Drug Solubilization by Mixtures of Cyclodextrins: Additive and Synergistic Effects

Supporting Information

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Modelling of the phase-solubility diagrams

Solving the system of equations 1-7 in the manuscript yields the concentrations of all species and thereby permits the theoretical construction of phase-solubility diagrams. In addition to these equations, some region specific restrictions are required. In region I and II, a solid phase of pure drug is present, and the concentration of free drug is therefore equal to its intrinsic solubility. In region II and III, a solid phase of higher-order complexes is present, and the concentrations of free CD and drug are constrained by the solubility product of the higher-order complex.

Analytical expressions for the concentrations of drug and cyclodextrin in the case of a 3:2 precipitation ratio are given in a previous paper.[1] Analogous to these, the expressions in the case of a 2:1 precipitation ratio can be obtained. In the case of mixed CD samples, the theoretical phase-solubility diagram is derived below on page S4.

<u>Derivation of equation 8 in the manuscript</u>

As shown below, the solubility product of the 3:2 precipitate, $K_S^{32} = [L]^3[S]^2$, can be calculated from the drug concentration, S_{eq}, in region II.

In region II, the concentration of free drug is equal to the intrinsic solubility, so the mass conservation in eq. 1 in the manuscript can be written as:

$$S_{eq} = S_0 + [LS] \qquad \Leftrightarrow \qquad \text{(S1)}$$

$$S_{eq} - S_0 = [LS] \qquad\qquad \text{(S2)}$$

Elimination of [LS] using eq. 6 in the manuscript yields:

$$S_{eq} - S_0 = K \cdot [L] \cdot S_0 \qquad\qquad \text{(S3)}$$

In region II, the solubility product may be written as:

$$K_S^{32} = [L]^3 S_0^2 \tag{S4}$$

Isolating [L] from eq. S3 and inserting into eq. S4 yields the final expression:

$$\boldsymbol{K_S^{23}} = \frac{(S_{eq} - S_0)^3}{K^3 \times S_0} \tag{S5}$$

Derivation of equation 9 in the manuscript

The solubility product of the 2:1 precipitate, $K_S^{21} = [L]^2[S]$, can be calculated from the drug concentration, S_{eq}, in region IIA. In region IIA, the concentration of free βCD is equal to the intrinsic solubility of βCD, L_0, so eq. 6 in the manuscript can be written as:

$$[LS] = K \cdot L_0 \cdot [S] \tag{S6}$$

Using eq. S6 to eliminate [LS] in eq. 1 in the manuscript yields:

$$S_{eq} = [S] + K \cdot L_0 \cdot [S] = [S](1 + K \cdot L_0) \tag{S7}$$

In region IIA, the solubility product may be written as:

$$K_S^{21} = L_0^2[S] \tag{S8}$$

Isolating [S] from eq. S8 and inserting into eq. S7 yields:

$$S_{eq} = \frac{K_S^{21}}{L_0^2}(1 + K \times L_0) \tag{S9}$$

Rearranging eq. S9 yields the final expression:

$$\boldsymbol{K_S^{21}} = \frac{S_{eq} \times L_0^2}{K \times L_0 + 1} \tag{S10}$$

Modelling the phase-solubility diagram with combinations of CDs

A notational clarification:

To provide a better overview of the sometimes long mathematical expression, a shorthand notation is used for βCD and γCD, namely β and γ. For instance, the concentration of free βCD is denoted by [β], instead of [βCD].

Region I:

[L] can be isolated from equation 6 in the manuscript and inserted into equation 2:

$$L_{eq} = [LS]\left(1 + \frac{1}{K \times [S]}\right) \qquad \Leftrightarrow \qquad \text{(S11)}$$

$$[LS] = \frac{K \times [S]}{1 + K \times [S]} L_{eq} \qquad \text{(S12)}$$

The solution concentration of a drug, S_{eq}, is the sum of free and complexed drug:

$$S_{eq} = [S] + [\beta S] + [\gamma S] \qquad \text{(S13)}$$

Here, the 1:1 complexes of drug with βCD and γCD are denoted [βS] and [γS], respectively.

