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Co-solubilization of poorly soluble drugs by micellization and complexation

Venkatramana M. Rao [a,*], M. Nerurkar [a], S. Pinnamaneni [a], F. Rinaldi [b], K. Raghavan [a]

[a] *Biopharmaceutics R&D, Bristol-Myers Squibb Co., NJ 08903, United States*
[b] *Analytical R&D, Bristol-Myers Squibb Co., NJ 08903, United States*

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Abstract

The use of combined approach of surfactants and cyclodextrins in solubilization of poorly soluble drugs has been described in literature. In this report, a mathematical model has been developed to provide the quantitative basis for this approach. First, by way of hypothetical examples and simulations, the influence of various interaction parameters on the phase solubility profile is presented. Additionally, the model results are compared with (a) results reported by Yang et al., with NSC-639829, sodium lauryl sulfate (SLS) and sulfobutyl-ether-β-cyclodextrin ($(SBE)_{7M}$-β-CD) and (b) solubility of methylprednisolone, a model poorly soluble drug, in the presence of its water-soluble 'surfactant-like' prodrug, methylprednisolone 21-hemisuccinate, and $(SBE)_{7M}$-β-CD. The model shows good agreement with experimental data. Furthermore, theoretical simulations show that the combined solubility is less than the sum of the individual solubility values in cyclodextrins and surfactants. Based on the hypothetical case and the two examples, the factors affecting the phase solubility profile in mixed solutions of surfactants and cyclodextrins are presented. Finally, the limitations of the model to explain co-solubilization by surfactants and cyclodextrins are discussed.
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1. Introduction

Solubilization of a new chemical entity in a pharmaceutically acceptable solvent system remains to be a major challenge in development of a solution dosage form. The most common techniques employed by a formulation scientist to enhance the solubility of a drug involve in situ salt formation (pH-adjustment), or by use of additives such as complexing agents, surfactants and co-solvents. Moreover, it is common to find that a single approach of solubilization such as use of cyclodextrin or surfactant is not adequate to improve the aqueous solubility to the desirable extent. For ionizable compounds, a synergistic solubilization effect by in situ salt formation (pH-adjustment) and addition of cyclodextrins or surfactants or co-solvents have been reported (Tinwalla et al., 1993; Li et al., 1999a,b). The combined effect of complexation and co-solvents was addressed by Li et al. (1999a,b), where the authors presented mathematical models to explain the observed phenomenon of both synergistic and antagonistic effects of co-solvency and complexation.

Very few reports have discussed the use of combined approach of surfactants and cyclodextrins in improving solubility or stability of drugs. Veiga and Ahsan (1998) reported the effect of presence of both surfactants and β-cyclodextrin on solubility of tolbutamide. The authors noted that the changes in tolbutamide solubility in the presence of β-cyclodextrin were dependent on the type and concentration of surfactant. Horsky and Pitha (1996) noted that solubilization effect of bile salts micelles was disrupted because of the formation of complexes between bile salt molecules and cyclodextrins. Muller and Albers (1991) pointed that sodium dexoycholate competed with methyltestosterone for the cyclodextrin cavity.

A combination of self-associating "surfactant-like" solubilizing agent and cyclodextrins may also be encountered during the formulation of water-soluble prodrug of an insoluble drug. Many of the water-soluble prodrugs of insoluble drug candidates show self-associating properties and these aggregate forms can in turn solubilize the parent molecules depending on their solubilization capacity. The limiting factor in the shelf-life of a ready-to-use (RTU) prodrug solution is not only the chem-

* Corresponding author at: P.O. Box 191, Bristol-Myers Squibb Pharmaceutical Research Institute, New Brunswick, NJ 08903-0191, United States. Tel.: +1 732 227 6124; fax: +1 732 227 3986.
E-mail address: venkatramana.rao@bms.com (V.M. Rao).

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ical stability of the prodrug itself, but also the physical stability of the formulation which depends on the solubilization of the insoluble parent drug in that solution. One solution Narisawa and Stella (2000) offer is to add cyclodextrins to solubilize the parent drug molecule (phenytoin) that is generated during the storage of the RTU prodrug solution (fosphenytoin), thus improving the shelf-life of the formulation. However, it is not apparent if this approach can be applied to other prodrug, cyclodextrin and insoluble drug systems.

A semi-quantitative analysis of drug solubility in combined solutions of surfactant and cyclodextrin was presented by Yang et al. (2004). In this report, the authors demonstrated that the combined effect of SLS and $(SBE)_{7M}$-β-CD on NSC-639829 solubility was less than additive, which was explained qualitatively based on the solubility behavior.

In this paper, we have developed a theoretical model describing the solubilization of drugs in the presence of surfactant and cyclodextrins. The term 'surfactant' is broadly applied to any molecule with micellization properties used for solubilization of an insoluble drug. First, by way of hypothetical examples and simulations, the influence of various interaction parameters on the phase solubility profile is presented. Additionally, the model results are compared with (a) results reported by Yang et al. (2004), with NSC-639829, SLS and $(SBE)_{7M}$-β-CD and (b) solubility of methylprednisolone (MP), a model poorly soluble drug, in the presence of its water-soluble 'surfactant-like' prodrug, methylprednisolone 21-hemisuccinate (MPHS), and $(SBE)_{7M}$-β-CD. Finally, the limitations of this model to explain the co-solubilization offered by surfactant/cyclodextrin systems are described.

2. Theoretical model

2.1. Drug solubilization using cyclodextrin

The total drug solubility (S_T) in the presence of cyclodextrin (CD_T), for a 1:1 inclusion complex, is defined by the following equation:

$$S_T = S_0 + \frac{K_D S_0}{1 + K_D S_0} CD_T \quad (1)$$

where K_D is the binding constant and S_0 is the intrinsic solubility.

2.2. Drug solubilization using surfactant

The solubility of a drug in the presence of a surfactant alone can be expressed by considering the two-phase model wherein it is assumed that the micellization is seen only above the critical micellar concentration (CMC) and that the monomer concentration is constant irrespective of the total surfactant concentration above the CMC. For such a system, the total solubility of the drug in the presence of the surfactant (P_T) is given by the following equation (Yang et al., 2004):

$$S_T = S_0 + K_M(P_T - CMC) \quad (2)$$

where K_M is a proportionality constant and indicates the solubilizing capacity of the surfactant.

