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| REVIEW ARTICLE

The relationship of hydrogen bond formation with solubility increment of poorly soluble drugs

Lina S. Hussein
Department of pharmacognosy, College of Pharmacy, University of Thi-Qar, 64001, Thi-Qar, Iraq.
Corresponding Author: Lina S. Hussein, **E-mail**: linasalim@utq.edu.iq

| ABSTRACT
The study of drug solubility provides an information about the structure and the nature and strength of intermolecular forces of drug molecules. There are different augmentation techniques for improvement of the solubility of the poorly soluble compounds. These techniques can improve their solubility by different mechanisms. One of them including the formation of intermolecular hydrogen bonds between the drug and another hydrophilic compound or solvent. Also these bonds can be resulted from change the drug structure into a salt or prodrug form. Which has more tendency for intermolecular hydrogen bonding with water molecules. Hence will largely increases their solubility. Others include only break or weakened the intramolecular hydrogen bonding that is present among the molecules of these drugs.

| KEYWORDS
Poorly soluble drugs, Hydrogen bonds, Solubility augmentation

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Introduction

An overview of poorly soluble drugs

Solubility is a property of a substance in a specific solvent. The usage of combinatorial chemistry established a continued development process belonging to many chemical compounds that have good pharmacological action but unfortunately low aqueous solubility. Bad bioavailability may result from these compounds depending on their low solubility and rate of dissolution, which will certain affect their inherent efficacy (1, 2). The biopharmaceutical classification system (BCS) is a system used for drug categorizing depending on solubility and permeability in GIT. These two properties predict their abilities to enter the circulation **(3).** According to BCS, drug substances can be divided into four different classes (Table 1).

Table (1): Biopharmaceutical Classification System (4)

Class	Solubility	Permeability	Considerations in formulation of dosage form
I	High	High	Solubility and permeability do not affect the absorption
II	Low	High	Dissolution is the rate-limiting factor for drug absorption
III	High	Low	Permeability is the rate-limiting factor for drug absorption
IV	Low	Low	Challenging to develop because both dissolution and permeability are the rate-limiting.

Despite high permeability, the low solubility of class II drugs is related to low dissolution rate in GIT, resulting in low bioavailability. Sequentially poor absorption is mentioned with these drugs. In comparison to class IV drugs, they have low aqueous solubility and permeability, which largely reduces their absorption capabilities. Generally, class IV drug represent a poor drug candidate for development. because the restricted membrane permeability, so solubility and dissolution improvement may not be enough to increase its bioavailability. So this class drugs can be developed through the same methods used to class II drugs but with absorption enhancers (5, 6).

Overview of some techniques for solubility augmentation

Different methodologies are accessible to improve the solubility of poorly soluble drugs (7). Many of them are listed briefly below:

- **Particle size reduction:** such as nanosuspension and nanocrystals
- **Modification of the crystal habit:** such as polymorphs and hydrates/solvates**(8)**.
- **Complexation:** there are many types of complexes, such as inclusion complexes, which are formed by the use of cyclodextrins that have a hydrophilic outside and a hydrophobic cavity (9, 10).
- **Particle dispersion:** Such as solid dispersions, which can be defined as a solid products group consisting of a hydrophobic drug dispersed in one or more hydrophilic carriers, resulting in improved wettability, dispersion ability, and reducing aggregation of drug (11).
- **Hydrotrophy** is a compound that solubilizes hydrophobic ones in aqueous solutions. Hydrotropes include a hydrophilic and a hydrophobic parts like surfactants. But the hydrophobic part is too tiny to make self-aggregation spontaneously (12).
- **Co-crystallization:** is a multicomponent system that combines a hydrophobic drug with a suitable coformer(s) in an accurate stoichiometric ratio via a non-covalent bond (13, 14).
- **Prodrug approach:** Though not all prodrug approaches were made to improve solubility. This technique can be used to modulate pharmacokinetic properties and poor solubility. Examples of products presented for poor solubility were esters, amides, and amino acids. Other chemical groups are used, but to a lesser extent, like glycol groups and glycosides (15**)**.
- **Salt formation:** The drug (must be in ionizable form) is ionized by a proton transfer with the aid of an acid or base counter ion (16).

