties regarding size (270 µm), surface texture and of a low porosity (2.3%).

When the drying process was too rapid, it resulted in suboptimal formation of the first drug-containing layer. However, extending the drying time by adjusting the coating liquid and process parameters led to the formation of spherical granules with relatively smooth surfaces and a median diameter of 420 µm (Figure 2). The sub-coated and enteric-coated granules closely resembled the core pellets in terms of geometric shape and surface texture.

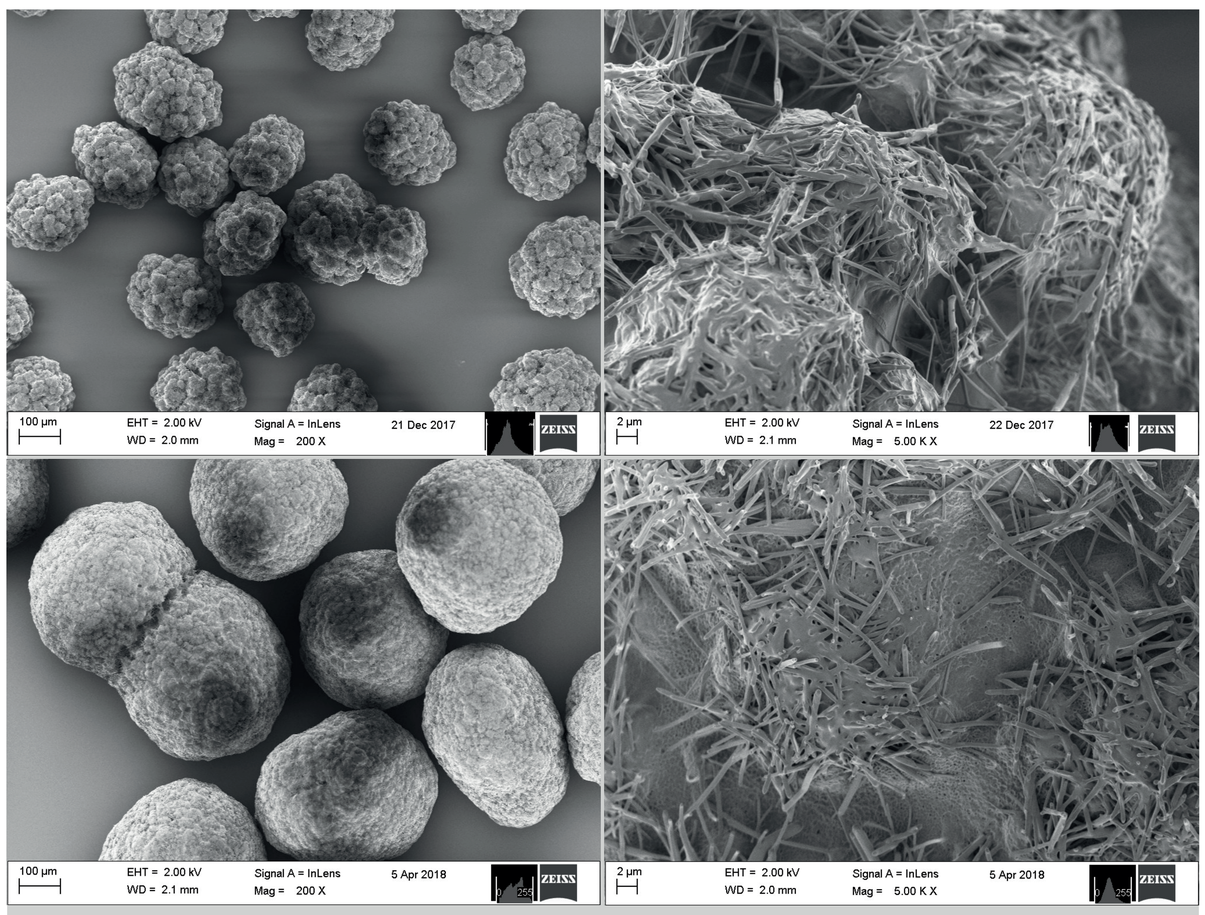

Figure 2. Scanning Electron Microscope images, 200x and 5000x. G2 granules after the first layer, too rapid drying (above) or extended drying (below).