2.3. Drug solubilization using cyclodextrin and surfactant

When describing drug solubility in solutions containing both surfactants and cyclodextrins, several interactions (equilibria) can co-exist and need to be considered: (a) complexation of drug to cyclodextrin, (b) complexation of monomer of the surfactant to cyclodextrin, (c) equilibria between the monomer and micellar aggregate of the surfactant, (d) interaction of drug and micelles, (e) inclusion complexation of micelle/aggregate(s) to cyclodextrin and (f) incorporation of cyclodextrin or drug–cyclodextrin complex into micelles.

It is generally accepted that large molecules do not complex strongly with cyclodextrins and therefore equilibrium (e) can be ignored (Dorrego et al., 2001). Additionally, given the hydrophilic nature of the external surface of cyclodextrin, the internalization of either cyclodextrin alone or drug–cyclodextrin complex into micelles described in equilibrium (f) can also be neglected. In addition, equilibria involving micelles (c) and (d) are established only when the "free" concentration of the surfactant reaches concentration greater than the CMC. This follows the assumption that the two-phase theory is appropriate for describing the micellar behavior of the surfactant. Specifically, it is assumed that the existence of the micelles occurs only when the monomer concentration is greater than the CMC. Based on this assumption of two-phase model and the assumption that only monomers complex with cyclodextrin, it becomes apparent that the first step in understanding various equilibria is to determine the surfactant concentration that is unbound to cyclodextrin. Following this determination, solubility expressions are derived either taking only solubilization by cyclodextrin and competition between drug and surfactant for the cyclodextrin if the monomer concentration is below CMC or considering solubilization by cyclodextrin, micellar solubilization by surfactant and competition between drug and monomer of the surfactant for the cyclodextrin cavity. Fig. 1 provides a schematic representation of various equilibria present in the surfactant/cyclodextrin system as a function of increasing surfactant concentration.

Mathematical expressions to describe the above phenomena are derived below. To this end, we consider a system containing excess solid drug equilibrating with a cyclodextrin solution. Increasing amounts of surfactant are added to the above solution and solubility in these solutions is determined as a function of surfactant concentration. In the following section, two scenarios are considered around the CMC of a surfactant.

2.3.1. Scenario 1: free surfactant (unbound to CD) at a concentration below CMC (pre-CMC scenario)

At low surfactant concentrations (pre-micellization) as shown in Fig. 1a, addition of surfactant to the aqueous cyclodextrin solution induces competitive displacement of drug complexed to cyclodextrin due to complexation of monomers of surfactant ([P–CD]). The total surfactant concentration ($[P_T]$) defined as the sum of the free surfactant ($[P_f]$) and surfactant complexed to cyclodextrin ([P–CD]) is mathematically expressed as Eq. (3):

$$[P_T] = [P_f] + [P\text{–}CD] = [P_f] + \frac{K_P \times [P_f] \times [CD_T]}{1 + K_P \times [P_f] + K_D \times [D_f]} \quad (3)$$

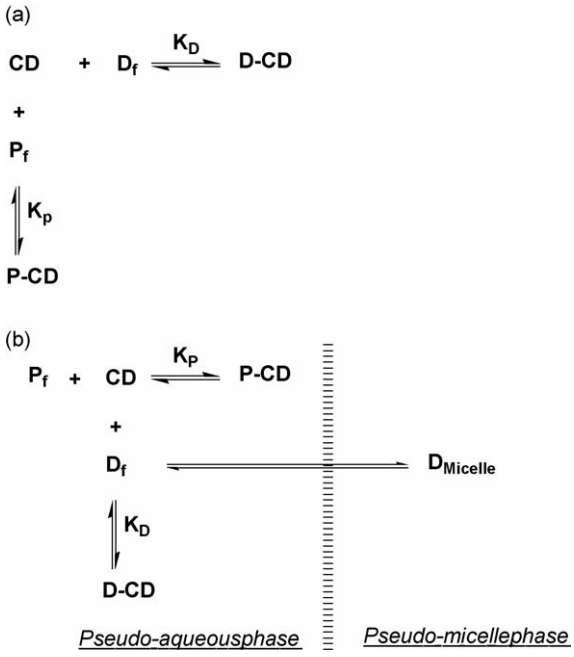

Fig. 1. (a) Scheme illustrates the competitive complexation of drug to cyclodextrin and surfactant to cyclodextrin. This schematic is valid until the surfactant unbound to cyclodextrin, P_f, is less than CMC. (b) Scheme illustrates the complexation of drug to cyclodextrin and surfactant to cyclodextrin and drug solubilization into micellar phase of the surfactant. This scheme is valid when the surfactant unbound to cyclodextrin ($[P_T] - [P–CD]$) is greater than CMC. Under saturation solubility experimental conditions, $[D_f]$ is equal to the intrinsic solubility, S_0.

where $[CD_T]$ is the total concentration of cyclodextrin, K_D and K_P are the binding constants of drug–cyclodextrin and surfactant(monomer)–cyclodextrin, respectively. In the current system, where the excess solid drug is in equilibrium with solution i.e., at saturation conditions, the free drug, $[D_f]$ is equal to its intrinsic solubility, S_0. Accordingly, the total surfactant concentration P_T (Eq. (3)) and total drug solubility, S_T can be expressed as Eqs. (4) and (5), respectively:

$$[P_T] = [P_f] + [P–CD] = [P_f] + \frac{K_P \times [P_f] \times [CD_T]}{1 + K_P \times [P_f] + K_D S_0} \quad (4)$$

$$S_T = [D_f] + [D–CD] = S_0 + \frac{K_D S_0 \times [CD_T]}{1 + K_P \times [P_f] + K_D S_0} \quad (5)$$

Eq. (4) suggests that as the total surfactant concentration is increased, the drug complexed to cyclodextrin ([D–CD]) decreases due to competitive displacement by the increasing concentration of free surfactant ($[P_f]$). Clearly Eqs. (4) and (5) are applicable only when the free surfactant concentration $[P_f]$ is less than the CMC. Rearranging Eq. (4):

$$K_P \times [P_f]^2 + (1 + K_P \times CD_T + K_D S_0 - K_P \times P_T) \times [P_f] - (P_T + P_T \times K_D S_0) = 0 \quad (6)$$

2.3.2. Scenario 2: free surfactant (unbound to CD) at a concentration above CMC (post-CMC scenario)

If the value of surfactant concentration that is unbound to cyclodextrin is greater than the CMC, as shown in Fig. 1b, an additional pseudo-phase (micellar phase) needs to be considered. The total surfactant concentration is the sum of free surfactant $[P_f]$, surfactant bound to cyclodextrin [P–CD] and micellized surfactant $[P_{micelle}]$. In view of the two-phase theory, it is assumed that the free surfactant concentration in the micellized solution is constant and equal to CMC.

