SELF FORMULATION PROTOCOL: PART I - SOLUBILITY DETERMINATION IN LIQUID AND SOLID EXCIPIENTS

V. JANNIN[1,*], M. MICHENAUD[1,2], S. BELOTTI[1,3], C. ANDRÉ[1,4], S. CHEVRIER[1], Y. CHAVANT[1], C. VOUTSINAS[1], F. DEMARNE[1]
[1] Gattefossé, Saint-Priest, France, [2] Université Paris-Sud, Chatenay-Malabry, France
[3] University of Parma, Parma, Italy, [4] University of Lyon, Villeurbanne, France
* Email: vjannin@gattefosse.com

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]. These SELF are generally used in order to increase the solubility and bioavailability of poorly water-soluble drugs, mainly BCS class II drugs. The bioavailability of this class of molecules is limited by their low solubility in aqueous fluids. Lipid-based formulations are able to increase their bioavailability by delivering the drug directly as a solution in the gastrointestinal tract. To do so, formulators have to select the best solvents and surfactants to be able to dissolve the dose in a self-emulsifying formulation. In this first part, we assayed the solubility of four BCS class II model compounds in thirteen liquid and solid lipid-based excipients.

2 - METHODS

Ibuprofen, cinnarizine, piroxicam, and fenofibrate are chosen as model poorly water-soluble drugs possessing a log P between 3 and 6. The physicochemical properties of these model drugs are shown in Table 1.

Drugs	Water solubility (mg/L) – 25°C	Melting point (°C)	Log P	pKa	Molecular weight	Therapeutic dose (mg)
Ibuprofen	21	76	3.97	4.91	206	200
Cinnarizine	750	120	5.77	7.88	368	25
Piroxicam	23	198	3.06	1.87-6.3	331	10
Fenofibrate	250	81	5.3	NA	360	67

NA = Not applicable

Table 1. Physico-chemical properties of four model BCS class II drugs: Ibuprofen, Cinnarizine, Piroxicam, Fenofibrate.

Liquid and solid excipients tested in this study are presented in Table 2. These excipients are classified in four types: water-soluble surfactants, water-insoluble surfactants a.k.a. co-surfactants, oils, and hydrophilic cosolvents (Table 2).

Functionality	Chemical name	Commercial name	HLB
Surfactants (water-soluble)	PEG-32 stearate	Gelucire® 48/16	12
	Lauroyl polyoxyl-32 glycerides	Gelucire® 44/14	11
	Caprylo caproyl polyoxyl-8 glycerides	Labrasol® ALF	12
	Polyethylene-20 sorbitan oleate	Tween® 80	15
	Polyethylene-40 hydrogenated castor oil	Cremophor® RH40	14
Co-surfactants (water-insoluble)	Oleyl polyoxyl-6 glycerides	Labrafil® M1944CS	9
	Propylene glycol monocaprylate	Capryol™ 90	5
	Propylene glycol monolaurate	Lauroglycol™ 90	3
	Polyglyceryl-3 dioleate	Plurol® Oleique CC 497	3
Oils	Medium chain triglycerides	Labrafac™ CC	1
	Glyceryl monolinoleate	Maisine™ 35-1	1
	Glyceryl mono-oleate	Peceol™	1
Hydrophilic cosolvent	Diethylene glycol monoethylether	Transcutol® HP	NA

HLB=Hydrophilic Lipophilic Balance, NA=Not applicable

Table 2. Classification of lipid-based excipients.

• Solubility of drugs in liquid excipients

Solubility of drugs in liquid excipients is assayed by HPLC analysis. Solubility is determined at 37°C because it was not possible to assay viscous excipients (e.g. Plurol® Oleique or Tween® 80) at 25°C, and there is also only a slight increase of solubility from 25 to 37°C (about 5%, see Table 3 for the example of Ibuprofen and Cinnarizine).

Excipients	Ibuprofen			Cinnarizine		
	Solubility (mg/mL)		Difference (%)	Solubility (mg/mL)		Difference (%)
	25°C	37°C		25°C	37°C	
Labrasol® ALF	351.9	357.0	1.4	27.8	28.3	1.8
Labrafil® M1944CS	17.4	18.1	3.9	10.5	12.4	15.3
Capryol™ 90	274.8	296.0	7.2	36.1	37.8	4.5
Lauroglycol™ 90	248.7	249.9	0.5	28.0	30.5	8.2
Labrafac™ CC	16.1	17.3	6.9	24.4	26.6	8.3
Transcutol® HP	434.1	437.0	0.7	41.8	42.7	2.1

Table 3. Influence of temperature on the solubility of Ibuprofen and Cinnarizine in liquid lipid-based excipients.

