Effects of solubility enhancing excipients on model compounds studied using potentiometric pKa and solubility methods

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Purpose

The solubility of insoluble compounds can be increased using solubility enhancing excipients. The behavior of different drug compounds in the presence of these solubility enhancing excipients can be measured using potentiometric pKa and solubility methods. This technique can be used to assess the relative effects on supersaturation and intrinsic solubility to give a better understanding of how the excipients enhance the solubility of the compounds.

Methods

A set of model compounds: sulfathiazole, chlorpromazine hydrochloride, and ibuprofen; were selected for solubility enhancement studies with several commonly used excipients: Kolliphor P407 micro, hydroxypropyl-ß-cyclodextrin, Tween 20, and Tween 80. Potentiometric pKa and solubility experiments were run on the Sirius Analytical SiriusT3 (Figure 1). Acid-base titration methods tested compounds in weights ranging from 1 mg to 84 mg that were dissolved in water with and without excipient in its ionized form and then titrated to the point of precipitation with real-time turbidity detection using an in-situ UV/Vis fiber optic probe. Solution concentrations in the presence of precipitate were determined using the principles of mass and charge balance from measured pH data. Excipients were added in a 5:1 excipient:compound weight ratio for Kolliphor and cyclodextrin, or in a 5% initial solution volume for Tween 20 and Tween 80.

Figure 1: SiriusT3

Results

Table 1: pKa, intrinsic solubility, and kinetic solubility of sulfathiazole with and without excipients

Compound	pKa(s) A=acid B=base	Intrinsic Solubility (mM)	Kinetic Solubility (mM)
Sulfathiazole	B 2.12 A 7.17	1.92	8.99
Sulfathiazole in Kolliphor	B 2.43 A 7.27	4.41	21.71
Sulfathiazole in cyclodextrin	B <2.00 A 8.06	13.68	42.84
Sulfathiazole in Tween 20	B 2.21 A 7.31	5.69	24.13
Sulfathiazole in Tween 80	B 2.07 A 7.28	2.94	18.02

Table 2: pKa, intrinsic solubility, and kinetic solubility of chlorpromazine with and without excipients

Compound	pKa(s) A=acid B=base	Intrinsic Solubility (mM)	Kinetic Solubility (mM)
Chlorpromazine	B 9.24	0.01	0.01
Chlorpromazine in Kolliphor	B 7.21	8.45	10.36
Chlorpromazine in cyclodextrin	B 8.58	0.96	0.79
Chlorpromazine in Tween 20	B 7.65	5.83	6.69
Chlorpromazine in Tween 80	B 7.49	10.66	11.28

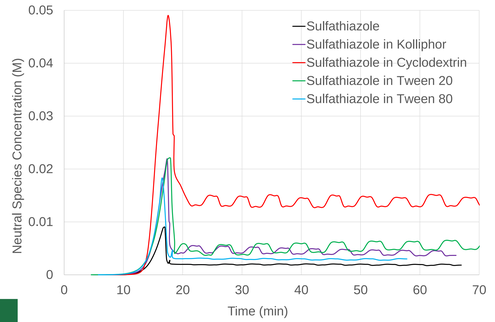

Figure 2: Neutral species concentration profiles of sulfathiazole with and without excipients

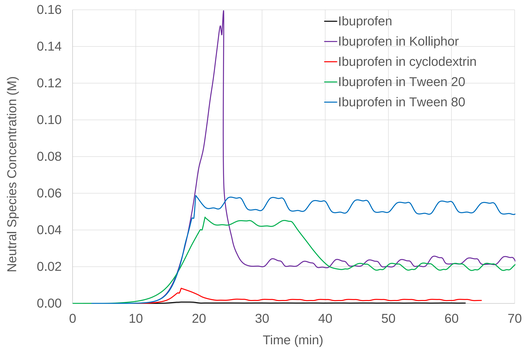

Figure 3: Neutral species concentration profiles of ibuprofen with and without excipients

Table 3: pKa, intrinsic solubility, and kinetic solubility of ibuprofen with and without excipients

Compound	pKa(s) A=acid B=base	Intrinsic Solubility (mM)	Kinetic Solubility (mM)
Ibuprofen	A 4.35	0.19	0.61
Ibuprofen in Kolliphor	A 6.20	21.40	151.00
Ibuprofen in cyclodextrin	A 4.76	1.85	5.70
Ibuprofen in Tween 20	A 6.13	19.90	40.20
Ibuprofen in Tween 80	A 6.22	54.70	46.50

Results

When combined with excipients, each compound showed a shift in their apparent pKas. The kinetic solubility and intrinsic solubility results showed increased solubility for all excipients for each compound. For sulfathiazole (Table 1), solubility enhancement was greatest with cyclodextrin, then Tween 20, then Kolliphor, and finally Tween 80. In Figure 2, the kinetic solubility values (for sulfathiazole) were consistently higher than the intrinsic solubility, indicating a propensity for supersaturation followed by crystallization. In the case of chlorpromazine (Table 2), solubility enhancement was greatest with Tween 80, then Kolliphor, then Tween 20, and finally cyclodextrin. Here, the kinetic and intrinsic solubilities were similar; this type of behavior has been observed for compounds undergoing liquid-liquid phase separation, oiling out, or precipitating in amorphous form. For ibuprofen (Table 3), solubility enhancement was greatest with Tween 80, then Kolliphor, then Tween 20, and finally cyclodextrin. In Figure 3, the use of excipients showed how each excipient could effect and extend the duration of supersaturation with Kolliphor and Tween 20 providing some extension of duration of supersaturation and Tween 80 providing an extension of supersaturation lasting over 40 minutes.

Conclusions

The solubility behavior and solubility enhancement properties of several excipients have been studied with three model compounds. The various solubilizing excipients can each be used to increase the solubility of compounds, but each excipient has its own mechanism of binding and interacting with a molecule and affecting the compounds supersaturation and precipitation kinetics, so each excipient will produce different behavior in-vitro and potentially in-vivo. Therefore experimental determination of the solubility enhancing effects of excipients with their compounds is critical to determining how they affect the molecule, its bioavailability, and how well each excipient performs. The SiriusT3 allows for small sample quantities to be used when screening and optimizing excipients for a drug delivery formulation.