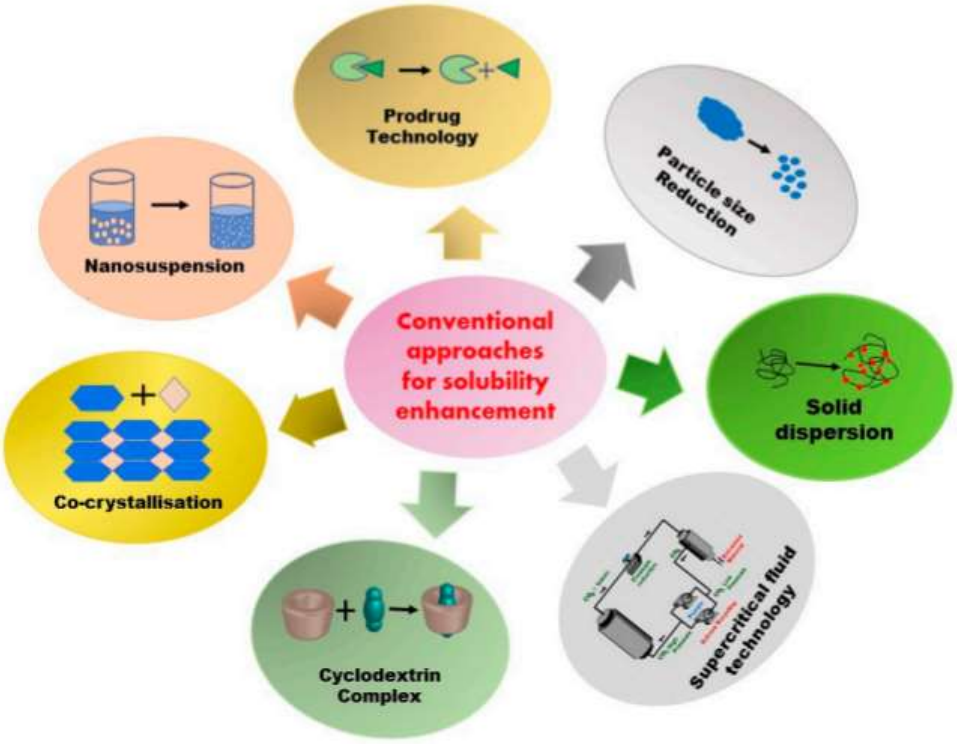

Figure 1.Some methods of solubility augmentation (17).

An overview of hydrogen bonds

The hydrogen bond is an interesting bond that occurs between a hydrogen atom of a certain molecule or a molecular fragment X-H, at which X is more electronegative than the hydrogen atom, and an atom or a group of atoms at the same or a different molecule, leading to evidence of bond formation. It will be found in two types: intramolecular and intermolecular hydrogen bonds. Generally, hydrogen bonding can be examined by different methods, like measurements of dipole moments, solubility behavior, freezing-point lowering, and heats of mixing. The presence of hydrogen bonding can be confirmed mainly by FTIR or Raman, electronic, and NMR (18, 19). The simplest hydrogen bond consists of three atoms: donor, acceptor, and hydrogen (20**)**.

Relationship of hydrogen bond formation with solubility of poorly soluble drugs

The solubility of these drugs is largely affected by their abilities to form intermolecular hydrogen bonds with another hydrophilic compound or with a polar solvent. Also depend on the capability of the solvent or the other hydrophilic compound to break or weakend the intramolecular hydrogen bonding that is present among the molecules of these compounds. Generally, the action or effect of hydrogen bonding on the solubility profile can be summarized in many ways, as below:

A-Drugs with more hydrogen bond donors and acceptors: These drugs can interact strongly with a hydrophilic polymer, increasing their solubility by forming an intermolecular hydrogen bond between them (21, 22).

B-Crystalline and amorphous drug forms: When poorly soluble drugs exist in crystalline forms, being more ordered and having strong intermolecular hydrogen bonds within their structure, they need more energy for breakage, so have less solubility. While when these drugs exist in amorphous forms, they have a less ordered structure, fewer intermolecular hydrogen bonds, and hence less energy required for molecules to go to solution (23, 24**)**.

C-Salt drug forms: Change the drug structure into a salt form, which has more tendency for intermolecular hydrogen bonding with water molecules (25**)**.

D-Prodrug forms: changing the drug structure into prodrug form (if being more soluble forms) has more tendency for hydrogen bonding with water molecules (15**)**.

E-Solvent properties: The coordination effect of either the solvent (26**)** or cosolvent (27**)** with the drug molecule that can break or weaken intramolecular drug molecules interactions depending on the hydrogen bond donor or acceptor effect of these solvents resulted in an improvement of drug solubility. Generally, the drug aqueous solubility can be measured by relative strength of the interactions between its molecules in the solid state and the interaction whose molecules can make with water or other polar solvent (28). By another meaning, if hydrogen bonding is possible between solute and solvent, this will increase solute solubility largely or infinitely (19**)**.

But if there is a strong hydrogen bond formation between the drug molecules and any of these five possible ways cannot overcome or disrupt the intramolecular forces, the poor solubility may remain unchanged or decrease (29). In this condition, the hydrogen bond formation has a negative effect on its solubility.

