The solubility of drug compounds in the presence of excipients used in lipid based formulations

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Purpose

Lipid based formulations are known to enhance the solubility of drug compounds [1]. The purpose of this study was to determine the intrinsic solubility enhancement of several drug compounds in the presence of a lipid based formulation at 37°C. The ratio of the components in the formulation were varied to investigate the effect of composition on the solubility of the compound.

Methods

Labrasol®, Capryol™ 90 and Labrafac™ Lipophile WL 1349 are all components used in Self-emulsifying Lipid Formulations (SELF). Ternary phase diagrams have been used to describe the structure of the emulsion. Labrasol® and Capryol™ 90 (Lab-Cap) are water dispersible and water insoluble surfactants, respectively. These are typically mixed to a weight ratio of 6:1, respectively, and are considered as one component in a ternary phase diagram. Water and Labrafac™ (an oily vehicle) are the two other components in the ternary phase diagram used in this study.

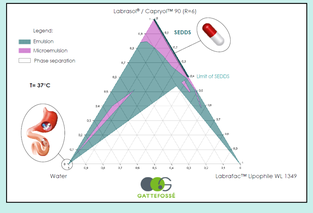

Figure 1. The capsule in the picture points to the region in the diagram that represents the phase of the mixture in the dosage form (0% w/w water). As water is added (right to left on the base axis), the mixture is diluted. The circled area indicates the dilution expected in the GI trac (>97% w/w water). In this study, the water content was kept at 99.5% w/w with 0.5% of the formulation mixture at different ratios of Lab-Cap:Labrafac™.

The phases of the formulation in this diagram were determined at 37°C by Gattefossé [2], which was also the temperature used to measure the intrinsic solubility in this study.

Figure 2. SiriusT3

Water %	LabCap %	Labrafac %	Ratio (LabCap:Labrafac)	Phase
99.5	0	0.5	0:1	Immiscible
99.5	0.08	0.42	0.2:1	Immiscible
99.5	0.25	0.25	1:1	Immiscible
99.5	0.42	0.08	5:1	Emulsion
99.5	0.5	0	1:0	Emulsion

Table 1. The % w/w of the formulation and the relative ratios of the excipients Lab-Cap and Labrafac™ used in this study. The phase of the formulation was obtained from the phase diagram in Figure 1. determined by Gattefossé [2].

The intrinsic solubility of six ionizable drug compounds was studied on a SiriusT3 (Figure. 2) using the CheqSol [3] technique in the presence of different mixtures of Lab-Cap and Labrafac™.

A sample of the precipitate was analyzed using a Nikon Eclipse E200 microscope. A x10 condenser lens and a x20 objective lens with a numerical aperture of 0.4 was used to collect the images.

References

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Results

For the compounds tested here, the addition of the Labrafac™ in absence of the surfactants (ratio 0:1), did not affect the intrinsic solubility of the compounds. A relatively high interfacial surface tension between the aqueous medium and Labrafac™, which caused the immiscibility [5], may inhibit any solubilization by the lipid vehicle or partitioning of the compound into the lipid. Only when the surfactant mixture (Lab-Cap) was introduced did the intrinsic solubility begin to increase. The higher surface activity of the Lab-Cap mixture, may have reduced the surface tension between the aqueous medium and lipid vehicle, thereby enabling a solubilization/ partitioning process.

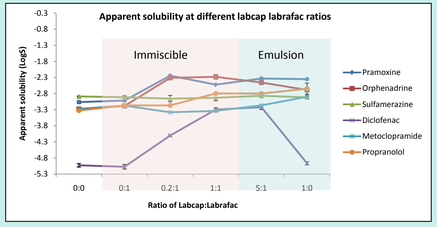

Figure 3. The intrinsic solubility of the compounds (log_{10} of molarity) was plotted against the ratio of the surfactant mixture (Lab-Cap):lipid vehicle (Labrafac™).

The total mass of excipient(s) used was kept at 0.5% (w/w) of the medium.

Each data point was repeated in triplicate.

For two of the compounds (metoclopramide and propranolol), the maximum intrinsic solubility was found when Labrafac™ was absent altogether (ratio 1:0), which suggested a very low affinity between these compounds and the lipid vehicle. For sulfamerazine, the intrinsic solubility was largely unaffected by the presence of the surfactants or lipid, which again suggested a very low affinity between this compound and the excipients used in this study.