In region I, the concentration of free S is equal to its intrinsic solubility so [S] in equations S12 and S13 can be substituted with S_0. Then the concentrations of the 1:1 complexes are calculated according to equation S12 and inserted into S13:

$$S_{eq} = S_0 + \frac{K_\beta S_0}{1 + K_\beta S_0}\beta_{eq} + \frac{K_\gamma S_0}{1 + K_\gamma S_0}\gamma_{eq} \qquad \text{(S14)}$$

where β_{eq} and γ_{eq} denote the total concentrations of βCD and γCD, respectively, and K_β and K_γ are the equilibrium constant for formation of 1:1 complexes with βCD and γCD, respectively.

Since no CD has precipitated in region I, the concentration of each CD is equal to the added

amount:

$$\beta_{eq} = \beta_t \tag{S15}$$

$$\gamma_{eq} = \gamma_t \tag{S16}$$

Region II

Whenever a CD is in region II, the concentration of its 1:1 complexes can be derived as shown

below. From the solubility product and the 1:1 binding constant:

$$K_S^{21} = [\beta]^2 \cdot [S] = \left(\frac{[\beta S]}{[S] \cdot K}\right)^2 \cdot [S] \qquad \Leftrightarrow \tag{S17}$$

$$[\beta S] = K \sqrt{K_S^{21}[S]} \tag{S18}$$

Similarly, for a 3:2 complex:

$$[\gamma S] = K \cdot \sqrt[3]{K_S^{32}[S]} \tag{S19}$$

[S] can be substituted with S_0, and the expressions can be inserted into the mass balance in equation

S13 to calculate the drug concentration, S_{eq}, in region II.

Inserting equations S18 and S19 into S11 yields the concentrations of CDs in region II:

$$\beta_{eq} = K\sqrt{K_S^{21}[S]}\left(1 + \frac{1}{K \times [S]}\right) \tag{S20}$$

$$\gamma_{eq} = K \cdot \sqrt[3]{K_S^{32}[S]}\left(1 + \frac{1}{K \times [S]}\right) \tag{S21}$$

The concentration of free S, [S], can be replaced by S_0.

Region III

Adaptation of equation 4 and 5 in the manuscript yields the following equations of mass conservation:

$$\beta_t = \beta_{eq} + 2 \times \beta_2 S^{prec} \quad\quad\quad\quad\quad (S22)$$

$$\gamma_t = \gamma_{eq} + 3 \times \gamma_3 S_2^{prec} \quad\quad\quad\quad\quad (S23)$$

$$S_t = S_{eq} + \beta_2 S^{prec} + 2 \times \gamma_3 S_2^{prec} \quad\quad\quad\quad (S24)$$

By combining these three equations, the precipitated complexes can be eliminated:

$$4\gamma_t + 3\beta_t - 6S_t = 4\gamma_{eq} + 3\beta_{eq} - 6S_{eq} \quad\quad\quad (S25)$$

The concentrations on the right-hand side of equation S25 are given by equation S13 and:

$$\beta_{eq} = [\beta] + [\beta S] \quad\quad\quad\quad\quad (S26)$$

$$\gamma_{eq} = [\gamma] + [\gamma S] \quad\quad\quad\quad\quad (S27)$$

Insertion of these into the right-hand side of equation S25 yields:

$$4\gamma_t + 3\beta_t - 6S_t = 4[\gamma] + 3[\beta] - 6[S] - 2[\gamma S] - 3[\beta S] \quad\quad (S28)$$

No explicit analytical expression can be found for any of the concentrations on the right-hand side of equation S27. Instead they must be found by numerical solution of equation S27 together with the 4 equations for the 4 equilibrium constants, K^β, K^γ, K_S^{21}, and K_S^{32}. This forms a set 5 equations with 5 unknowns (the species concentrations in square brackets).

Region IIA

This region resembles region II in that 3 solid phases are present: Solid βCD, solid 2:1 βCD:DX complex, and solid 3:2 γCD:DX complex. Concentrations of the 1:1 complexes can be calculated as in region II (equations S18 and S19) with the important difference that [S] is no longer equal to S_0 but must be calculated from the solubility product of the 2:1 βCD:DX complex:

$$[S] = \frac{K_S^{21}}{[\beta]^2} \tag{S29}$$

The concentration of free βCD, [β], is equal to the intrinsic solubility of βCD, β_0, as solid βCD is present.

Transitions between regions

To plot theoretical phase-solubility diagrams, the transitions between the regions must be calculated.

