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Quantifying Synergistic Effects on Drug Solubility in Cyclodextrin Systems

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INTRODUCTION & AIM

The aqueous solubility of an active pharmaceutical ingredient (API) is a key factor in oral drug formulation, as poor solubility often limits bioavailability. Cyclodextrins (CDs)—cyclic oligosaccharides of 6–8 glucose units—are widely employed to enhance solubility, stability, and absorption of lipophilic drugs. Among them, γ-CD is the most water-soluble, followed by α- and β-CD.

Beyond binary complexes, **ternary inclusion systems** — comprising a drug, CD, and an auxiliary agent — exhibit **superior complexation efficiency and stability**, while requiring lower CD concentrations. Auxiliary agents such as hydrophilic polymers, hydroxy acids, amino acids, or metal ions synergistically improve solubilizing capacity and dissolution rate. The **synergistic effect** results from cooperative molecular interactions, leading to improved dissolution rates and solubility, particularly under acidic conditions. This approach provides a practical and safe strategy to enhance the physicochemical and biological performance of poorly water-soluble drugs.

Aim of the study: to identify the thermodynamic conditions that promote synergistic solubilization and to introduce a quantitative parameter describing the degree of this cooperative effect, providing a framework for optimizing ternary drug–CD systems.

METHOD

The first step of the thermodynamic analysis consists in identifying the chemical species that the main components of ternary heterogeneous systems *HD – CD – HA* can adopt across a range of pH values, where *HD* represents a poorly soluble drug, such as flurbiprofen, or benzydamine, *CD* denotes cyclodextrin, and *HA* refers to an auxiliary agent such as citric acid.

In the next stage, the relevant chemical equilibria involving the three main components of the HD – CD – HA system are identified and systematically analyzed. This step is essential for developing a comprehensive equilibrium model of the heterogeneous multicomponent system:

- *Drug ionization (weak acid or weak base)*
- *Protolytic equilibria of the auxiliary ligand*
- *Drug - cyclodextrin complex formation (D – CD)*
- *Drug - auxiliary ligand (organic acid) complex formation (HD – HA)*
- *Ternary complex formation (HD – CD – HA)*

Next, the mass balance equations, taking into account both phases, are formulated by accounting for the interactions of the drug (*HD*) with cyclodextrin (*CD*) and citric acid (*HA*), including the formation of binary (*HD–CD*, *HD–HA*) and ternary (*HD–CD–HA*) complexes, as described in equations (8), (9), and (13)–(17):

$$C_D^0 = [D^-] + [HD] + [HD_s] + [H_2D^+] + [HD-CD] + [HD-HA] + [HD-CD-HA] \quad (1)$$

$$C_{CD}^0 = [CD] + [HD-CD] + [HD-CD-HA] \quad (2)$$

$$C_A^0 = [A^-] + [HA] + [H_2A^+] + [HD-HA] + [HD-CD-HA] \quad (3)$$

Using the corresponding equilibrium constants, these concentrations can be expressed as:

$$C_D^0 = [HD_s] + [HD]\left(1 + K_{a1}^{-1}[H^+] + K_{a2}[H^+]^{-1} + K_{1:1}[CD] + K_{HD:HA}[HA] + K_{HD:CD:HA}[CD][HA]\right) \quad (4)$$

$$C_{CD}^0 = [CD](1 + K_{1:1}[HD] + K_{HD:CD:HA}[HD][HA]) \quad (5)$$

$$C_A^0 = [HA](1 + \beta_1^{-1}[H^+]^{-1} + \beta_2[H^+] + K_{HD:HA}[HD] + K_{HD:CD:HA}[HD][CD]) \quad (6)$$

Provided that the initial chemical composition of the heterogeneous system is determined, the values of the variables $[HD_s], [CD]$ and $[HA]$ are determined through the solution of equations (5) - (6). Consequently, using the total concentrations C_D^0, C_{CD}^0, and C_A^0, representing the initial composition of the system, the respective equilibrium constants, the analyzed heterogeneous system is described by three equations with three unknowns: $[HD_s]$, [*CD*], and [*HA*]. These equations are solvable using standard computational tools.

Until now, no quantitative parameter has been established to assess the extent of the synergistic phenomenon. To quantitatively assess the synergistic effect, the concept of the Synergistic Coefficient (***SC***) is introduced for the first time:

$$SC = log\frac{S_{app,ternary\ system}}{S_{app,binary\ system}}, \quad (7)$$

where $S_{app,binary\ system} = [S_0]\left(1 + K_{a1}^{-1}[H^+] + K_{a2}[H^+]^{-1} + K_{1:1}[CD] + K_{HD:HA}[HA]\right)$ (8)

The subscript “ternary system” refers to parameters associated with the formation of ternary complexes $HD - CD - HA$ comprising the drug, cyclodextrin, and a secondary additional ligand (e.g., citric acid).