But, for three of the compounds (pramoxine, orphenadrine and diclofenac), the intrinsic solubility maxima were found where Lab-cap and Labrafac™ were both present, but at differing ratios (0.2:1, 0.2:1 and 5:1, respectively). This showed that the composition of the formulation can be optimized for compound solubility.

For metoclopramide and propranolol, the largest enhancement in solubility was observed where the phase of the formulation was an emulsion, according to Figure 1. Conversely, the solubility of orphenadrine and pramoxine was enhanced the greatest where the formulation consisted of two immiscible phases. Furthermore, the intrinsic solubility of diclofenac was enhanced by a factor of 64 and showed significant enhancement where the formulation was either immiscible or an emulsion.

To investigate this phase behaviour, the precipitates were collected in the absence and presence (1:1) of the formulation and analyzed under a light microscope.

Compound	Ratio at solubility maximum	Formulation phase	Maximum solubility enhancement factor	LogP [4]	Precipitate form without excipient(s)	Precipitate form with excipient(s)
Sulfamerazine	5:1	emulsion	1.1	0.15	crystal	crystal
Metoclopramide	1:0	emulsion	2.4	2.74	crystal	crystal
Propranolol	1:0	emulsion	4.7	3.48	crystal	crystal
Pramoxine	0.2:1	immiscible	6.6	3.56	oil	oil
Orphenadrine	0.2:1	immiscible	9.3	3.84	oil	oil
Diclofenac	5:1	emulsion	63.7	4.51	crystal	oil

Table 2. Summary of results

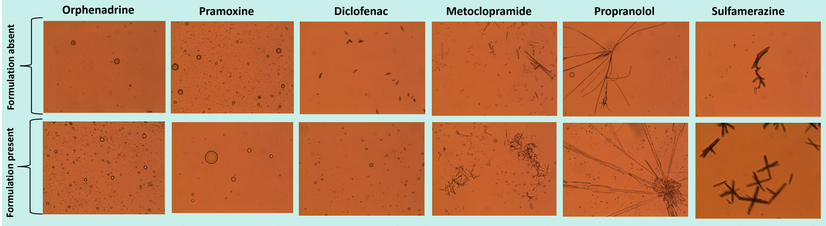

Figure 4. Microscope images of the precipitate collected in the absence of any formulation ingredients (upper row) and the in in the presence of 0.5% (w/w) of the formulation (lower row) . The ratio of Lab-Cap: Labrafac was kept at 1:1.

Orphenadrine and pramoxine appeared to precipitate as an oil in both the absence and presence of the formulation. The droplets of the sample may have fused with the droplets of the immiscible formulation and hence enable the observed enhancement of the intrinsic solubility.

Metoclopramide, propranolol and sulfamerazine all appeared to precipitate as crystals in both the absence and presence of the formulation. This may indicate a poor affinity of these compounds with the immiscible formulation and explain the lack of enhancement in the intrinsic solubility at the immiscible ratios tested here. As an emulsion, metoclopramide and propranolol both resulted in increased solubility, which indicated a preference for the surfactant mixture over the lipid vehicle.

Diclofenac appeared to precipitate as a crystal in the absence of the formulation, but as oil-like droplets in the presence of the formulation. This is a clear indication of a strong affinity with the formulation and may explain the observed 64 fold enhancement.

Conclusion

Using CheqSol, it was possible to readily evaluate the solubility of ionizable compounds at elevated temperatures in the presence of lipid based formulations, which enabled optimization of the composition of the formulation to attain maximum solubility enhancement.

In general, the solubility enhancement improved with the lipophilicity of the compound. However, the extreme enhancement observed for diclofenac may also be influenced by the stabilization of the oily/amorphous form.

The ratio of surfactant:lipid vehicle, at which maximum solubility enhancement was observed, varied between the compounds. For those compounds that have a propensity to form oily droplets (pramoxine, orphenadrine and diclofenac), the ratio was biased towards the lipid vehicle (Labrafac™). However, it was not clear whether this was influenced by the form of the precipitate or to the lipophilicity of the compound or both.

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