The drug is added in excess to 60 mL amber borosilicate glass bottle containing 10 g lipid-based excipient. 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 is 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 is considered as reached when the difference between two consecutive values is less than 5%. For most of the excipients, the equilibrium is reached in less than 3 days.

• Solubility of drugs in solid excipients

For solid lipid-based excipients (Gelucire® 48/16 and Gelucire® 44/14), the solubility of drugs is assayed by differential scanning calorimetry (DSC). According to the Raoult's law, the variation of melting enthalpy is linked with the concentration of drug dissolved within the excipient. Different concentrations of the drug in the excipient are prepared to determine its solubility in the solid-state excipient. Samples are prepared by melting the excipient and dispersing a specified amount of drug under stirring. These samples are let at 50°C to equilibrate overnight, vortexed, then aliquoted in aluminum pans, and let at 25°C to solidify / crystallize for 24 hours before DSC analysis.

Sample (2.5-5 mg) was sealed in aluminum pan and analyzed using a DSC (Pyris Diamond, Perkin-Elmer, USA) calibrated with indium (T_m = 156.6°C, ΔH_m =26.6 J.g^{-1}). Thermal analysis is carried out between -20 and 120°C at a heating rate of 3°C.min^{-1}.

The drug solubility is observed when there is a change of slope in the curve fitting the evolution of melting enthalpy of the excipient as a function of the drug concentration in the sample [3].

3 - RESULTS AND DISCUSSION

Figure 1 presents the evolution of the melting enthalpy of Gelucire® 48/16 as a function of the concentration of two model drugs as an example. Cinnarizine and Ibuprofen decreases the melting enthalpy of this excipient indicating its solubility within the solid excipient and as a consequence the disorganization of its crystalline matrix. When the solubility of these drugs is reached, the melting enthalpy either stays constant or increases again. Depending on the drugs, the decrease of enthalpy can be more or less pronounced: 16 J/g for Cinnarizine and 130 J/g for Ibuprofen.

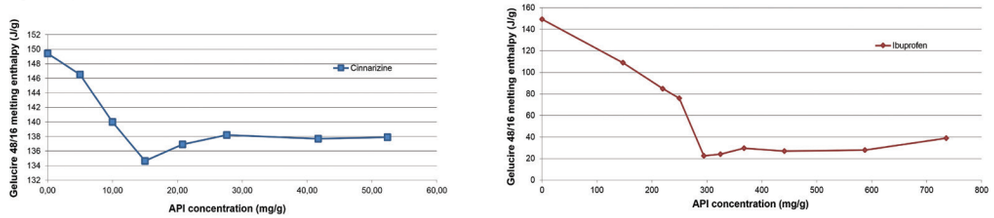

Figure 1. Evolution of the melting enthalpy of Gelucire® 48/16as a function of the concentration of Ibuprofen or Cinnarizine.

Table 4 summarizes the equilibrium solubility determined for all four model drugs. The same group of excipients always shows the highest solvent capacity: the hydrophilic cosolvent Transcutol® HP, all the water-soluble surfactants (Labrasol®, Gelucire® 44/14, and Gelucire® 48/16 for example), and among co-surfactants Capryol™ 90 is always the most efficient. This confirms the need of water-soluble components such as surfactants with high HLB and solvents to dissolve this type of poorly soluble drugs.

Excipients		Solubility (mg/mL)			
		Ibuprofen	Cinnarizine	Piroxicam	Fenofibrate
Surfactants	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	Labrafil® M1944CS	18.1	12.4	3.5	34.2
	Capryol™ 90	296.0	37.8	6.4	127.8
	Lauroglycol™ 90	249.9	30.5	3.7	94.6
	Plurol® Oleique CC 497	14.6	7.7	2.6	32.4
Oils	Labrafac™ CC	17.3	26.6	2.5	54.4
	Maisine™ 35-1	168.9	11.9	2.9	59.8
	Peceol™	162.5	11.7	2.5	62.3
Hydrophilic solvent	Transcutol® HP	437.0	42.7	19.9	123.0

Table 4. Solubility of four model BCS class II drugs in liquid and solid lipid-based excipients.

4 - CONCLUSIONS

This case study shows that BCS class II drugs with a log P between 3 and 6 are more soluble in hydrophilic cosolvents and water-soluble surfactants than in oils (with long or medium fatty acid chain). It also demonstrates the ability of DSC to determine the solubility of drug in solid lipid-based excipients.

5 – REFERENCES

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