Table (2): Examples of some poorly soluble drugs that have hydrogen bonding through different solubility augmentation techniques

Drug example	BCS class	Technique of solubility augmentation	Characterization technique of hydrogen bond	Reference
Felodipine	II	Solid dispersion	FTIR and NMR spectroscopy	(30)
Ciprofloxacin	IV	Prodrug	Not characterized	(31)
Curcumin	II	liquisolid technology	FTIR	(32)
Paclitaxil	IV	Complexation	FTIR	(33)

Haloperidol and droperidol	II	Solid dispersion	FTIR	(34)
Loratadine	II	Nanosuspension	FTIR	(35)
Nifedipine and ketoconazole	II	Coamorphous formation	FTIR	(36)
Sorafenib	II	Salts formation	Not characterized	(37)
Dapsone	IV	Salt formation or cocrystals	Not characterized	(38)
		Deep eutectic solvents	FTIR, NMR	(39)
Indomethacin and sulindac	II	drug–drug amorphous formulations	FTIR and Raman spectroscopy	(40)

Conclusion

There are a lot of techniques for improvement the solubility of poorly soluble compounds. These poorly soluble drugs are class II and class IV of BCS. Many of them including the formation of intermolecular hydrogen bonds between the drug and another hydrophilic compound or with hydrophilic solvent molecules. Others change the drug structure into a salt or prodrug form, which has more tendency for intermolecular hydrogen bonding with water molecules. Usually the presence of hydrogen bonding can be confirmed mainly by FTIR or Raman and NMR.

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References

[1] Vojinovi ̧ T, Medarevi ̧ D, Vrani ̧ E, Potpara Z, Krsti ̧ M, Djuri ̆ J, et al. Development of ternary solid dispersions with hydrophilic polymer and surface adsorbent for improving dissolution rate of carbamazepine. Saudi Pharmaceutical Journal. 2018;26(5):725–732.Smith BT.
[2] Solubility and dissolution. In: Remington physical pharmacy. London: Pharmaceutical Press; 2016. p 31-50.
[3] Singhal P, Singhal RV, Kumar VJ, Verma A, Kaushik R. D. The biopharmaceutics classification system (BCS): Review. WJPPS.2018; 7(1):269-283.
[4] Fox SC. Bioavailability, bioequivalence and the biopharmaceutical classification system. In: Remington Education Pharmaceutics. London: Pharmaceutical Press; 2014. p 169-187.
[5] Kumari, L., Choudhari, Y., Patel, P., Gupta, G. D., Singh, D., Rosenholm, J. M., & Kurmi, B. D. Advancement in solubilization approaches: a step towards bioavailability enhancement of poorly soluble drugs. Life.2023; 13(5): 1-32.
[6] Khadka, P.; Ro, J.; Kim, H.; Kim, I.; Kim, J.T.; Kim, H.; Cho, J.M.; Yun, G.; Lee, J. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian J. Pharm. Sci. 2014, 9, 304–316.
[7] Bhalani, D. V., Nutan, B., Kumar, A., & Singh Chandel, A. K. (2022). Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics. Biomedicines. 2022;10(9), 2055.
[8] Narmada, I. Contemporary Review on Solubility Enhancement Techniques. Journal of Drug Delivery and Therapeutics.2023; 13(2), 110-120.
[9] Munnangi, S. R., Youssef, A. A. A., Narala, N., Lakkala, P., Narala, S., Vemula, S. K., & Repka, M. Drug complexes: perspective from academic research and pharmaceutical market. Pharmaceutical Research.2023; 40(6), 1519-1540.
[10] Vaishnavi Dilip Chaudhari, 2Rajeshree Aasaram Khandre. Solubility Enhancement Techniques:An Overview. International Journal of Creative Research Thoughts. 2022; 10(10), 794-815.
[11] Tran P, Pyo YC, Kim DH, Lee SE, Kim JK, Park JS. Overview of the manufacturing methods of solid dispersion technology for improving the solubility of poorly water-soluble drugs and application to anticancer drugs. Pharmaceutics. 2019;11(3):1–26.
[12] Arjaria P, Goyal M, Jain S. Hydrotropic solubilization. International Journal of Pharmaceutical and Phytopharmacological Research. 2013; 3 (1): 17-23.
[13] Qiao N, Li M, Schlindwein W, Malek N, Davies A, Trappitt G. Pharmaceutical cocrystals: An overview. Int. J. Pharm. 2011;419(1-2):1–11. DOI: 10.1016/j.ijpharm.2011.07.037.
[14] Miroshnyk I, Mirza S, Sandler N. Pharmaceutical co-crystals-an opportunity for drug product enhancement. Expert Opin. Drug Del. 2009;6(4):333–41. DOI: 10.1517/17425240902828304.
[15] Jornada, D. H., dos Santos Fernandes, G. F., Chiba, D. E., De Melo, T. R. F., Dos Santos, J. L., & Chung, M. C. The prodrug approach: a successful tool for improving drug solubility. Molecules. 2015; 21(42): 1-31.
[16] Lüdeker, D., & Briel, T. Improving API Solubility by Salt and Cocrystal Formation.
[17] Kumari, L., Choudhari, Y., Patel, P., Gupta, G. D., Singh, D., Rosenholm, J. M., Bansal K. K. & Kurmi, B. D. Advancement in solubilization approaches: a step towards bioavailability enhancement of poorly soluble drugs. Life. 2023; 13(5), 1-32.
[18] Sinko PJ. States of matter. In: Martin's physical pharmacy and pharmaceutical sciences. 6th ed. Baltimore: Lippincot Williams and Wilkins; 2011. p17-53.
[19] Smith, Michael B. Bonding weaker than covalent. In: March's advanced organic chemistry: reactions, mechanisms, and structure. 6th ed. John Wiley & Sons, 2007. p 106-135.
[20] Kolesov, B. A. Hydrogen bonds: Raman spectroscopic study. International journal of molecular sciences. 2021; 22(10): 1-35.

