Solidification of liquid self-emulsifying lipid formulations by loading on solid mesoporous carriers

Vincent Jannin[a]; Stéphanie Chevrier[a]; Cédric Miolane[a]; Margaux Metin[a]; Hamza Benhaddou[a]; Yann Chavant[a]; Fred Monsuur[b]; Frédéric Demarne[a]
[a] Gattefossé SAS, 36 chemin de Genas, 69804 Saint-Priest cedex, France, vjannin@gattefosse.com
[b] Grace Material Technologies, Brandstraat 12, Lokeren, Belgium, fred.monsuur@grace.com

INTRODUCTION

Lipid-based formulations (LBFs) can be effective drug delivery systems for poorly water-soluble chemical entities, provided they are designed with careful selection of the excipients, based on their role in the delivery system and in relation to the API properties. The primary factor leading to increased bioavailability by LBFs is the administration of the drug in a pre-dissolved state thus avoiding the dissolution limiting step. The fate of a drug formulated in a LBF is dependent on the ability of the formulation components to keep the drug in solution during the initial dispersion and/or digestion processes.

These systems should therefore be formulated by the informed selection and appropriate combination of excipients. Most of the excipients used for the design of LBFs are liquids or semi-solids and should therefore be encapsulated in soft or hard gelatin capsules. Since tablets is the preferred dosage form for patients, the ability to transform liquid LBFs into solid particles and consequently tablets is a key step to facilitate the development of new drug products. The aim of this study was to develop solid Self-Emulsifying Lipid Formulations (SELFs) of Piroxicam by loading of liquid SELFs on solid carriers.

EXPERIMENTAL METHODS

The loading of LBFs on solid carriers is the most common technology to transform liquid formulations into solid particles. The carrier should have a large specific surface area and high mesoporosity in order to permit the loading of large amount of liquid SELF into the particles. Silica gels and silicates are the preferred solid carriers because of their good adsorption capacity for oils and surfactants, and also for their good flowability and compressibility – key criteria to ensure a successful tablet development. Physico-chemical properties of solid carriers: Syloid® XPD3050 (Grace), Aeroperl® 300 (Evonik), Neusilin® US2 and Fujicalin® (Fuji Chemical) were evaluated by isothermal gas adsorption measurements (specific surface area - BET, mesoporosity - BJH), particle size distribution analysis, and flowability. The loading capacity of solid carriers was determined by adding lipid excipients or SELF onto the carrier in a mixer with a low impeller speed (Diosna). The maximum loading capacity was considered reached when the mixture increases in size and/or is no longer free-flowing. To assay the capacity of the solid carrier to release the SELF, a dispersion test was performed in a dissolution bath. The fineness of the dispersion was measured by Dynamic Light Scattering (Nicomp). The combined *in vitro* dispersion and digestion assay was performed with a pH-stat apparatus[1]. Samples were taken during dispersion and digestion phases, centrifuged and the supernatant collected for further HPLC analysis.

RESULTS AND DISCUSSION

Among the tested solid carriers, the silica gel (Syloid® XDP3050) possesses the highest specific surface area (BET), mesoporosity (BJH) and lipid excipient adsorption capacity (Table 1). The adsorption capacity of all carriers increases with the hydrophilicity of lipid-based excipients (i.e. higher loading capacity for excipients with high Hydrophilic Lipophilic Balance).

Table 1. Physico-chemical properties of selected solid carriers.

Solid carrier	Syloid® XDP3050	Aeroperl® 300	Neusilin® US2	Fujicalin®
Specific surface area (m²/g)	317	270	303	22
Mesoporosity (mL/g)	1.787	0.527	1.343	0.144
Median size (µm)	62	45	100	139
Angle of repose (°)	29	N/A	29	32
Ability to settle (mL)	12	32	19	15
Loading capacity of Labrasol® ALF (%)	160	150	120	60

All selected carriers possess good to excellent flowability and compressibility, except Aeroperl® 300.

Figure 1 shows that solid carriers are not inert in term of their capacity to release the formulation. The colloidal phases formed by the exemplar SELF - Labrasol® ALF - are not identical after desorption from the carriers. Particle size distributions are significantly lower for porous and hydrophilic carriers showing a possible interaction between the silanol groups and surfactants by hydrogen bonding. In addition, the release capacity of Neusilin® US2 varies overtime as the particle size distribution of colloidal phases decreases even further after 3 months storage.