As the surfactant concentration is further increased to micellar region, the free surfactant concentration is constant (equal to CMC) and the surfactant bound to the cyclodextrin is also constant [P–CD] leading to a corresponding increase in micellized surfactant concentration, $[P_{micelle}]$. The reason for no change in the [P–CD] value is that the concentration of two free species complexing with cyclodextrin, i.e. free drug and free surfactant are constant and equal to intrinsic solubility (S_0) and CMC, respectively. An increase in surfactant concentration only leads to increase in micellized surfactant and a corresponding increase in the amount of drug that is solubilized by the micelle.

The total surfactant concentration is represented by Eq. (7):

$$P_T = [P_f] + [P_{micelle}] + [P–CD] = CMC + [P_{micelle}] + \frac{K_P\,CMC \times [CD_T]}{1 + K_P\,CMC + K_D S_0} \quad (7)$$

Rearranging to estimate the micellized surfactant concentration:

$$[P_{micelle}] = [P_T] - CMC - \frac{K_P\,CMC \times [CD_T]}{1 + K_P\,CMC + K_D S_0} \quad (8)$$

The total drug solubility, S_T is represented by Eq. (9):

$$S_T = [D_f] + [D_{micelle}] + [D–CD] = S_0 + K_M[P_{micelle}] + \frac{K_D S_0 \times [CD_T]}{1 + K_P\,CMC + K_D S_0} \quad (9)$$

Substituting Eq. (8) into Eq. (9):

$$S_T = S_0 + K_M \left(P_T - CMC - \frac{K_P\,CMC \times [CD_T]}{1 + K_P\,CMC + K_D S_0} \right) + \frac{K_D S_0 \times [CD_T]}{1 + K_P\,CMC + K_D S_0} \quad (10)$$

The above equation applicable for the micellar region suggests that for a fixed cyclodextrin concentration, the drug solubility increases linearly as a function of the surfactant concentration with a slope K_M similar to the slope observed in the absence of cyclodextrin. This is because as the surfactant concentration is increased, only the micellized surfactant increases and the drug solubility is linearly dependent (K_M) on the micellar surfactant concentration. The equation also predicts that the total drug solubility in the presence of cyclodextrin and surfactant is expected to be less than additive, i.e., solubility expressed by Eq. (10) is always less than the sum of the solubility values in Eqs. (1) and (2) provided the assumptions are valid.

The above analysis assumes that the two-phase model accurately describes the self-association of the surfactant. Mathe-

matical treatment assuming mass action model is described in Appendix A (Mukerjee and Cardinal, 1976). For the sake of simplicity, the current work uses the two-phase model to describe the solubility of drug in the presence of self-associating species and cyclodextrins. It has been argued convincingly that the assumption of two-phase model is not accurate for describing a number of self-associating molecules (Mukerjee, 1974). It has also been pointed that significant errors can be incurred especially in those cases where availability/concentration of the monomer is critical. Since cyclodextrins are assumed to interact strongly with monomer species relative to the self-associating forms of the surfactant, the application of the above analysis could lead to deviations from the experimental observations. However, the application of mass action theory requires knowledge of many micro-constants to describe the step-wise equilibria which a formulation scientist rarely has. Therefore, we propose the application of the above theoretical framework as a first approach. The observed deviations in various regions of the phase solubility diagram can perhaps be used to determine which of the assumptions are incorrect.

Both intuition and the above equations suggest that the total drug solubility is dependent on the binding constants of drug–CD (K_D), surfactant–CD (K_P), the solubilization capacity of the micelles (K_M), the concentration of the surfactant (P_T), the concentration of cyclodextrin (CD_T), intrinsic solubility of the drug (S_0) and CMC of the surfactant. The importance of intrinsic solubility and critical micellar concentration are more readily apparent than the other terms such as the binding constants and the solubilization capacity. The relative differences between the binding constants for drug–CD and surfactant–CD are less important than the complexation efficiency (Ma et al., 2000) defined as the product of binding constant and concentration of the substrate (drug or monomer). In order to get a better understanding of the combined effect of these parameters, the following two cases are examined:

- Case (a) $K_P\,CMC \sim K_D S_0$ or $K_P\,CMC > K_D S_0$:

  In this particular case, the extent of complexation or complexation efficiency between the monomer of the surfactant and cyclodextrin is considered to be comparable or greater than that for drug and cyclodextrin. To illustrate the effects of various factors, let us consider a hypothetical drug with a solubility (S_0) of 1×10^{-04} M. Let the 1:1 binding constant of the drug with a cyclodextrin (K_D) be $5000\,M^{-1}$. We select a surfactant with CMC of 5 mM and assume that the monomers of the surfactant complex with the cyclodextrin with a binding constant (K_P) of $1000\,M^{-1}$. The values of K_P CMC and $K_D S_0$ are 5 and 0.5, respectively. The surfactant solubilization capacity (K_M) is assumed to be 0.2. The solubility of drug in the presence of both cyclodextrin and surfactant were calculated using equations described in the previous section. At first, for a given cyclodextrin and surfactant concentration, Eq. (6) was used to calculate the free surfactant concentration (P_f). If P_f was less than CMC, then there is no micellar phase and the drug solubility was calculated using Eq. (5). When P_f value was greater than CMC, Eq. (10) which also accounts for micellar solubilization was used.

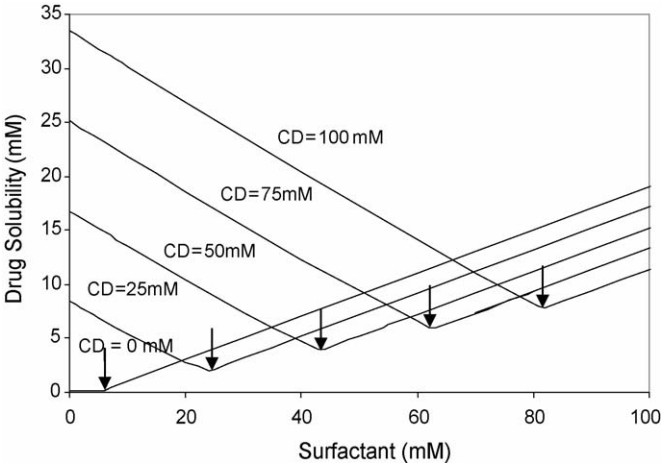

Fig. 2. Drug solubility as a function of surfactant concentration at various cyclodextrin concentrations. The lines represent calculated drug solubility values as a function of surfactant concentrations at various cyclodextrin concentrations of 0, 25, 50, 75 and 100 mM. Arrows represent the apparent CMC value at each cyclodextrin concentration.