Curing of the coated G2 granules in the fluid bed coater yielded a typical enteric release profile, and the final capsule's *in vitro* release aligned well with the target product profile (Figure 3).

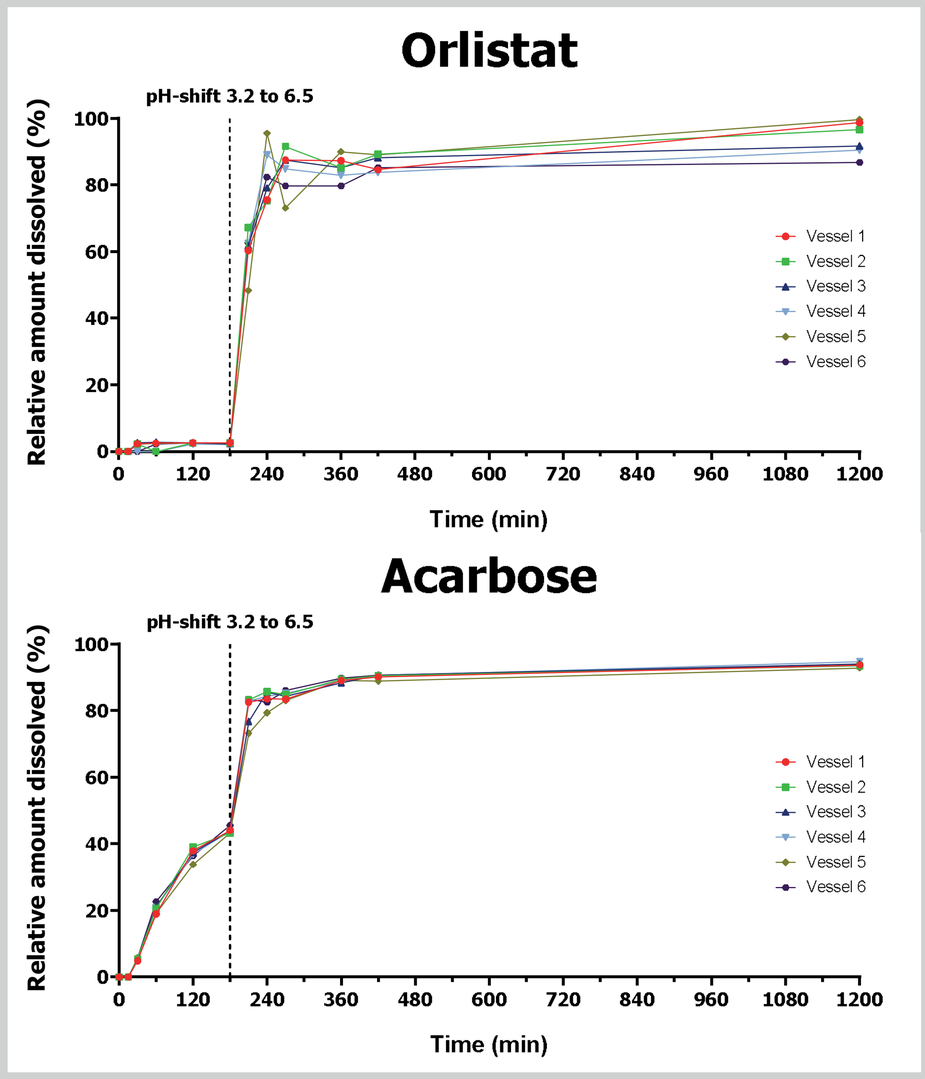

Figure 3. EMP16 60/20 mg (orlistat/acarbose) capsule *in vitro* release.

CONCLUSION

This study showed that, by employing the appropriate processes and excipients, it is possible to successfully develop an oral capsule formulation of a reproducible and effective controlled-release fixed-dose combination of the highly contrasting drugs acarbose and orlistat.

REFERENCES

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