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Impact of Polymer Addition on Compound Precipitation Inhibition from Lipid-Based Formulations through *In-Vitro* Dispersion and Digestion Testing

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Key words: Lipid-based formulation, precipitation inhibition, formulation development, solubility screening, polymer excipients

PURPOSE

The aim of the study was to evaluate the impact of polymer addition on compound precipitation from type IV Lipid-Based (LB) formulations developed for a poorly water soluble compound. Lipid-based formulations were developed with a BCS class II model Compound with a poor solubility (< 65 µg/mL) and high apparent permeability (> 1 × 10-6 cm/s). Formulations with and without the addition of polymers at varying concentrations were prepared and evaluated through *in-vitro* dispersion and digestion testing.

METHODS

Formulation Development

First, a kinetic solubility screening was carried out in twenty orally acceptable pharmaceutical excipients. The solubility screening was performed for different Compound concentrations at a set temperature depending on the melting point of the excipients.
Based on the solubility screening, excipients were selected to be combined in single, binary or ternary formulations. For binary and ternary formulations, the selection of the appropriate excipient combinations were facilitated by the use of phase diagrams from the Capsugel proprietary Lipidex Database.

In-vitro testing

Diluability testing

The equivalent weight of a size 0 capsule was placed in a glass beaker. Then, 250 mL of pH 1.2 medium at 37°C was added progressively while stirring. Microscopic observations at defined time points were performed to check absence of Compound precipitation.
The solubility of Compound in the dilutions was determined after 3 hours using a HPLC method.

Digestion testing

The potential digestion of the developed formulations was assessed by dispersing 1g of formulation in 36 ml of digestion buffer.
The digestion of formulations was followed by potentiometric measurements of the fatty acids formed and the potential impact of the digestion on the solubilisation capacity of LB formulations was evaluated by assay of the Compound in the digestion medium using a HPLC method.

RESULTS

Based on the solubility screening and assisted by the Capsugel Lipidex Database, two placebo LB formulations were selected for this study: a LB formulation (Formulation 1) composed of known non digestible excipients (i.e. PEG ethers) and a LB formulation (Formulation 2) composed of a known digestible excipient (i.e. PEG ester) and a known non digestible excipient (i.e. PEG ether).

The Compound was solubilized at the target concentration (i.e. ~ 200 mg/g) in both defined formulation compositions. The same formulations were prepared with the addition of different polymers such as povidone (PVP), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC) or methylcellulose (MC).

All developed LB formulations were submitted to dispersion testing in pH 1.2 medium. All formulations dispersed rapidly in the dispersion medium and formed a micro-emulsion spontaneously. Compound precipitation was observed over time for all LB formulations. In order to discriminate the formulations, the percentage of Compound solubilized in the aqueous phase was determined after 3 hours by HPLC (Table 1).

	% of Compound solubilised in pH 1.2 medium after 3 hours	
	LB Formulation 1	LB Formulation 2
Without polymer	2.43	1.31
+ 1% MC	5.45	1.55
+ 1% HPC	11.46	2.46
+ 1% HPMC	6.88	2.08
+ 1% PVP	8.74	1.52

Table 1: Compound assay in dilution for each LB formulation after 3 hours

Based on Compound assay results, a significant improvement of Compound aqueous solubility was observed by addition of precipitation inhibiting polymers in the selected LB formulations, in particular with HPC.

Different concentrations of HPC (i.e. from 0.5% to 2%) were tested in order to determine the optimal concentrations to be added. According to the results (Table 2), a concentration of 1% seemed to be optimal to prevent Compound precipitation upon dilution in pH 1.2 medium.

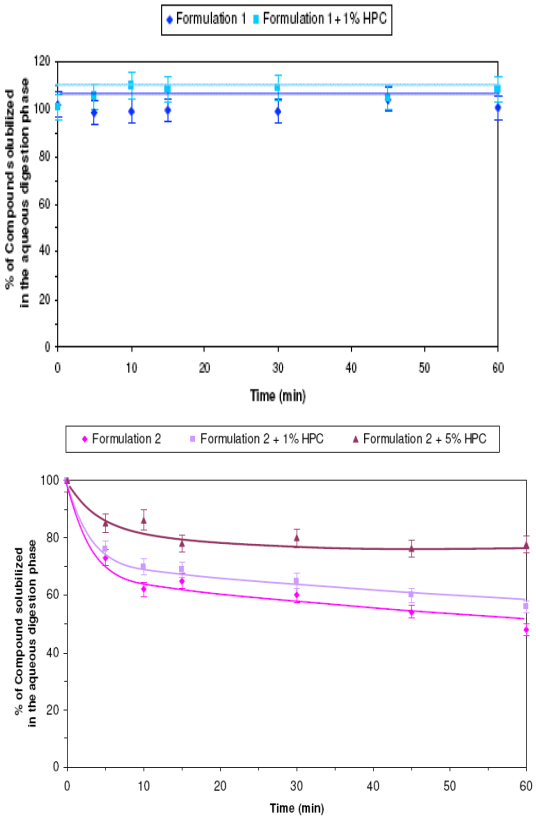
	% of Compound solubilised in pH 1.2 medium after 3 hours	
	Formulation 1	Formulation 2
Without polymer	2.43	1.31
+ 0.5 HPC	4.34	2.16
+ 1% HPC	11.46	2.46
+ 2% HPC	5.30	2.40

Table 2: Compound assay in dilution with different concentrations of HPC

Afterwards, the digestibility of LB formulations with and without HPC and their solubilization

capacities upon digestion were evaluated through *in-vitro* digestion testing. The compound precipitation from the LB formulations was directly dependent on their excipient composition for the investigated Compound. Indeed, the solubilization capacity of the formulation containing digestible excipients was significantly reduced compared to the formulation containing non digestible PEG ethers.

The addition of polymers at varying concentrations reduced significantly Compound precipitation throughout digestion testing (Graph 1) for the formulation containing digestible excipients.



Based on these results, it can be concluded that the addition of HPC into LB formulations can inhibit compound precipitation upon dispersion and digestion. However, the extent of compound precipitation inhibition is dependent on the polymer concentration and on the formulation composition.

CONCLUSION

As demonstrated the addition of polymers into Type IV LB formulations can stabilize these LB formulations, prevent compound precipitation upon *in-vitro* dispersion and digestion, and could therefore enhance *in-vivo* solubility of poorly water soluble compounds.

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REFERENCES

- Gao, P., et al. Journal of Pharmaceutical sciences, 2009. 98(2): p.516-528
- Miller, D., et al. Pharmaceutical research, 2008a. 25(6): p.1450-1459
- Miller, D., et al. Drug Development and Industrial Pharmacy, 2008b. 34(8): p 890-902
- Raghavan, S.L., et al. International Journal of Pharmaceutics, 2001b.212(2): p. 213-221
- Usui, F., et al. International Journal of Pharmaceutics, 1997. 154(1): p.59-66

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