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ESTABLISHMENT OF A BINARY PHASE DIAGRAMS DATABASE FOR THE DEVELOPMENT OF SELF-EMULSIFYING LIPID-BASED FORMULATIONS

Vincent Jannin[1,*], Hamza Benhaddou[2], Camille Dumont[3], Stéphanie Chevrier[1], Yann Chavant[1], Frédéric Demarne[1]
[1] Gattefossé SAS, Saint-Priest, France, [2] University of Parma, Parma, Italy, [3] CPE Lyon - University of Lyon, Lyon, France, * vjannin@gattefosse.com

INTRODUCTION

Lipid-based formulations (LBFs) are a viable option to address modern drug delivery challenges such as oral bioavailability of poorly water-soluble active pharmaceutical ingredients. Self-Emulsifying Lipid Formulations (SELFs), also known as Type II and III formulations in the Lipid Formulation Classification System, are able to form finely dispersed colloidal phases after dilution in aqueous fluid [1]. The self emulsification mechanism is induced by (i) the diffusion of hydrophilic components from LBF to the aqueous phase, and (ii) the formation of lamellar mesophases by the surfactant at the LBF/water interface. It is controlled by the appropriate selection of the water-soluble surfactant and the inclusion of polar co-excipients. In addition, each surfactant has a limited emulsification capacity and can be associated with a limited amount of oil. Hence, the aim of this study was to establish a database of binary phase diagrams in order to facilitate the selection of SELFs.

EXPERIMENTAL METHODS

Binary phase diagrams were constructed by associating a water-soluble surfactant to promote the self-emulsification of the mixture with a co-excipient pertaining to the co-surfactant, oil or hydrophilic cosolvent category (Table 1). A two steps protocol is used:

• 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® 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. Two grams of miscible mixture are introduced in 400 mL of purified water at 37°C under paddle agitation at 100 rpm. Performance criteria are: ease of emulsification (i.e. time needed for the complete dispersion of the LBF), homogeneity and fineness of the dispersion. The fineness of the dispersion is assayed by dynamic light scattering (DLS, Particle Sizing Systems Nicomp).

Table 1: Excipients classified by functionality and practical Hydrophilic Lipophilic Balance value (pHLB).

Functionality	Chemical name	Commercial name	pHLB
Surfactants (water-soluble)	Caprylo caproyl polyoxyl-8 glycerides	Labrasol® ALF	12
	Lauroyl polyoxyl-32 glycerides	Gelucire® 44/14	11
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

RESULTS AND DISCUSSION

Binary phase diagrams were designed with two lipid-based surfactants: Labrasol® ALF and Gelucire® 44/14.

When in contact with water, Labrasol® forms turbid dispersions with particle size ranging from 150 to 450 nm. At a dilution of 1g/200mL this excipient cannot form finer dispersions such as microemulsions. As a matter of fact, to form microemulsions Labrasol® concentration should be higher than 31g/L (i.e. >6.2g/200mL) [2].

The addition of liquid co-excipients leads to miscible mixtures whatever the ratio between these excipients. The only exception is Transcutol® HP for which the quantity of Labrasol® should be higher than 10% - otherwise two non miscible phases are obtained. The addition of these co-excipients doesn't have a dramatic impact on the fineness of dispersions. If the concentration of co-excipient stays within the limits of emulsification of Labrasol®, it always forms turbid and fine emulsions with particle size ranging from 150 to 450nm. The maximum concentration of additional excipient depends on its own ability to interact with water. Co-surfactants like Plurol® oleique CC497 (figure 1A), can be added up to 50%, whereas oily excipients such as Maisine™ 35-1 (figure 1B) are limited to 25%. The inclusion of these components increases steadily the average particle size of aqueous dispersions from 200 nm to 400nm (e.g. Plurol® oleique CC497 and Peceol™). This evolution can be explained by the inclusion of longer fatty acid chains in the aqueous dispersion of Labrasol®. On the other hand, with Labrafac® Lipophile the average particle size remains the same as the fatty acids comprised in this oily excipient are equivalent to those of Labrasol®. Hence the swelling of the emulsion is limited.

When in contact with water Gelucire® 44/14 forms very fine microemulsions with particle size below 30nm. The addition of other excipients, which are liquid at room temperature, leads to a lot of non miscible mixtures for two reasons:

• The quantity of Gelucire® 44/14 is too low and the mixture is composed of a continuous liquid phase where Gelucire® crystallizes as small particles.

• The quantity of the liquid excipient is too high and part of it exudes on top of the solid Gelucire® matrix.

The two excipients which are particularly not miscible with Gelucire® 44/14 are the propylene glycol esters: Capryol™ 90 and Lauroglycol™ 90.