Fig. 2 offers interesting trends on drug solubility as a function of surfactant concentration. In the absence of any cyclodextrin, the drug solubility is constant up to a surfactant concentration (CMC) and increases linearly with surfactant concentration. In the presence of cyclodextrin, the drug solubility first decreases with an increase in surfactant concentration because of the sequestration of the cyclodextrin by the surfactant (monomers). Additionally, the complexation of the surfactant monomers with cyclodextrin also leads to a decrease in the free surfactant concentration until when the free surfactant concentration is equal to the CMC, beyond which micelles are formed. Solubilization by the micellar phase is illustrated in the ascending portion of the solubility curve and the intersection of the descending and ascending portion represents the value at which the free surfactant concentration is equal to CMC and the analytical (total) surfactant concentration is referred to as apparent CMC. This transition point (apparent CMC) is shown in Fig. 2 with an arrow symbol. It is interesting to note that the slope of the solubility versus surfactant concentration line in the micellar phase is same irrespective of the cyclodextrin concentration. At higher cyclodextrin concentration, the apparent CMC (denoted by the arrow symbol) is higher due to the decreased availability of the free surfactant molecules and therefore a delay in the onset of micellization is observed. The descending portion of the plot may not be linear whereas in the micellar portion (beyond the CMC) a linear relationship between drug solubility and surfactant concentration is observed.

Fig. 3 illustrates the total drug solubility as a function of cyclodextrin concentration for a given surfactant concentration. As expected, in the absence of surfactant, the drug solubility linearly increases with cyclodextrin concentration. However, in the presence of surfactant, the shape of the curve is dependent on several factors including whether the surfactant concentration is below or above CMC and the relative solubilization by cyclodextrin and surfactant. The "inflection

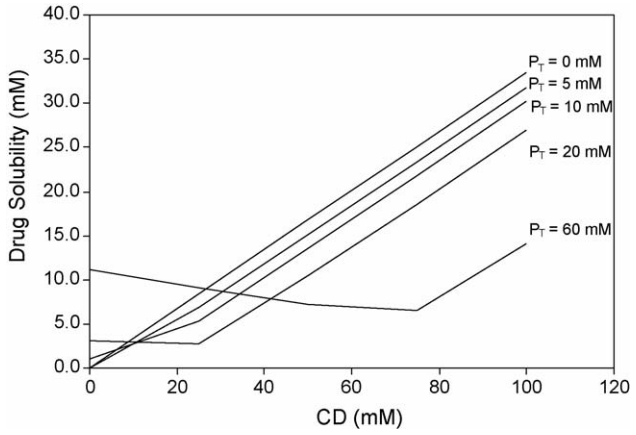

Fig. 3. Drug solubility as a function of cyclodextrin concentration at various surfactant concentrations. The lines represent calculated drug solubility values as a function of cyclodextrin concentrations at various surfactant concentrations of 0, 5, 10, 20 and 60 mM.

point" in each line represents the change in micellar phase to pre-micellar phase wherein the later portion of the graph represents pre-micellar region and earlier portion represents micellar region. Depending on the relative solubilization of drug by micellization and complexation, the shape of the curve can vary from linear to bi-phasic.

- Case (b) $K_P\,\mathrm{CMC} < K_D S_0$:

  In this case, the complexation efficiency of the surfactant–CD is assumed to be negligible compared to that of drug–CD. When $K_P\,\mathrm{CMC}$ is very less than $K_D S_0$, mathematically, Eqs. (5) and (10) become

$$S_T \sim S_0 + \frac{K_D S_0 \times [\mathrm{CD_T}]}{1 + K_D S_0} \quad \text{when } P_f < \mathrm{CMC} \tag{11}$$

  and

$$S_T \sim S_0 + K_M(P_T - \mathrm{CMC}) + \frac{(K_D S_0 - K_P\,\mathrm{CMC}\,K_M) \times [\mathrm{CD_T}]}{1 + K_D S_0} \tag{12}$$

  and further noting that $K_P\,\mathrm{CMC}\,K_M$ is small compared to $K_D S_0$ as K_M is typically less than 1:

$$S_T \sim S_0 + K_M(P_T - \mathrm{CMC}) + \frac{K_D S_0 \times [\mathrm{CD_T}]}{1 + K_D S_0} \tag{13}$$

  This implies that when the competition from the monomer of the surfactant is negligible, the combined solubility of the drug is nearly additive of the solubilization by surfactant and cyclodextrin.

3. Materials and methods

3.1. Materials

Methylprednisolone 21-hemisuccinate (MPHS) and methylprednisolone (MP) were purchased from Sigma–Aldrich, St. Louis, MO. $(SBE)_{7M}$-β-CD was purchased from Cydex Inc., Kansas, MO. Phosphate buffer salts (analytical grade), sodium phosphate monobasic monohydrate and sodium chloride were obtained from Mallinckrodt Baker Inc., Phillipsburg, NJ and EM Science, Gibbstown, NJ, respectively.

3.2. Methods

3.2.1. Data retrieval from the published manuscript authored by Yang et al. (2004)

Yang et al. (2004) presented solubility of NSC-639829 in the presence both of SLS and $(SBE)_{7M}$-β-CD in the manuscript entitled, "combined effect of SLS and $(SBE)_{7M}$-β-CD on the solubilization of NSC-639829". The data from this manuscript was obtained by reading it off using a software program, Get Data®. The scanned graphs were read and the data points were digitized using this software.