Transition from region I to region II

Precipitation of higher-order complexes (Region II) will set in once the total concentration of CD in solution exceeds the total concentration of CD in solution in region II. Those concentrations are given by equations S20 and S21. In region I, all added CD goes into solution ($CD_t = CD_{eq}$) so transitions from region I to region II will take place when:

$$\beta_t = K\sqrt{K_S^{21} S_0} \left(1 + \frac{1}{K \times S_0}\right) \tag{S30}$$

$$\gamma_t = K \cdot \sqrt[3]{K_S^{32} S_0} \left(1 + \frac{1}{K \times S_0}\right) \tag{S31}$$

Transition from region II to region III

In the phase-solubility diagram in Figure 5 in the manuscript varied amounts of βCD were added to vials containing constant amounts of DX and γCD. The transition calculated below is for the situation where both CDs are present as solid higher-order complexes in both region II and region III. We wish to find the amount of added βCD that corresponds to the point, at which all solid DX is depleted. Starting from equation S22, we wish to find the value of β_t at which there is no solid DX. We start by finding the amount of βCD in the precipitate to be inserted into equation S22. This is isolated from equation S24. Notice that no solid S is present in the mass conservation expressed in equation S24. This ensures that we find the transition from region II to region III.

$$\beta_2 S^{prec} = S_t - S_{eq} - 2 \times \gamma_3 S_2^{prec} \qquad (S32)$$

S_{eq} is eliminated by insertion of equation S13:

$$\beta_2 S^{prec} = S_t - [S] - [\beta S] - [\gamma S] - 2 \times \gamma_3 S_2^{prec} \qquad (S33)$$

The amount of γCD in the precipitate is isolated from equation S23 and inserted into equation S33:

$$\beta_2 S^{prec} = S_t - [S] - [\beta S] - [\gamma S] - \frac{2}{3}\left(\gamma_t - \gamma_{eq}\right) \qquad (S34)$$

Now equation S34 can be inserted into equation S22:

$$\beta_t = \beta_{eq} + 2\left(S_t - [S] - [\beta S] - [\gamma S] - \frac{2}{3}\left(\gamma_t - \gamma_{eq}\right)\right) \qquad (S35)$$

Expressing β_{eq} and γ_{eq} by equation S11 and reducing the expression yields:

$$\boldsymbol{\beta_t} = [\boldsymbol{\beta S}]\left(\frac{1}{K^\beta \cdot S_0} - 1\right) + [\boldsymbol{\gamma S}]\left(\frac{4}{3}\frac{1}{K^\gamma \cdot S_0} - \frac{2}{3}\right) + 2\left(S_t - S_0 - \frac{2}{3}G_{add}\right) \qquad (S36)$$

In equation S36 [S] has been replaced by S_0. [βS] and [γS] can be calculated by equations S18 and S19 and inserted into equation S36 to give the transition from region II to III.

Transition to from region III to region IIA

In region III the concentration of free βCD increases until it reaches its intrinsic solubility, β_0. The location of this transition is calculated using the expression for the transition from region II to region III (equation S36) as a starting point. Whereas the concentration of free S in equation S36 was equal to S_0, the concentration of free S is now given by the 2:1 solubility product and the intrinsic solubility of βCD, as expressed by equation S29. The concentration of 1:1 complexes with βCD can be expressed as:

$$[\beta S] = K^\beta \times [D] \times \beta_0 = K^\beta \times \frac{K_S^{21}}{\beta_0} \tag{S37}$$

The concentration of 1:1 complexes with γCD is the same as in region II (S19). Inserting equation S37 and S19 into equation S36 and substituting all occurrences of S_0 and [S] by equation S29, yields the following expression for the transition from region II to region IIA:

$$\boldsymbol{\beta_t = \beta_0 - \frac{K^\beta K_S^{21}}{\beta_0} + K^\gamma \sqrt[3]{\frac{K_S^{32} K_S^{21}}{\beta_0^2}} \left(\frac{4}{3} \frac{\beta_0^2}{K^\gamma K_S^{21}} - \frac{2}{3} \right) + 2 \left(S_t - \frac{K_S^{21}}{\beta_0^2} - \frac{2}{3} \gamma_t \right)} \tag{S38}$$

References

(1)   Schönbeck, C.; Madsen, T. L.; Peters, G. H.; Holm, R.; Loftsson, T. Soluble 1:1 Complexes and Insoluble 3:2 Complexes – Understanding the Phase-Solubility Diagram of Hydrocortisone and γ-Cyclodextrin. *Int. J. Pharm.* **2017**, *531* (2), 504–511.