Drug solubility in excipients of lipid based formulations

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ABSTRACT SUMMARY
The aim of this study was to investigate solubility in lipid excipients to provide tools for rationalizing the formulation process of lipid based formulations (LBFs). Solubility of 20 poorly soluble drug molecules was determined in seven excipients. From the obtained data it was found that solubility in one glyceride could be used to calculate the value in another. Further the solubility in ethylated surfactants and co-solvents were strongly correlated.

INTRODUCTION
Insufficient aqueous solubility has become a significant barrier to effective drug development. When drug candidates feature a low solubility it causes erratic absorption from the GIT, which negatively influences the effect and raises safety concerns. Thus, the interest in enabling formulations that have solubilizing effects and facilitate absorption has increased.1,2 LBFs possess this capacity and have in recent years been studied extensively for this purpose, but still has limited usage at the market. This can be connected to the complex optimization of LBFs, at date mainly performed experimentally. Hence, tools that can guide the formulation work hold great potential.3 We showed in a recent study that the development of LBFs can be rationalized at several stages, either by optimized experimental screening or through computational prediction from calculated molecular properties.4 The aim of this study was to further explore these findings by extending the number of excipients to allow the general applicability of the previous findings to be explored.

EXPERIMENTAL METHODS
A dataset of 20 structurally diverse compounds were selected, all with a calculated logP greater than 2 to focus on compounds with poor aqueous solubility. The thermodynamic solubility was determined in seven commonly used excipients (Figure 1 and 2) in 37°C with a small scale shake-flask method (n=3). Prior to sampling, the vials were centrifuged at 37°C, 2,800g for 30 minutes (Eppendorf centrifuge 5804R). Drug concentrations were determined by reverse phase HPLC (Waters 2795 alliance HT, Waters 2489 UV/visible detector), using a Phenomenex C18 Gemini 5µm column (3.0 x 150 mm), except for Capmul, Cremophor EL and Carbitol samples which were analyzed with a plate reader (Tecan, Safire2). Equilibrium solubility was determined as the value when the solubility between two consecutive samples points (24 h time difference) differed by less than 10%.

Figure 1. Measured solubility (presented as average ± standard deviation) in glycerids. Soy bean oil (a long chain triglyceride), Captex355 (a medium chain triglyceride) and Capmul (a mixed mono- and diglyceride) were studied.

RESULTS AND DISCUSSION
The determined values in the seven excipients ranged from a low to high solubility (Figure 1 and 2). Solvation capacity of the triglycerides were close to equal on a mol per mol scale and also showed to be linearly correlated with the solubility in a mixed mono-diglyceride (Figure 3a). Additionally, strong
correlations were found between polyethylene glycol 400 and three other excipients, including both surfactants and co-solvents (Figure 3b). These unexpected relationships identify the importance of the ethoxylated parts of the molecules for their solvation capacity.

Our findings indicate that the extensive screening efforts can be significantly reduced. Through determinations in key excipients such as a glyceride and an ethoxylated excipient the solubility in other glycerides and ethoxylated vehicles can be estimated. A study by Prajapati and colleges has implied that solubility in a formulation can be predicted by summing the amount possible to dissolve in each of the included excipients. This knowledge in combination with our new findings reveals a potential to estimate loading capacity in complex LBFs through a small number of experimental determinations. More importantly these outcomes provide tools to make informed decisions when developing new dosage forms.

CONCLUSION
This study confirms our earlier observations on a broader scale; solubility measured in one excipient can be used to calculate solubility in another excipient. Further, ethoxylated excipients display, regardless whether they are co-solvents or surfactants, linearly correlated solvation capacities. These findings reduce the experimental screening efforts needed during development of LBFs. Moreover, the amount of drug compound needed during excipient screening is significantly reduced.

REFERENCES

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