3.2.2. Solubility of MP in MPHS and $(SBE)_{7M}$-β-CD solutions

All the solubility studies of the parent compound, MP, were conducted in pH 7 phosphate buffer (buffer concentration 50 mM, ionic strength 0.5). In this study, the excess drug was added the buffer and the suspension was shaken on a wrist-action shaker at room temperature for 1–4 days. The filtrate (saturated solution of MP) of the equilibrated suspension sample was obtained by ultracentrifuging the sample through Spin-X® 0.22 μm nylon centrifuge tube filter. MP solubility was determined by HPLC analysis after appropriate dilution of the filtrate. Similar solubility studies of MP were done with varying concentrations of MPHS, in pH 7 phosphate buffer. Additionally, the solubility studies of MP were also conducted in the solutions of 5% (w/w) $(SBE)_{7M}$-β-CD in pH 7 phosphate buffer in the presence of varying concentrations of MPHS. Appropriate dilutions with 50% acetonitrile in water were made to determine both the MPHS and MP concentrations in the filtrate samples by HPLC analysis. A reverse phase gradient high-pressure liquid chromatographic technique was used to analyze the samples for MP concentration. The C-18 column (S-3μ, 120A, 4.6 × 150 mM) and sample temperature was maintained at 25 °C. The flow rate of the mobile phase (water with 0.05% trifluoroacetic acid and acetonitrile with 0.05% trifluoroacetic acid) was maintained at 0.8 ml/min and the samples were analyzed at 254 nm.

3.2.3. Diffusion coefficient of MPHS in $(SBE)_{7M}$-β-CD solutions

Diffusion coefficient of MPHS in the presence of 5% (w/w) $(SBE)_{7M}$-β-CD solutions was determined using the standard Varian diffusion ordered spectroscopy (DOSY) experiment of version 6.1 B. The gradient strength was calibrated using 1% H_2O in 0.1 mg/mL $GdCl_3$ D_2O sample and the standard "profile" pulse sequence. Samples of MPHS with 5% $(SBE)_{7M}$-β-CD dissolved in 50 mM phosphate buffer ($I \sim 0.5$ M) at pD = 7.0 (pH reading 6.6), obtained from corrected pH values (Glasoe and Long, 1960), were prepared. A minimum of signal-to-noise ratio ≥50 was obtained in order to produce a good exponential fit. The resonance intensity decays were fit to a single exponential curve, with the derived time constant used in the diffusion coefficient calculation (Stejskal and Tanner, 1965; Tanner, 1970).

4. Results and discussion

4.1. Validation of the proposed model using the experimental data from Yang et al.

Yang et al. (2004) presented solubility of NSC-639829 in the presence of both SLS and $(SBE)_{7M}$-β-CD. In order to estimate the total solubility of the drug in the presence of both $(SBE)_{7M}$-β-CD and SLS, the following parameters need to be known: S_0, K_D, CMC, K_M and K_P. Yang et al. (2004) reported that for the NSC-639829/SLS/$(SBE)_{7M}$-β-CD system, the values of S_0, K_D and K_M to be 6.5×10^{-5} mM, 92 mM^{-1} and 0.049 M^{-1}, respectively. The CMC of SLS used in the study was not experimentally determined but the authors cite a literature value of 7.98 mM. In fact, the use of equation with a K_M value of 0.049 M^{-1} and CMC value of 7.98 mM predicts slightly lower values of solubility than the experimental values (data not shown). This can be attributed to the lower CMC value than the reported value. For the sake of discussion, we assume that the 7.98 mM is the CMC of the SLS used in this study.

The value of K_P is unknown and was not experimentally obtained by Yang et al. (2004). Therefore, K_P is determined by using the declining portion of the solubility data (pre-micellar behavior) presented in Yang et al. (2004) (Fig. 2 in the reference) in the presence of 46.2 mM $(SBE)_{7M}$-β-CD and as a function of SLS. MS Excel® Solver was used to solve for the K_P value that gave the lowest value for the sum of the residual squares between the theoretical and experimental data. Fig. 4 shows the fitted line with the experimental data and a K_P was found to be 1983 M^{-1}. A wide range of binding constant between cyclodextrins and SLS has been reported in the literature (Turco Liveri et al., 1992; Lin et al., 2001). Many of these studies have focused on neutral cyclodextrins such as β-CD and HP-β-CD. The binding constant between anionic $(SBE)_{7M}$-β-CD and anionic SLS is expected to be lower than that for neutral cyclodextrins such as β-CD and HP-β-CD.

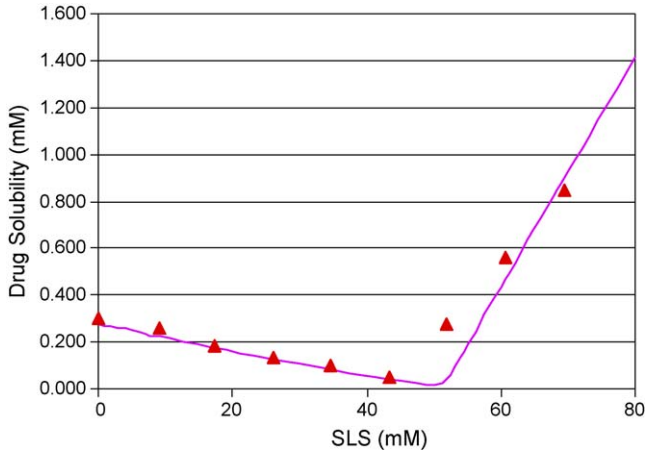

Fig. 4. Effect of increasing concentration of SLS on the Solubility of NSC-639829 at 46 mM $(SBE)_{7M}$-β-CD Concentration. Triangles represent the experimental points from Yang et al. (2004) and line represents the best fit to the data.