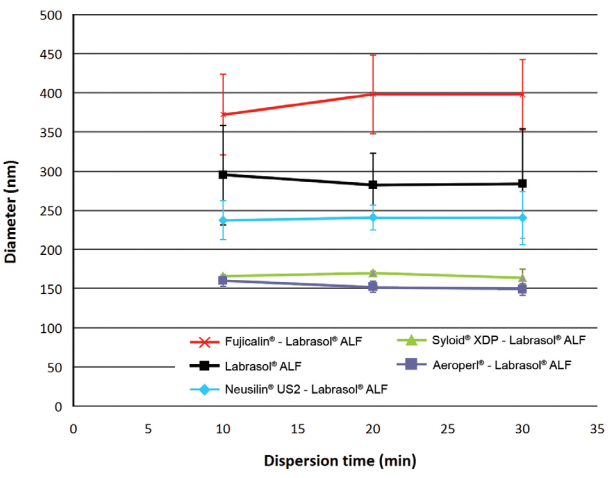

Figure 1. Influence of solid carrier on the colloidal phases formed by Labrasol® ALF during the dispersion test.

As a consequence the release of Piroxicam is not completely achieved during the combined dispersion and digestion test (Figure 2), as already observed with other drugs[2]. The release of Piroxicam is significantly slower from Neusilin® US2 due to the specific architecture of its pores in bottleneck shape[3].

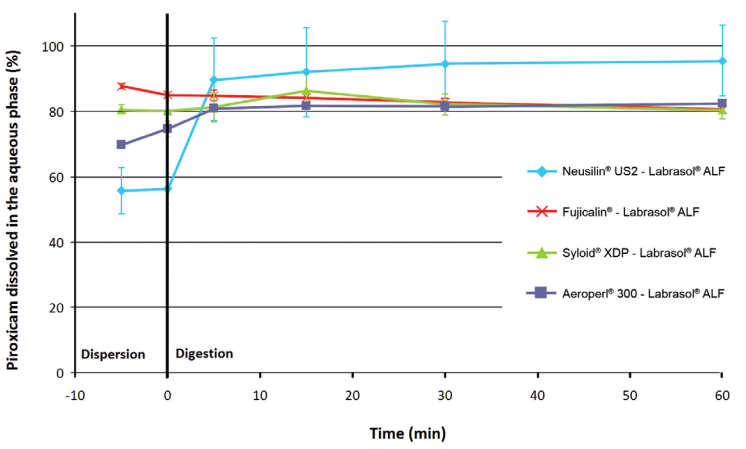

Figure 2. Impact of the solid carrier on the percentage of Piroxicam dissolved in the aqueous phase during the combined *in vitro* dispersion / digestion test (mean ± std. deviation, n=3).

The incomplete release of Piroxicam could be due to either (i) the interaction of the drug by hydrogen bonding with the polar surface of the carrier or (ii) the partial ionization of the drug at the pH of the intestinal lumen. Figure 3 presents the release of Piroxicam from a modified dispersion / digestion test with the pH-stat.

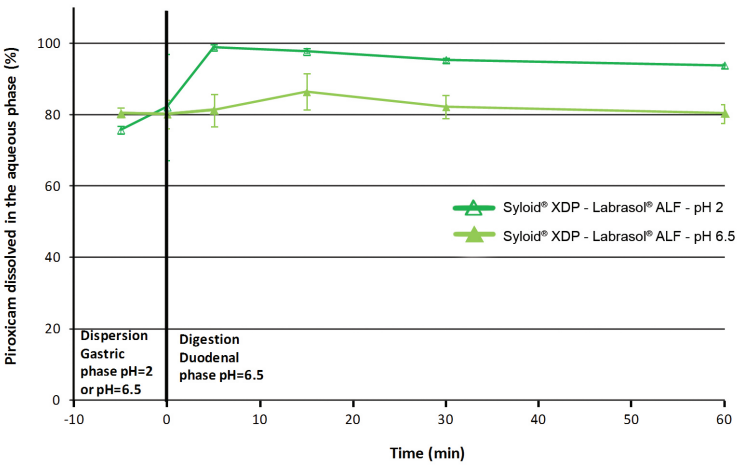

Figure 3. Impact of the ionization of Piroxicam on the percentage of Piroxicam dissolved in the aqueous phase.

In this case the dispersion phase was conducted at pH=2 to mimic the fasted gastric condition and the duodenal phase at pH=6.5 to mimic the fasted intestinal lumen. The reduced interaction between the drug (in protonated form) and carrier surface allows a complete release of Piroxicam. These latter conditions mimics well the fate of solid dosage forms after oral administration and suggests that this Labrasol® ALF/ Syloid® XDP could efficiently release the drug in the gastrointestinal tract.

CONCLUSION

The selection of the solid carrier is not a trivial step during the drug product development. It is not an inert material as it can interact with the drug and/or the formulation hence modifying the performance of the LBF. The choice of the carrier should be adapted to the physico-chemical properties of the drug and the composition of the SELF.

Hence there is no generic solid carrier that can be used for all LBFs; it should be selected specifically for the combination of excipients needed to dissolve the drug. So far, the silica gel Syloid® XDP3050 is one of the most promising solid carrier to load and fully release LBFs.

REFERENCES

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