

Excipients influencing droplet size in a SEDDS system

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Introduction

Formulators are challenged with new chemical entities that are insufficiently soluble in aqueous media. It is estimated that between 40% to 70% of NCE's are poorly soluble, which challenge adequate and reproducible absorption from the gastrointestinal tract following oral administration. Therefore, oral lipid-based formulations given as liquid or liquid in capsule dosage forms can have beneficial influence on gastrointestinal absorption. There are numerous of lipid excipients used to prepare drug products of this type including fatty acids, natural oils and fats, semi synthetic glycerides, polyglyceryl fatty acid esters, cholesterol, and phospholipids. This work evaluates a list of excipients employed in placebo formulation that are stable in gastrointestinal environment (GI) and if tested in-vivo could improve absorption in humans.

Objectives

To provide a list of excipient prototype combinations capable of remaining intact upon dispersion in Simulated Gastric Fluid (SGF) and produce micron size droplets that can influence the absorption.

Methods

Prototype Formulations

A list of placebo prototype formulations were manufactured with commercial grade co-solvents, solvents, and surfactants (low and high HLB values) such as Capmul® MCM, Captex® 500 P, Cremophor® EL, Ethanol (200 proof), Imwitor® 988, Labrafac™ Lipophile WL 1349, Labrasol®, Lipoxol® 400 Med, Miglyol® 812, Olive Oil, and Tween® 80. The prototypes included combination of these excipients at various levels normally employed in a typical marketed drug product.

Preparation of Placebo Prototypes

The prototypes were prepared by simple mixing at room temperature. At the end, the prototypes were vortexed on Thermolyne Maxi Mix II for 2 minutes before checking the miscibility of the excipients. A visual observation was performed on the prototypes to check the miscibility and for inclusion in further experiments.

Dispersion in SGF

The above formulated prototypes were dispersed in SGF without Pepsin (USP 29, Gastric Fluid, Simulated Test Solution) at 1:9 proportions. The dispersion was vortexed on Thermolyne Maxi Mix II for 15 seconds before performing visual and microscopic (10x) observations. The dispersion droplet dimension was measured by adding few drops of the dispersion on a glass slide for observation under Olympus® BX51 Polarizing Microscope fitted with Digital Camera at initial, 1 hour, and 2 hours time points. In-between the time points the dispersions were stored at room temperature with out disturbance.

Results

The visual examination of the developed prototypes with combination of excipients showed that either they remained intact as a uniform single layer or separated into two distinguishable layers.

The visual observation of the prototypes in the SGF demonstrated formation of droplets, which meant that the developed placebo prototypes were stable in the SGF. Most of the prototypes visually looked hazy in nature while the prototypes which visually showed to have precipitated were not considered for microscopic observation. The formation of droplets at micron size indicates that the high HLB value excipients demonstrate stability in the GI environment.

Among many prototype combinations evaluated the inclusion of ethanol with equal proportions of high HLB value Cremophor EL and low HLB value Miglyol 812 and lower proportion of high HLB value Labrasol demonstrated droplets between 21 to 60 micron size (figure 1). This indicates that the combination with low and high HLB value excipients demonstrate stability in the gastrointestinal (GI) environment. Also, observed is the fact that this prototype had small droplets and was less varied in droplet size.

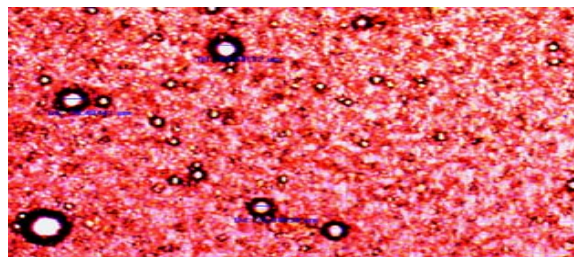


Figure 1: Prototype with small and less varied size droplets after 2 hours of dispersion in SGF

One another prototype of interest (need to remain intact) upon dispersion in SGF was the combination of pure olive oil with equal proportions of low HLB value Miglyol 812 and high HLB value Cremophor EL and Labrasol showed droplets between 10 to 71 micron size (figure 2). Also, observed is the fact that this prototype upon microscopic observation had most number of small droplets and probably remained intact through the 2 hours study period with no noticeable droplet agglomeration.

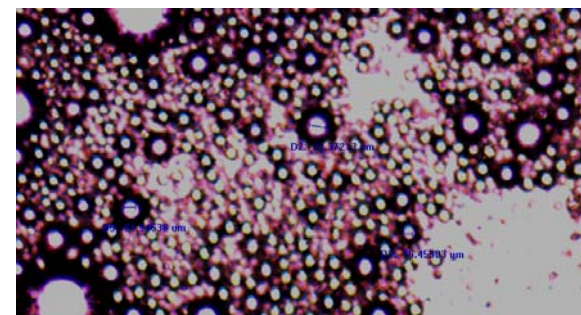


Figure 2: Prototype with most smallest droplets after 2 hours of dispersion in SGF

The prototypes evaluated with surfactant blends demonstrate that a combination can provide better self-emulsifying properties. Interestingly, there is no supporting information claiming benefit that the small size droplets can promote increased GI absorption in humans. So far all the work performed is in rats which lacks the lipid processing capabilities.

Conclusions

The excipients employed in the placebo formulations are thermodynamically stable in SGF and produced micron size droplets capable of increasing absorption due to increased surface area.

References

1. Wasan EK, et al. (2009). Development and Characterization of Oral Lipid-based Amphotericin B formulations with Enhanced Drug Solubility, Stability, and Antifungal Activity in Rats Infected with Aspergillus Fumigatus or Canadian Albicans. *Int J. Pharm.* 372 (1-2), 76-84.
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