SELF FORMULATION PROTOCOL: PART II - EXCIPIENT SELECTION, DIAGRAM DESIGN AND SELECTION OF PROTOTYPE FORMULATIONS

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1 - PURPOSE

The aim of this study was to develop a sound formulation protocol for Self Emulsifying Lipid Formulation (SELF) with the latest characterization tools proposed by the LFCS Consortium [1,2]. In this second part, we constructed binary and ternary diagrams composed of excipients possessing the higher solvent capacity for BCS class II model drugs. We also tested the ability of these prototype formulations to self-emulsify in contact with aqueous media in order to select prototype formulations.

2 - METHODS

Lipid-based excipients exhibiting the highest solvent capacity for Ibuprofen, Cinnarizine, Piroxicam, and Fenofibrate were Transcutol® HP, water-soluble surfactants, and Capryol™ 90 as summarizes in Table 1.

Table 1. Selection of excipients (in bold) able to dissolve the dose of four model BCS class II drugs in 1g.

Exipients		Solubility (mg/mL)			
		Ibuprofen	Cinnarizine	Piroxicam	Fenofibrate
Surfactants (HLB>10)	Gelucire® 48/16	**300**	15	**20**	**150**
	Gelucire® 44/14	**300**	6	**20**	**150**
	Labrasol® ALF	**357.0**	**28.3**	**15.0**	101.9
	Tween® 80	**306.6**	20.0	**18.5**	107.2
	Cremophor® RH40	368.9	28.9	**28.3**	86.9
Co-surfactants (HLB<10)	Capryol™ 90	296.0	**37.8**	6.4	127.8
	Lauroglycol™ 90	249.9	30.5	3.7	94.6
Oils	Labrafac™ CC	17.3	26.6	2.5	54.4
Hydrophilic solvent	Transcutol® HP	**437.0**	**42.7**	19.9	123.0
Therapeutic dose (mg)		200	25	10	67

To develop lipid-based formulations we constructed binary or ternary phase diagrams consisting of surfactants to promote the self-emulsification, and solvents and/or co-surfactants to allow for the dissolution of the dose into a capsule.

- Miscibility of selected excipients

Miscibility of excipients is checked at 37°C overnight. In the case of mixtures containing a solid lipid-based excipient (Gelucire® 48/16 or Gelucire® 44/14), the miscibility is additionally checked at 25°C overnight to avoid the exudation of liquid from the solid mixture.

- Dispersion of miscible mixtures

A dispersion test is performed on miscible mixtures in a USP dissolution bath. One gram of miscible mixture is introduced in 200 mL of purified water or simulated gastric fluid (SGF) at 37°C under agitation with a paddle at 60 rpm [3]. Performance criteria are: ease of emulsification, homogeneity and fineness of the dispersion. The fineness of the dispersion is assayed by dynamic light scattering (DLS, Particle Sizing Systems Nicomp).

- Solubility of the drug within selected mixtures

The theoretical solubility of the model drug is calculated in each selected mixture with Equation 1 to verify that it could theoretically dissolve the selected dose. Then the equilibrium solubility of the drug is measured with the same method as for excipients. In brief, the drug is added in excess to 60 mL amber borosilicate glass bottle containing 10 g lipid formulation. Bottle are allowed to equilibrate at 37°C under magnetic stirring with periodic vortex mixing to ensure that undissolved drug particles are homogeneously suspended in the lipid slurry. At intervals, bottles are sampled and these aliquots are centrifuged (Universal centrifuge 320R) at 2800g and 37°C for 30 min [1]. This separated samples into a solid pellet phase and a particle-free supernatant. The supernatant was sampled and diluted with an appropriate solvent (a solution of valerophenone in acetonitrile (0.35 mg/mL) for Ibuprofen, acetonitrile for Cinnarizine and Piroxicam, and methanol for Fenofibrate) for further HPLC analysis. The equilibrium solubility was considered as reached when the difference between two consecutive values is less than 5%. This equilibrium solubility is then used to calculate the percentage of saturation of the drug within the mixture, with Equation 2.

Equation 1 $Cs_T = \sum (\%_{ex} * S_D)$

Cs_T: theoretical equilibrium solubility
$\%_{ex}$: percentage of excipient in the mixture
S_D: equilibrium solubility of the drug in excipient

Equation 2 $\%Sat = D / (V * Cs)$

%Sat: percentage of saturation of the drug within the mixture
D: therapeutic dose of the drug
V: volume of the dosage form (1mL)
Cs: equilibrium solubility

3 - RESULTS AND DISCUSSION

- Ibuprofen

For Ibuprofen, the best solvent is Transcutol® HP, then all water-soluble surfactants. The quantity of hydrophilic cosolvent that can be introduced in the formulation is generally limited to 15% in order to avoid massive precipitation of the drug after dispersion in aqueous media and incompatibility with capsules. All liquid water-soluble surfactants gave homogeneous mixtures with up to 15% of Transcutol® HP. For Gelucire® 48/16, a solid surfactant, the maximum quantity of liquid cosolvent that can be added is limited to 6% because for higher quantities, non homogeneous mixtures are obtained after storage at 25°C. These formulations are able to quickly self-emulsify in contact with aqueous media and form micellar solutions with mean particle size ranging from 2 to 7 nm (Figure 1B, 2). Mixtures containing Labrasol® ALF as water-soluble surfactant showed the quickest emulsification time when compared to other surfactants that are either viscous liquids or semi-solids.