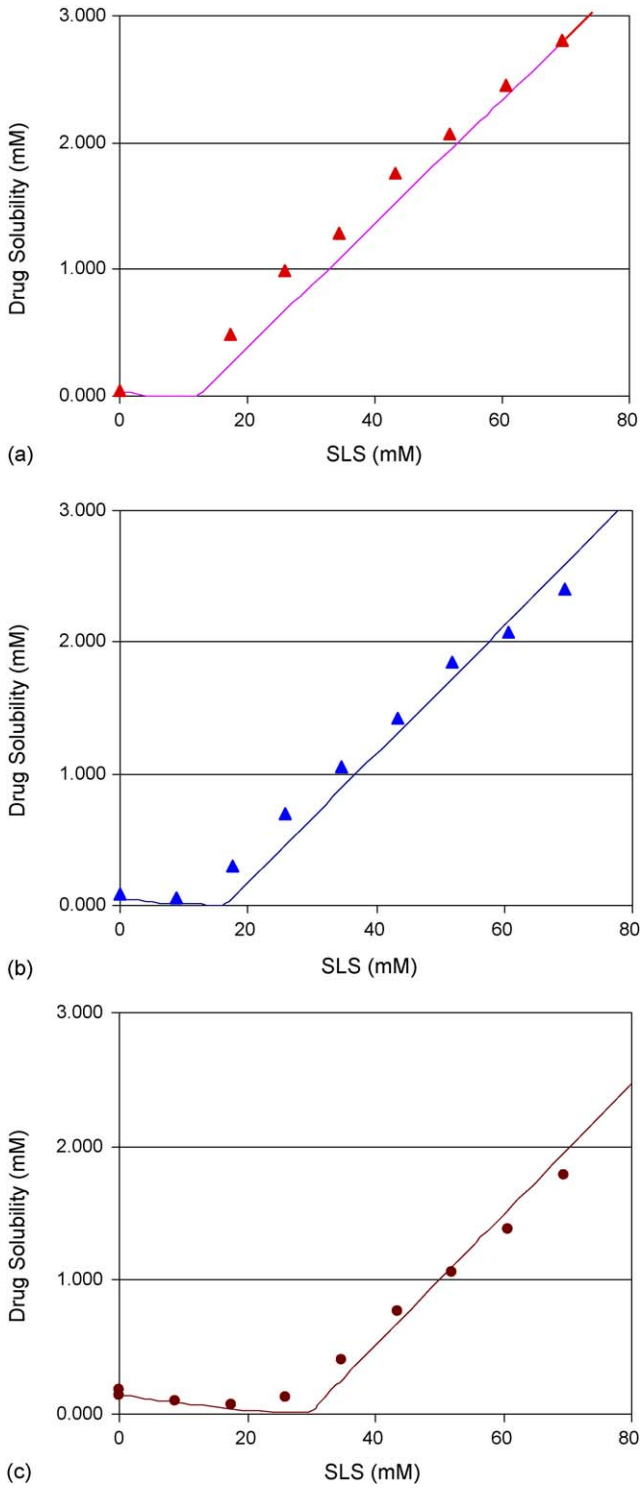

Fig. 5. Experimental vs. predicted values of drug solubility at fixed $(SBE)_{7M}$-β-CD values. In each figure triangles represent experimental points and lines represent predicted values: (a) 4.6 mM of $(SBE)_{7M}$-β-CD from Yang et al. (2004), (b) 9.2 mM of $(SBE)_{7M}$-β-CD from Yang et al. (2004) and (c) 23.1 mM of $(SBE)_{7M}$-β-CD from Yang et al. (2004).

In order to validate the model further, the solubility values are predicted for the rest of the SLS and $(SBE)_{7M}$-β-CD concentrations and are plotted in Fig. 5. The model shows good agreement with the experimental data. The drug solubility trends

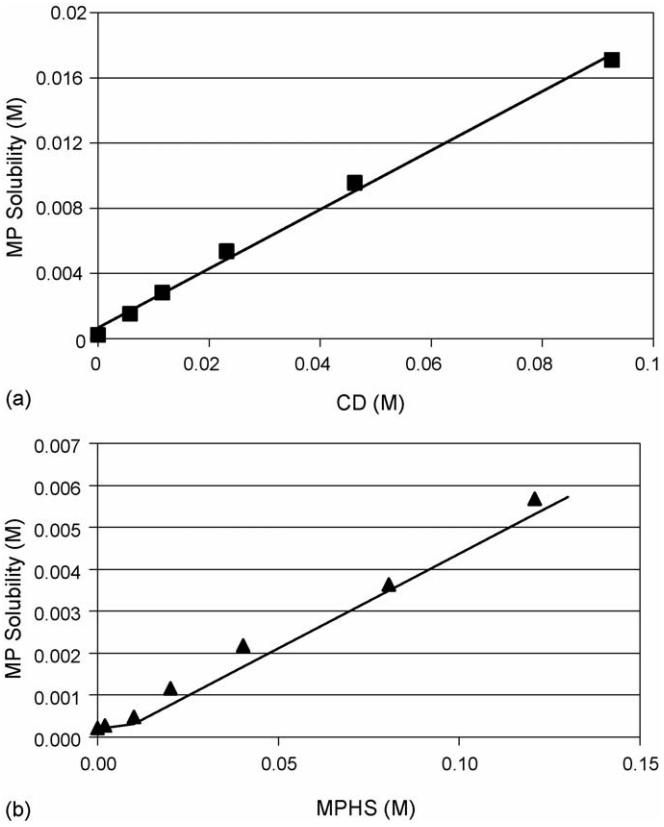

Fig. 6. (a) Solubility of MP in $(SBE)_{7M}$-β-CD solutions, square represents the experimental points and line represents the best fit to Eq. (1). (b) Solubility of MP as a function of MPHS concentration, square represents the experimental points and line represents the best fit to Eq. (2).

in mixed cyclodextrin–surfactant solutions are consistent with the theoretical predictions. Yang et al., noted that with increasing concentration of SLS, at a fixed $(SBE)_{7M}$-β-CD concentration, the total solubility decreases to a minimum and then linearly increases and that the molar ratio at the minimum of SLS to $(SBE)_{7M}$-β-CD is close to unity. As shown in the theoretical section, the minimum corresponds to that apparent CMC value and this observation of 1:1 molar ratio is just a coincidence and is dependent on the various interaction parameters.

4.2. MP solubility in MP-prodrug and SBE-β-CD solution

In this section we describe the application of the co-solubilization model to the cyclodextrin/prodrug example where MP is solubilized in the presence of $(SBE)_{7M}$-β-CD and MPHS.

The linear increase in MP solubility as a function of $(SBE)_{7M}$-β-CD concentration is shown in Fig. 6a. Assuming a 1:1 binding between MP and $(SBE)_{7M}$-β-CD, and using the slope and experimentally determined S_0 value 0.2 mM, the binding constant between the drug and CD, K_D, was determined to be 1017 M^{-1}.

