Prediction of Drug Solubility in Lipid Mixtures from Individual Ingredients

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Abstract

Purpose: The purpose of this research was to investigate the relationship of drug solubility in complex lipid mixtures to that of the individual ingredients, with the goal of substantiating a quantitative equation that can be applied in formulation development of lipid dosage forms.
Methods: The solubility of four drugs (genistein, probucol, nifedipine and indomethacin), that span a large range of physicochemical properties, was evaluated in eighteen lipid ingredients that cover the major lipid classes, namely, triglycerides, mono/diglycerides, propylene glycol esters, polyoxylglycerides, polyglyceryl esters, surfactants and cosolvents. To assess the solubility relation in complex lipid mixtures in an unbiased manner, the experiments were created as a simplex lattice mixture design of degree 3, with the ability to detect cubic curvature in the solubility-lipid composition space.
Results: The solubility results for the four drugs covered a significant range of 20-200 mg/g, i.e., from lower to higher solubility. This range reflected the diverse chemistry of the selected drugs, e.g., from neutral, high melting (genistein) and low melting (probucol) to acids (indomethacin) and bases (nifedipine). The results demonstrated that the solubility of a drug in complex lipid mixtures in general can be modeled with quadratic curvature arising from excipient interactions. However, if the drug solubility values in pure lipid components are close in magnitude, the solubility in a lipid mixture is accurately predicted by a weighted average of the solubility values in the pure components. There was only marginal improvement in the Pearson correlation coefficient by using a full quadratic regression model compared to the simple weighted average equation. Given the weighted average model requires no data fitting to calculate solubility in complex lipid mixtures, it is of simple, predictive value.
Conclusions: This research has demonstrated that when a drug's solubility in individual lipid ingredients is within a factor of 10, it is accurate to calculate the drug solubility as a weighted average of the solubility in the single component lipids. This finding is valuable to formulators in that the solubility in complex lipid mixtures can be calculated and modeled from the individual excipients to aid in formulation development.

Introduction

Lipid formulations are used in commercial products (1) and are an important aspect of the strategy of enhancing bioavailability of poorly soluble drugs (2, 3). There are two important objectives with regard to the lipid vehicle from a formulation development perspective. First, it should provide high solubility for the drug, and, second, it should emulsify with no precipitation of the drug. To achieve these objectives, formulation development must as a first step encompass solubility screening in a range of lipid materials. This research was dedicated to assessing the solubility of low water solubility drugs in a broad range of lipid materials specifically to determine if there is any global relationship of solubility to composition variables in complex lipid mixtures.

Materials

The drugs were sourced as follows: genistein (DSM, 98%), probucol (MP Biomedical, 99.7%), nifedipine (Tokyo Chemical Industry Co., >98%), indomethacin (Sigma-Aldrich, 99%).

Table 1 – Physicochemical Properties of the Drugs

Drug	Intrinsic S (mg/mL)	log P	Melting point (°C)	pKa
Genistein	~0.001	3.04	299	NA
Probucol	0.004-0.005 µg/mL	10	126	NA
Nifedipine	0.006	3.17	174	2.7 (base)
Indomethacin	0.002-0.007	4.27	155	4.50 (acid)

Materials (continued)

The lipids were sourced as follows: Soybean oil (Spectrum), Castor oil (Fluka), Miglyol 812 (Sasol), Capmul MCM (Abitec), Maisine 35-1 (Gattefosse), GMO (Abitec), Capmul PG-8 (Abitec), Lauroglycol (Gattefosse), Labrasol (Gattefosse), Labrafil M 1944 CS (Gattefosse), Plurol oleique CC497 (Gattefosse), Caprol MPGO (Abitec), Polysorbate 80 (Spectrum), Cremophor RH40 (BASF), Vitamin E TPGS (Eastman), PEG400 (Fisher Scientific), Propylene glycol (Sigma-Aldrich), Ethanol (Decon Labs). We are particularly thankful to Abitec, Gattefosse, Sasol and BASF for supplying gratis samples for this research.

Methods

The solubility procedure involved weighing the drugs to excess in 4-mL clear glass vials and adding 1 mL of vehicle. Samples were placed on a rotator at 40°C and aliquots taken at 3-7 days. It was generally found that 3 days equilibration was sufficient to achieve equilibrium. All assays were by HPLC, using either an Agilent HP1100 or Dionex Ultimate 3000 system with UV-VIS detection.

Experimental Design

Lipid mixtures were created using experimental design, specifically a simplex lattice mixture design of degree 3 with axial points and a center point repeated 3 times (Minitab 15 statistical software). This design enables exploration of the solubility space with minimal samples to determine cubic curvature in the response.

Results

Solubility results for the four drugs are given in Table 2.

Table 2 – Solubility Results in Pure Components

Lipid or cosolvent	Genistein (mg/g)	Probucol (mg/g)	Nifedipine (mg/g)	Indomethacin (mg/g)
Soybean oil	0.059	86.33	1.56	2.38
Castor oil	3.02	67.92	7.19	22.41
Miglyol 812	0.34	161.79	4.78	6.04
Capmul MCM	4.12	75.48	14.86	31.68
Maisine 35-1	0.51	74.38	5.17	13.48
Glyceryl monooleate (GMO)	0.65	39.18	6.04	15.42
Capmul PG-8	7.14	183.31	26.61	44.77
Lauroglycol	3.27	157.84	12.81	26.82
Labrasol	51.17	105.88	69.04	108.06
Labrafil M 1944 CS	1.61	118.82	8.75	18.21
Plurol oleique CC497	1.31	57.78	4.83	17.14
Caprol MPGO	3.89	61.25	5.56	47.27
PEG400	101.12	29.40	94.41	134.15
Propylene glycol	12.29	2.10	10.72	21.66
Ethanol	16.49	224.74	46.53	65.04
Polysorbate 80	66.08	87.83	69.76	119.42
Cremophor RH40	53.74	61.86	85.75	118.77
Vitamin E TPGS	33.85	88.41	65.05	86.49

Results (continued)

Based on the lipids that provided high solubility and considering lipid functionality, four lipids were chosen for each drug. One lipid component was chosen in which the drug demonstrated lower solubility to assess the importance of curvature in the solubility space. Drug solubility results for mixtures created using the simplex lattice design of degree 3 are provided for genistein in Table 3. Results for the other three drugs are not included in the poster.