- Cinnarizine

For Cinnarizine, the best solvents are Transcutol® HP and Capryol™ 90, then most of the water-soluble surfactants. The same combinations are chosen for Cinnarizine as for Ibuprofen. Capryol™ 90 is also a good solvent for Cinnarizine and was used to draw binary and ternary phase diagrams. This co-surfactant is miscible with Labrasol® ALF alone or in combination with Transcutol® HP in all proportions. However, these mixtures are only able to give turbid and homogeneous dispersions after dispersion in aqueous media when the quantity of Labrasol® ALF is above or equal to 85%. These dispersions are very fine emulsions with mean particle size ranging from 150 to 450 nm (Figure 1A, 3).

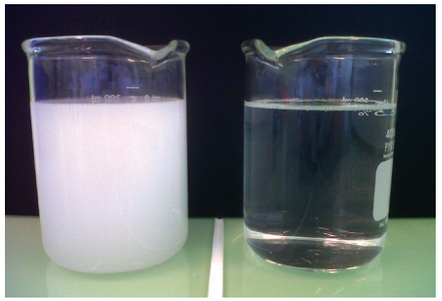

Figure 1. Example of turbid and transparent homogeneous dispersions:
A. Turbid and homogeneous dispersion of 94% Labrasol® ALF + 6% Transcutol® HP;
B. Transparent and homogeneous dispersion of 94% Gelucire® 48/16 + 6% Transcutol® HP.

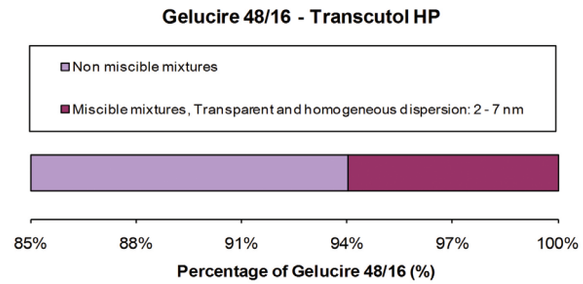

Figure 2: Gelucire® 48/16 - Transcutol® HP binary diagram.

- Piroxicam

For Piroxicam, only the water-soluble surfactants and Transcutol® HP are able to dissolve the dose within 1g. In order to compare the efficiency of these surfactants in term of emulsification and ability to maintain the drug in solution after dispersion and digestion, formulations containing each surfactant individually are selected.

- Fenofibrate

For Fenofibrate, the best solubilizers are the solid water-soluble surfactants: Gelucire® 44/14 and Gelucire® 48/16. As for Piroxicam, simple one-excipient formulations are selected to compare both solid surfactants.

All selected prototype formulations are listed in Table 2. The key characteristics of these formulations are presented: LFCS type of formulation, mean particle size after dispersion in water (expressed in volume, mean ± standard deviation), theoretical and measured equilibrium solubility, as well as the percentage of saturation of the drug.

Table 2. Selected prototype formulations for each model BCS class II drugs.

Drug	Prototype formulations	LFCS Type	Size of aqueous dispersion (nm)	CsT (mg/mL)	Cs (mg/mL)	%Sat
Ibuprofen	94% LAS / 6% TRA	IIIB	185±41	361.8	330.1	61
	94% 4816 / 6% TRA	IV	2±0.2	308.1	231.5	86
	94% T80 / 6% TRA	IV	<5	314.4	267.7	75
	100% 4816	IV	7±1	300	300	67
	100%4414	IIIB	15±2	300	300	67
Cinnarizine	90% LAS/10% C90	IIIB	411±71	29.3	34.9	72
	75% LAS/10% C90/15% TRA	IIIB	373±76	31.4	23.9	105
Piroxicam	100% LAS	IIIB	412±70	15.0	15.0	67
	100% T80	IV	9.9±2	18.5	18.5	54
	100% RH40	IV	9±2	28.3	28.3	35
	100% 4816	IV	7±1	20	20	50
	100% 4414	IIIB	15±2	20	20	50
Fenofibrate	100% 4816	IV	7±1	150	150	45
	100% 4414	IIIB	15±2	150	150	45

with: LAS=Labrasol® ALF, TRA=Transcutol® HP, 4816= Gelucire® 48/16, T80=Tween® 80, 4414=Gelucire® 44/14, C90=Capryol™ 90, RH40=Cremophor® RH40.

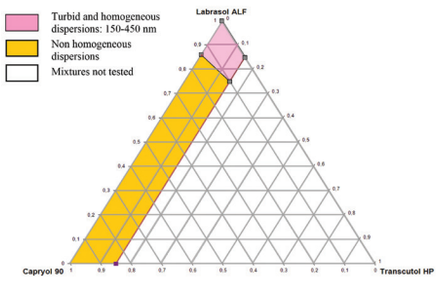

Figure 3: Labrasol® ALF – Capryol™ 90 - Transcutol® HP ternary diagram.

4 - CONCLUSIONS

The development of binary and ternary diagrams permits to define the percentage of each component in order to obtain a compromise between solubilisation in the dosage form, ease of dispersion and homogeneity of the aqueous dispersion. Formulations leading to homogeneous aqueous dispersions and able to dissolve the dose are selected as prototypes for the next step of SELF formulation protocol: the digestion assay.

5 – REFERENCES

[1] Williams.H.D., Sassene.P., Kleberg.K., Bakala-N'Goma.J.C., Calderone.M., Jannin.V., Igonin.A. et al. 2012. Toward the establishment of standardized *in vitro* tests for lipid-based formulations. part 1: method parameterization and comparison of *in vitro* digestion profiles across a range of representative formulations. J. Pharm. Sci. 101. 3360-3380.
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