Fig. 6b illustrates the solubility of MP in the presence of MPHS. The solubility data in the micellar region showed a solubilizing capacity, K_M of 0.045. The CMC value is estimated to be 8 mM (4 mg/mL), however, this could be anywhere between 1 and 10 mM. Anderson et al. (1983) estimated the apparent CMC of MPHS in borate buffer (pH 4.5, ionic strength = 0.5) to

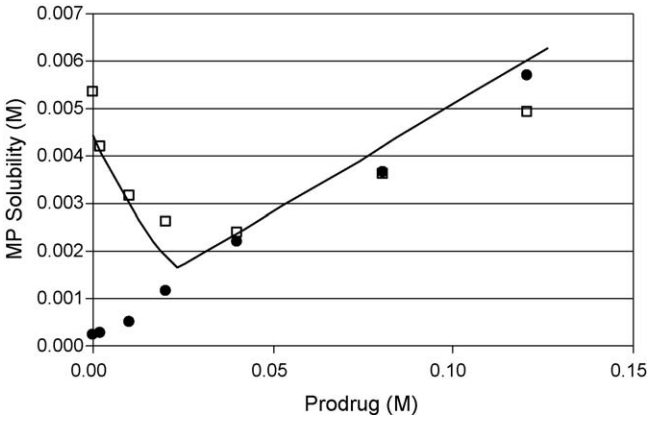

Fig. 7. Solubility of MP as a function of MPHS concentration in the absence and presence of 5% (w/w) $(SBE)_{7M}$-β-CD. Circles represent the experimental data in the absence of $(SBE)_{7M}$-β-CD and squares represent the experimental data in the presence of 5% (w/w) $(SBE)_{7M}$-β-CD and the lines represent the predicted values.

be about 20 mM. Partition studies (Anderson et al., 1983) also revealed that MPHS undergoes pre-micellar aggregation and as a consequence the monomer concentration is less than CMC. For the sake of simplicity and to be consistent with the two-phase theory assumptions, a CMC value of 8 mM is assumed for MPHS.

Given the high water solubility and self-association nature of MPHS, phase-solubility method cannot be easily applied to determine the binding constant between the monomers of MPHS and cyclodextrin (K_P). In order to determine the binding constant between the MPHS and $(SBE)_{7M}$-β-CD, solution stability studies were conducted at 25 °C. The hydrolysis of MP-prodrug to MP and MP-17-hemisuccinate is well known (Anderson and Taphouse, 1981). Degradation rate of MP-prodrug (0.1 mg/ml) to MP as a function of CD concentration was determined by using initial rate method. The binding constant of MPHS to $(SBE)_{7M}$-β-CD was estimated to be 290 M^{-1} by applying the method described earlier (Ma et al., 2000) to the stability data.

Fig. 7 shows the solubility of MP in MPHS solutions with and without 5% (w/w) $(SBE)_{7M}$-β-CD. The solubility of MP in the presence of 5% (w/w) $(SBE)_{7M}$-β-CD is always lower than the sum of the individual solubility values. The parameters needed for the simulation of phase solubility behavior of MP in the mixed solutions of cyclodextrin and MPHS i.e., K_P, K_M, CMC, S_0 and K_D are known. The model-derived data is compared with experimental data in Fig. 7. The overall trend of the plot is consistent with the experimental data. It is clear that the shape of the curve near the minimum is sharper for the predicted value compared to the experimental values. This is attributed to the assumption of two-phase theory where in a single CMC value is assumed. The slope of the line in the micellar region, which is an indicator of micellar solubilization capacity, appears to be lowered in the presence of $(SBE)_{7M}$-β-CD. Yang et al., had pointed out that this may be due to the dependence of micellar solubilization, K_M, on the cyclodextrin. Unlike the case of fosphenytoin and phenytoin, the MP solubility enhancement in MPHS micellar solutions by the addition of cyclodextrin is negligible.

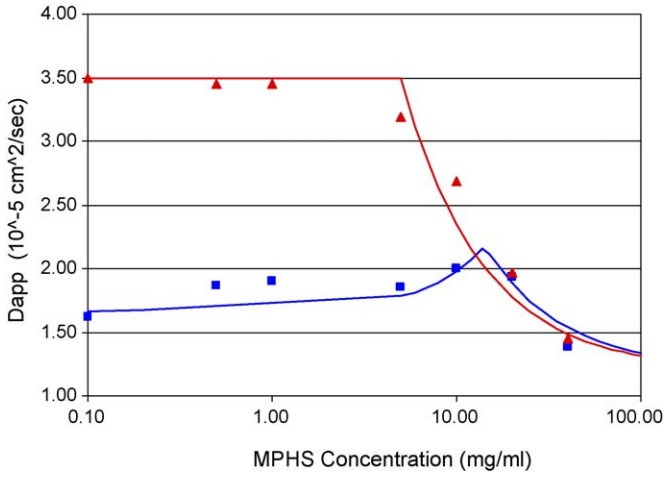

Fig. 8. Diffusion coefficient of MPHS as a function of its concentration in the absence and presence of 5% (w/w) $(SBE)_{7M}$-β-CD. Triangles represent the experimental data in the absence of $(SBE)_{7M}$-β-CD, squares represent the experimental data in the presence of 5% (w/w) $(SBE)_{7M}$-β-CD and the lines represent the predicted values.

In the presence of 5% (w/w) $(SBE)_{7M}$-β-CD, the apparent CMC of MPHS appears to increase from 4 mg/ml to 12 mg/ml. Diffusion coefficient values of MPHS in buffer alone and in the presence of 5% (w/w) $(SBE)_{7M}$-β-CD are shown in Fig. 8. The diffusion coefficient data was fitted to the following equations in the presence and absence of cyclodextrins, respectively.

$$D_{app} = D_{free} f_{free} + D_{mic} f_{mic} = D_{free} \times \frac{CMC}{[P_T]} + D_{mic} \times \frac{[P_T] - CMC}{[P_T]} \quad (14)$$

$$D_{app} = D_{free} f_{free} + D_{P-CD} f_{P-CD} + D_{mic} f_{mic} = D_{free} \times \frac{CMC}{[P_T]} + D_{P-CD} \times \frac{K_P\, CMC\, CD_T}{1 + K\, CMC} + D_{mic} \times \left(1 + \frac{CMC}{[P_T]} - \frac{K_P\, CMC\, CD_T}{1 + K\, CMC}\right) \quad (15)$$

The fitting of model to the experimental diffusion data reveals that the addition of 5% (w/w) $(SBE)_{7M}$-β-CD to MPHS solution increases the apparent MPHS CMC from 5 to 14 mg/mL and is in agreement with the change in apparent CMC (minimum) observed in the phase solubility studies.