Definition (8) represents the theoretical formulation of *SC*, which cannot be directly verified through experimental measurements. Alternative definitions (9) and (10) could be formulated, in which $S_{app,binary\ system}$ corresponds to the apparent solubility resulting from the separate interaction of the drug with either cyclodextrin or the additional ligand:

$$S_{app,binary\ system,1} = [S_0]\left(1 + K_{a1}^{-1}[H^+] + K_{a2}[H^+]^{-1} + K_{1:1}[CD]\right) \quad (9)$$

$$S_{app,binary\ system,2} = [S_0]\left(1 + K_{a1}^{-1}[H^+] + K_{a2}[H^+]^{-1} + K_{HD:HA}[HA]\right) \quad (10)$$

RESULTS & DISCUSSION

The Synergistic Coefficient serves as a quantitative descriptor of the extent to which the presence of a co-ligand enhances the interaction between the drug and cyclodextrin, thereby promoting the formation of more stable ternary complexes. A positive *SC* (*SC* > 0) signifies synergism, i.e., the co-ligand facilitates drug solubilization and release. In contrast, a negative *SC* (*SC* < 0) suggests antagonistic behavior, wherein the co-ligand interferes with complex formation, reducing the overall efficiency of the system.

To demonstrate the applicability of the developed thermodynamic methodology, repaglinide (RPG)—a commercially available antidiabetic drug—was chosen as a model compound. RPG, a carbamoylmethylbenzoic acid derivative of the meglitinide class, acts as a prandial glucose regulator for the treatment of type 2 diabetes mellitus (Vakani et al., 2015).

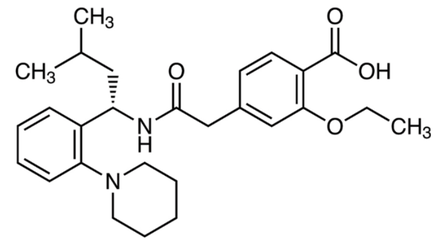

Figure 1. Chemical structure of repagnilide

It is an acid–base ampholyte (pK_{a1} = 4.2; pK_{a2} = 6.0) characterized by low aqueous solubility (34 μg/mL at 37 °C) and high lipophilicity (log P = 3.97). Its solubility depends strongly on pH, being highest in acidic media (3.15 ± 0.17 mg/mL in pH 1.2 HCl buffer) and lowest in weakly basic conditions (51 ± 1.8 μg/mL in pH 6.8 phosphate buffer). To enhance its solubility and physicochemical performance, inclusion complexation of RPG with hydroxypropyl-β-cyclodextrin (HP-β-CD) was explored by Vakani et al. (2015) in the presence and absence of auxiliary agents such as polyvinylpyrrolidone-K30 (PVP) and L-arginine (ARG). The complexes were prepared using three techniques: (i) physical mixing of the individual components (PM), (ii) kneading with a binder solution (KM), and (iii) co-evaporation employing a rotary evaporator (CE). Phase solubility studies indicated the formation of 1:1 inclusion complexes, both with and without auxiliary substances. The enhanced solubility was mainly attributed to the formation of stable inclusion complexes between RPG and HP-β-CD. Among the systems tested, the ternary co-evaporated complex (RPG–HP-β-CD–auxiliary) exhibited an approximately 475-fold increase in solubility, far exceeding the 6.2-fold improvement observed for the binary co-evaporated complex. The derived equations (7), (9), and (10) were applied to the experimental data for the RPG–HP-β-CD–ARG and RPG–HP-β-CD–PVP systems. The resulting synergic coefficient values obtained from these calculations are summarized in Table 1.

Table 1. Calculated synergic coefficients for the ternary inclusion complexes RPG–HP-β-CD–ARG and RPG–HP-β-CD–PVP, derived from the solubility data reported by Vakani et al. (2015).

System	Method	Synergic Coefficient
RPG–HP-β-CD–ARG	PM	1.67
	KM	1.78
	CE	1.91
RPG–HP-β-CD–PVP	PM	1.33
	KM	1.32
	CE	1.16

The SC calculated using different methods show slight variations, yet all values consistently confirm the synergic behavior of the investigated ternary systems. Among the auxiliary agents, L-arginine (ARG) displays a more pronounced synergic effect than polyvinylpyrrolidone (PVP). The proposed synergic coefficient was applied for the first time to quantitatively reveal this effect. Compared with the PVP-based complexes, the supramolecular inclusion complex with ARG exhibited a substantial improvement in the aqueous solubility of RPG.

CONCLUSION

For the first time in the scientific literature, the concepts of drug precipitation degree and synergic coefficient were introduced and quantitatively defined based on original mass balance equations. The proposed methodology was successfully validated using the repaglinide (RPG) system complexed with hydroxypropyl-β-cyclodextrin (HP-β-CD) and auxiliary agents L-arginine (ARG) and polyvinylpyrrolidone (PVP). The developed thermodynamic framework provides a powerful predictive tool for assessing drug solubility enhancement and intermolecular interactions in supramolecular inclusion complexes.

FUTURE WORK / REFERENCES

Vakani, S. S., Kajwe, A., Suvarna, V., & Sherje, A. P. (2015). Influence of auxiliary agents on solubility and dissolution profile of repaglinide with hydroxypropyl-β-cyclodextrin: Inclusion complex formation and its solid-state characterization. *Journal of Inclusion Phenomena and Macrocyclic Chemistry, 83*, 239–250. https://doi.org/10.1007/s10847-015-0559-y