Table 3 – Solubility Results for Genistein in Lipid Mixtures

Run	PEG400 (w/w)	Capmul PG-8 (w/w)	Labrasol (w/w)	Polysorbate 80 (w/w)	Solubility (mg/g)
1	0.000	0.333	0.667	0.000	33.64
2	0.333	0.667	0.000	0.000	27.91
3	0.250	0.250	0.250	0.250	53.62
4	0.000	0.000	0.667	0.333	61.70
5	0.000	0.333	0.000	0.667	44.99
6	0.000	0.000	1.000	0.000	53.45
7	0.667	0.333	0.000	0.000	63.05
8	0.625	0.125	0.125	0.125	77.34
9	0.125	0.125	0.125	0.625	66.14
10	0.000	0.667	0.333	0.000	18.16
11	0.333	0.333	0.333	0.000	48.51
12	0.333	0.333	0.000	0.333	54.89
13	0.250	0.250	0.250	0.250	53.90
14	0.125	0.625	0.125	0.125	23.79
15	0.000	0.667	0.000	0.333	19.53
16	1.000	0.000	0.000	0.000	99.98
17	0.333	0.000	0.000	0.667	83.66
18	0.125	0.125	0.625	0.125	52.85
19	0.333	0.000	0.333	0.333	76.17
20	0.667	0.000	0.000	0.333	95.43
21	0.667	0.000	0.333	0.000	86.90
22	0.333	0.000	0.667	0.000	68.98
23	0.000	0.000	0.000	1.000	74.20
24	0.000	0.000	0.333	0.667	67.35
25	0.000	1.000	0.000	0.000	7.48
26	0.250	0.250	0.250	0.250	52.37
27	0.000	0.333	0.333	0.333	36.67

Regression analysis results are provided in Table 4. Regression was also conducted using log S, which is a common transformation for solubility data, but it also resulted in quadratic terms with statistically significant p-values for each drug.

Table 4 – Regression Results for Genistein in Lipid Mixtures

Terms	Coefficients	p-value
	Genistein	
PEG400	101.35	*
Capmul PG-8	6.18	*
Labrasol	53.56	*
Polysorbate 80	74.82	*
PEG400*Capmul PG-8	-36.00	0.000
PEG400*Labrasol	1.01	0.863
PEG400*Polysorbate 80	7.91	0.188
Capmul PG-8*Labrasol	-20.58	0.002
Capmul PG-8*Polysorbate 80	-37.26	0.000
Labrasol*Polysorbate 80	-1.16	0.843
R^2	0.9973	

Discussion

A major observation in the results is that the regression equations for each drug contained statistically significant quadratic terms. Although the results clearly illustrate that the solubility space contains curvature as a function of lipid composition, it is worth assessing if the quadratic models provide a practical improvement in solubility estimation from a simple prediction perspective.

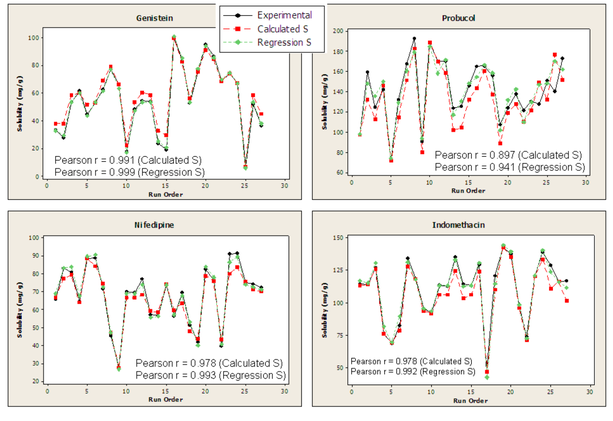
It is of great value from a formulator's perspective to be able to estimate a drug's solubility in a complex lipid mixture from solubility in pure components.

The simplest model to use is a weighted average for solubility as given by:

$$S_{mix} = \sum_i w_i S_i$$

The weighted average (Calculated S) and quadratic regression (Regression S) results are provided as overlays in Figure 1 for the four drugs. It is clearly observed that the improvement in accuracy using the quadratic model is practically insignificant in comparison to the simplicity of the weighted average model.

Figure 1 – Solubility Prediction from Linear and Quadratic Models



Conclusions

The results of this study illustrated that the solubility of drugs in complex lipid mixtures can be quantitatively predicted based on solubility in the pure lipid ingredients, using a simple weighted average model. This finding is of great value in formulation development in that solubility only needs to be measured in individual ingredients and can then be calculated in mixtures.

Acknowledgments

This research was supported by the George D. Zografi Educational Advancement Fund in the Pharmaceutical Sciences. Jeffrey B. Williams, Research Specialist in the Zeeh Pharmaceutical Experiment Station, is acknowledged for his technical support in developing the HPLC methods.

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