4.3. Limitations of the model

There are several assumptions including those that are inherent with the two-phase theory that may limit the universal applicability of the derived equations to the cyclodextrin/surfactant systems. As pointed out in an earlier section, the concentration of monomer species is of great importance to the competitive nature of complexation with cyclodextrins. However, the determination of monomer species is dependent on the assumption that with increasing concentration of surfactant in the system, the monomeric to micellar transition occurs without formation of pre-micellar aggregate species. In cases where these pre-micellar species are formed below the CMC of the surfactant, the determination of the free monomer concentration can be erroneous which in turn may result into the lack of agreement between the model and the experimental data.

Additionally, CMC of a given surfactant system can be dependent on impurities, ionic strength etc. For ionic surfactants such as SLS, the type and concentration of ionic species added to the system could also affect the CMC (Yalkowsky, 1999). For the case of SLS and $(SBE)_{7M}$-β-CD, the ionic strength is not controlled and each molecule of $(SBE)_{7M}$-β-CD contains seven sodium ions. Moreover, the solubilization of drug by the surfactant micelles may be influenced by other ions and additives. In fact, Yang et al. (2004) propose that the deviation from the slope (drug solubility versus surfactant concentration) is related to slight changes in solubilization capacity of SLS (K_M) at different $(SBE)_{7M}$-β-CD concentrations.

Another limitation of the applicability of this model is related to cases where cyclodextrin or drug–cyclodextrin complex interact with micelles. The existing model needs to be modified for cases where cyclodextrin or drug–cyclodextrin complex can be internalized within surfactant micelles. Some literature reports have suggested that this kind of interaction is possible (De Lisi et al., 2002; Valero et al., 2002; Loftsson et al., 2002). It is also to be noted that the model is applicable only for 1:1 complex formation. For cases where higher order complexes or ternary complexes are present, similar models with appropriate equilibria can be developed.

5. Conclusions

A theoretical model to describe the total drug solubility in the presence of cyclodextrins and surfactant solutions has been developed. The model assumes the two-phase theory to be applicable for the self-association (micellization) behavior of surfactant, both the drug and only the monomer species of the surfactant are forming 1:1 inclusion complexes with cyclodextrin.

The model shows good agreement with experimental data. Furthermore, theoretical simulations show that the combined solubility is less than the sum of the individual solubility values in cyclodextrins and surfactants. It is also possible that combined solubility is less than individual solubility values.

This is the case with the NSC-639829, SLS and $(SBE)_{7M}$-β-CD whereas with MP, MPHS and $(SBE)_{7M}$-β-CD, a minor solubility change is observed with the mixed solutions than the individual solution. Based on the hypothetical case and the analyses of the two examples, it is clear that the phase solubility profile in mixed solutions of CD and surfactant are dependent on number of factors. It is however possible to predict this behavior provided the binary interaction parameters between the drug, CD and surfactant are known.

Finally, in spite of all the above assumptions and limitations, a model based on easy to use and well-accepted two-phase theory and 1:1 complexation equilibrium is useful as the first approach to understanding the drug solubility behavior in mixed CD–surfactant solutions. Furthermore, the deviations from the theoretical predictions could be used to bolster or eliminate

assumptions thus aiding in improving the understanding of the phase solubility behavior in these multi-component systems.

Appendix A

Based on the mass action law model, self-association equilibrium is expressed as follows:

$$n\mathrm{P}_1 \overset{\beta_n}{\rightleftharpoons} \mathrm{P}_n$$

The total surfactant concentration, Pt can be defined by the following expression:

$$\mathrm{P_T} = [\mathrm{P}_1] + n \times [\mathrm{P}_n] = [\mathrm{P}_1] + n\beta_n \times [\mathrm{P}_1]^n$$

The drug solubilization in the surfactant solution is can be depicted by multiple equilibria between the self-associated surfactant, P_n and the drug:

$$\mathrm{D} + \mathrm{P}_n \overset{k_1}{\rightleftharpoons} \mathrm{D}_1\mathrm{P}_n$$

$$2\mathrm{D} + \mathrm{P}_n \overset{k_2}{\rightleftharpoons} \mathrm{D}_2\mathrm{P}_n$$

$$\vdots$$

$$i\mathrm{D} + \mathrm{P}_n \overset{k_i}{\rightleftharpoons} \mathrm{D}_i\mathrm{P}_n$$

The saturation solubility of the drug in a surfactant solution is given as

$$S_\mathrm{T} = S_0 + [\mathrm{P}_n]\sum_{i=1}^{M} ik_i \times [\mathrm{S}_0]^i = S_0 + k \times [\mathrm{P}_n] + kn\beta_n \times [\mathrm{P}_1]^n$$

Consider additional equilibria between cyclodextrins and the monomers P_1 and D:

$$\mathrm{CD} + \mathrm{P}_1 \overset{K_\mathrm{P}}{\rightleftharpoons} \mathrm{P}_1\,\mathrm{CD}, \qquad \mathrm{CD} + \mathrm{D} \overset{K_\mathrm{D}}{\rightleftharpoons} \mathrm{D}\,\mathrm{CD}$$

In the presence of all the above-mentioned equilibria, the following expressions can be derived to describe the solubility of the drug in the presence of both surfactant and cyclodextrin solutions:

$$\mathrm{P_T} = [\mathrm{P}_1] + n\beta_n \times [\mathrm{P}_1]^n + \frac{K_\mathrm{P} \times [\mathrm{P}_1] \times [\mathrm{CD_T}]}{1 + K_\mathrm{P} \times [\mathrm{P}_1] + K_\mathrm{D} S_0},$$

$$S_\mathrm{T} = S_0 + kn\beta_n \times [\mathrm{P}_1]^n + \frac{K_\mathrm{D} S_0 \times [\mathrm{CD_T}]}{1 + K_\mathrm{P} \times [\mathrm{P}_1] + K_\mathrm{D} S_0}$$

$$= S_0 + k\left([\mathrm{P_T}] - [\mathrm{P}_1] - \frac{K_\mathrm{P} \times [\mathrm{P}_1] \times [\mathrm{CD_T}]}{1 + K_\mathrm{P} \times [\mathrm{P}_1] + K_\mathrm{D} S_0}\right) + \frac{K_\mathrm{D} S_0 \times [\mathrm{CD_T}]}{1 + K_\mathrm{P} \times [\mathrm{P}_1] + K_\mathrm{D} S_0}$$

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