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Formulation design and evaluation of self-emulsifying API delivery systems (SEDDS) for a poorly water-soluble BCS II API

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encap drug delivery

PURPOSE

Robust SEDDS formulation development is based on in-depth analysis and understanding of a given API's physicochemical and biological characteristics and, if appropriate, the consequent selection of specific lipid-based excipients known to have physiological effects[1].

The purpose of this study was to leverage internal know-how and methodologies to develop lipid formulations that address solubility and metabolic barriers to the oral bioavailability of a BCS class II API.

The capacity of each formulation to increase API loading was also explored and was indirectly evaluated through supersaturation measurements during *in vitro* digestion.

METHODS

SEDDS were designed using API solubility and chemical stability data in a range of oils, cosurfactants and surfactants. Concept formulations were initially selected based on their ability to solubilise the API at the target dose, and formulation physical stability.

Dispersion behaviour was assessed in both SGF (Simulated Gastric Fluid) and SIF (Simulated Intestinal Fluid), focusing on emulsion stability and risk of API precipitation over six hours.

Based on the dispersion performance, concept formulations were progressed onto *in vitro* digestion assessment using the methods developed by the LFCS Consortium[2] to understand the fate of the API over time in simulated small intestinal conditions.

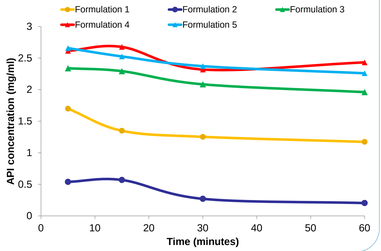
In addition, the extent of supersaturation on digestion was assessed for each formulation, with a view to identify the potential risk of API precipitation on increasing API loading.

RESULTS

APIs are considered good candidates if Log D values are >5 and solubility in long chain oils is >50 mg/g[3]. To promote the lymphatic delivery of the API, formulations were designed incorporating long chain lipids and high HLB surfactants at a target API loading of 125 mg/g.

Dispersion testing in SGF and SIF identified three lead formulations that formed stable emulsions (assessed visually), with no evidence of API precipitation (assessed microscopically).

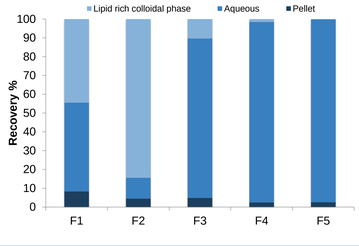
Figure 1 Solubilized API concentration in the aqueous-rich colloidal phase formed during *in vitro* digestion of 5 lipid formulations



These formulations were readily digested within 60 minutes, and measured solubilized API concentrations in the aqueous-rich colloidal phase (Figure 1) were 2.0 (F-3), 2.4 (F-4) and 2.3 mg/mL (F-5), i.e., over >60% of the incorporated API.

Critically, the amount of API solubilized by these optimized formulations was substantially higher when compared to two previously developed lipid formulations, F-1 and F-2 (1.2 and 0.2 mg/mL, Figure 1), wherein the majority of API (>50%) remained in a poorly dispersed and lipid-rich colloidal phase (Figure 2). The higher API concentrations in the F-2, F-3 and F-4 aqueous phase suggest better absorption *in vivo* relative to F-1 & F-2, since they present higher API concentrations in a readily available micellar form.

Figure 2: API distribution across lipid, aqueous and pellet phases at 60 minutes digestion, presented as the recovered API concentration in each phase.



In addition, for all optimized formulations, the calculated supersaturation ratio (solubilized API concentration / API solubility in digested lipid formulations) was <1, indicating that higher API loadings may be supported without inducing a risk of precipitation, providing greater dosing flexibility when the program is progressed to *in vivo* studies.

CONCLUSIONS

Three SEDDS formulations consisting of long-chain lipids and cosurfactant/surfactant were developed to support BCS II API solubilisation in the GI tract and to promote lymphatic uptake.

Formulation performance was assessed *in vitro*, against two previously developed formulations. The three newly developed formulations demonstrated formulation stability on dispersion, and increased API solubilisation in the aqueous phase during digestion, in comparison to the two formulations developed previously.

The developed SEDDS therefore offer the potential for bioavailability enhancement *in vivo* through optimized API solubilisation combined with long-chain lipids to promote API entry into the lymphatic system.

ACKNOWLEDGEMENTS

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