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Targeted, controlled delivery of a small molecule to the colon

CAPSUGEL®

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PURPOSE

Delivering dosage forms to the small intestine can provide benefits by reducing systemic toxicity, targeting specific sites for the treatment of local diseases and preventing degradation of acid-labile substances in the stomach [1]. Due to the neutral pH and low presence of protease enzymes in the colon, it has been explored as a suitable site for delivery of protein and peptide drugs.

Targeting to the large intestine can be achieved by the application of an enteric coat. Phloral™ technology provides benefits over traditional pH responsive polymers as it uses both pH and bacterial digestion to trigger API release in the large intestine [2].

Following erosion of the applied coat, the dosage form then faces further challenging conditions, including as low free water volume, decreased motility and large air occlusion. Liquid filled capsules may provide advantages over traditional dosage forms in these difficult conditions.

METHODS

Capsule preparation

Development work was carried out to determine a formulation which delivered release of the API over a 5 – 10 hour period. Hard gelatin capsules were filled with a 250 mg dose of the API, using a semi-automated filling machine. A gelatin band was applied to capsules using a Benchtop Qualiseal bander and capsules were coated with the Phloral ™ coat using an aeromatic Strea-1 fluid bed coater, see Figure 1. After coating capsules were subject to three phase disintegration testing in 0.1 M HCl, pH 6.5 phosphate buffer and pH 7.2 phosphate buffer.

Figure 1 – Aeromatic Strea-1 coater with solvent coating capacity

Faecal slurry testing

In addition to pH buffer testing, Phloral coated capsules (n=4) were pre-exposed to 0.1M HCl for 2 hours and hanks buffer (pH 6.8) for 2 hours. Capsules were transferred to faecal slurry (pH 7.4). The metabolic activity of colonic bacteria was assessed using sulfasalazine. Release of API was measured using HPLC-MS.

RESULTS

A prototype formulation was identified which had a release profile suitable for controlled release of the API. Dissolution of the API in simulated gastric fluid (SGF) was performed (Figure 2). Capsules were successfully coated with the Phloral coating suspension, Figure 3, and following drying, the capsules withstood two hours in 0.1 M HCl, two hours in pH 6.5 phosphate buffer, before breaching in pH 7.2 phosphate buffer.

Figure 2 – Release of API from uncoated hard gelatin capsules in simulated gastric fluid

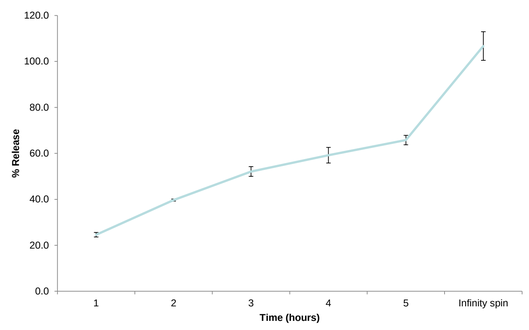


Figure 3 – Hard gelatin capsules coated with Phloral ™ coat

For the faecal slurry test, after pre-exposure of coated capsules to 0.1 M HCl and hanks buffer, no visible release of API was observed. The capsules then breached in the faecal slurry and the release profile is shown in Figure 4. For coated capsules, delayed API release was achieved, with Tmax of approximately 7 hours.

A further test was performed in order to assess the activity of the bacteria within the faecal slurry used. Slow degradation of sulfasalazine was observed, indicating low activity of the colonic bacteria (Figure 5). This may have a correlation with the digestion capacity of the bacteria on degradation of the coating and impacted on the release profile of coated capsules.

Figure 4 – Release of API in faecal slurry

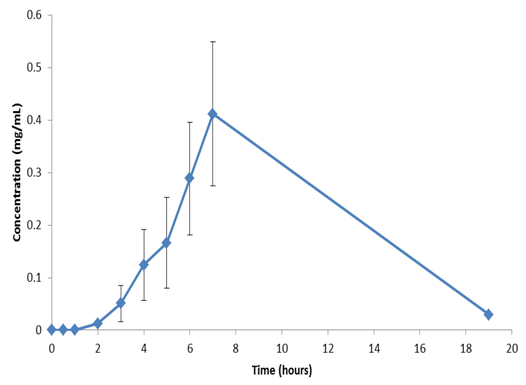
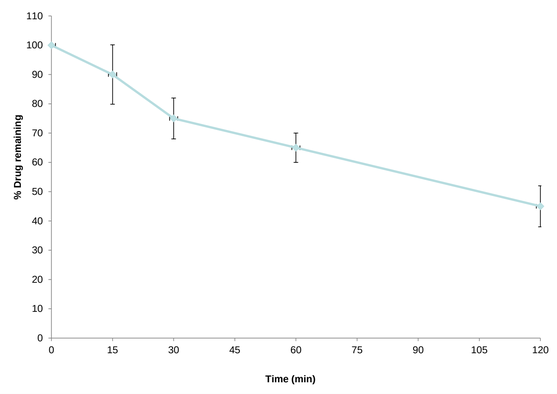


Figure 5 – Metabolism of sulfasalazine in faecal slurry



CONCLUSIONS

A controlled release formulation was able to be developed which would provide release of a small molecule over a therapeutically relevant timeframe. Capsules filled with this formulation were able to be successfully coated with a Phloral coat.

No visible drug release was observed after two hours of exposure to gastric and small intestinal conditions. Release of the capsule contents was observed in colonic conditions. Liquid filled hard capsules combined with a Phloral coat could provide targeted delivery of API to the colon.

ACKNOWLEDGEMENTS

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REFERENCES

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