In addition, the incorporation of co-surfactants or oily components within the Gelucire® 44/14 matrix provokes a dramatic increase of the particle size distribution of the aqueous dispersion (figure 2). It moves from the microemulsion to the fine emulsion size range.

The main advantage to include another excipient in the Gelucire® 44/14 matrix is the possible acceleration of its dispersion rate (figure 3). All co-excipients containing hydrophilic or amphiphilic liquid compounds accelerate the erosion of the lipid matrix by inducing its disintegration into smaller pieces, and hence accelerating the hydration of the polymer. On the other hand, lipophilic compounds such as Labrafac® Lipophile don't impact the erosion rate even if they are liquid.

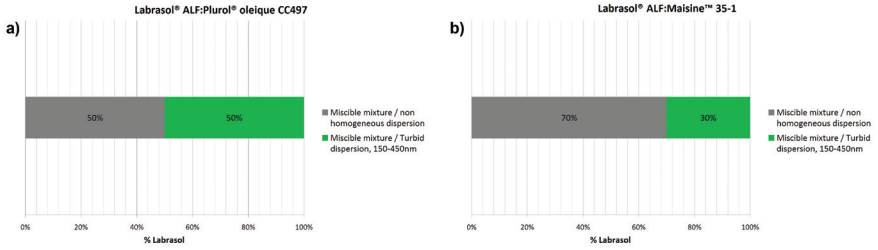

Figure 1: Effect of lipid excipient polarity on Labrasol® phase diagram. (A) Plurol® oleique CC497, (B) Maisine 35-1.

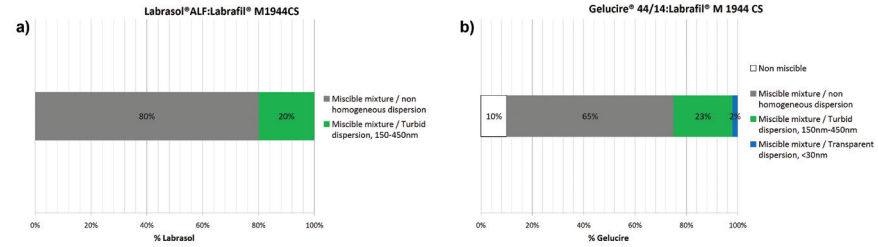

Figure 2: Effect of Labrafil® M1944CS on either Labrasol® (A) or Gelucire® 44/14 (B) phase diagrams.

Table 2 presents all combinations of excipients leading to miscible mixtures and homogeneous and fine aqueous dispersions.

Table 2: Miscible mixtures extracted from Labrasol® and Gelucire® 44/14-based binary phase diagrams.

Water-soluble surfactant	Can be associated with	
	Co-excipient	Concentration (% w/w)
Labrasol®	Labrafil® M1944CS	up to 20%
	Capryol™ 90	up to 30%
	Lauroglycol™ 90	up to 35%
	Plurol® oleique CC497	up to 50%
	Labrafac® Lipophile	up to 20%
	Maisine™ 35-1	up to 30%
	Peceol™	up to 30%
	Transcutol® HP	up to 90%
Gelucire® 44/14	Labrafil® M1944CS	up to 25%
	Capryol™ 90	up to 30%
	Lauroglycol™ 90	up to 20%
	Plurol® oleique CC497	up to 22%
	Labrafac® Lipophile	up to 20%
	Maisine™ 35-1	up to 6% & at 20%
	Peceol™	up to 6% & at 20%
	Transcutol® HP	more than 70%

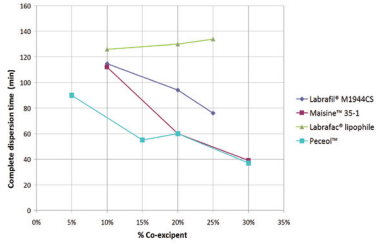

Figure 3: Evolution of the complete dispersion time of 2-gram plugs of Gelucire® 44/14 and co-excipient mixtures as a function of co-excipient quantity in the binary mixture.

CONCLUSION

The selected surfactants enable the formation of a wide range of colloidal phases: microemulsions to fine emulsions. Formulators can easily select within this database the appropriate combination of excipients that are able to dissolve the API and form stable colloidal phases.

REFERENCES

[1] Pouton, C. 2006. Formulation of poorly water-soluble drugs for oral administration: Physicochemical and physiological issues and the lipid formulation classification system, Eur. J. of Pharm. Sci, 29:278-287

[2] Fernandez, S., Jannin, V., Chevrier, S., Chavant, Y., Demarne, F., Carrière, F. 2013. *In vitro* digestion of the self-emulsifying lipid excipient Labrasol® by gastrointestinal lipases and influence of its colloidal structure on lipolysis rate. Pharm. Res., 30:3077-3087