[21] Lipinski C. A. "Drug-like properties and the causes of poor solubility and poor permeability." Journal of Pharmacological and Toxicological Methods. 2000; 44(1), 235-249.
[22] Budiman, A., Nurani, N. V., Laelasari, E., Muchtaridi, M., Sriwidodo, S., & Aulifa, D. L. Effect of Drug–Polymer Interaction in Amorphous Solid Dispersion on the Physical Stability and Dissolution of Drugs: The Case of Alpha-Mangostin. Polymers. 2023; 15(14):1-14.
[23] Lachman L., Lieberman H. A and Kanig J. L.: Theory and practice of industrial pharmacy, New Delhi: CBS Publishers and Distributors Pvt, Ltd; 2009, p. 171-196.
[24] Aldahhan E. S., & Radhi, A. A. Co-amorphous system: a promising strategy for delivering poorly water-soluble drugs. Iraqi Journal of Pharmaceutical Sciences.2020; 29(1), 1-11.
[25] Dwichandra Putra O., Umeda, D., Fujita, E., Haraguchi, T., Uchida, T., Yonemochi, E., & Uekusa, H. Solubility improvement of benexate through salt formation using artificial sweetener. Pharmaceutics. 2018;10(2),1-12.
[26] Behera, A. L., Sahoo, S. K., & Patil, S. V. Enhancement of solubility: A pharmaceutical overview. Der Pharmacia Lettre.2010; 2(2), 310-318.
[27] He, M., Zheng, W., Wang, N., Gao, H., Ouyang, D., & Huang, Z. Molecular dynamics simulation of drug solubilization behavior in surfactant and cosolvent injections. Pharmaceutics.2022; 14(11), 2366.
[28] Kenny P. W. Hydrogen-bond donors in drug design. Journal of Medicinal Chemistry 2022; 65(21), 14261-14275.
[29] Gaikwad SS, Morales JO, Lande NB, Catalán-Figueroa J, Laddha UD, Kshirsagar SJ. Exploring paediatric oral suspension development: Challenges, requirements, and formulation advancements. International journal of pharmaceutics. 2024.124169.1-10.
[30] Karavas, E., Ktistis, G., Xenakis, A., & Georgarakis, E. (2006). Effect of hydrogen bonding interactions on the release mechanism of felodipine from nanodispersions with polyvinylpyrrolidone. European Journal of Pharmaceutics and Biopharmaceutics.2006; 63(2), 103-114
[31] Tehler, U., Fagerberg, J. H., Svensson, R., Larhed, M., Artursson, P., & Bergström, C. A. Optimizing solubility and permeability of a biopharmaceutics classification system (BCS) class 4 antibiotic drug using lipophilic fragments disturbing the crystal lattice. Journal of medicinal chemistry. 2013;56(6), 2690-2694.
[32] Sharma, V., & Pathak, K. Effect of hydrogen bond formation/replacement on solubility characteristics, gastric permeation and pharmacokinetics of curcumin by application of powder solution technology. Acta Pharmaceutica Sinica B. 2016; 6(6), 600-613.
[33] Hirota, K., Hristova, T., Mitova, V., Koda, T., Fushimi, M., Kuniya, M., ... & Troev, K. Polyphosphoester-based paclitaxel complexes: biological evaluation. Anticancer research. 2016; 36(4), 1613-1620.
[34] Saluja, H., Mehanna, A., Panicucci, R., & Atef, E. Hydrogen bonding: Between strengthening the crystal packing and improving solubility of three haloperidol derivatives. Molecules 2016; 21(6):1-16.
[35] Alshweiat, A., Katona, G., Csóka, I., & Ambrus, R. Design and characterization of loratadine nanosuspension prepared by ultrasonic-assisted precipitation. European Journal of Pharmaceutical Sciences.2018; 122, 94-104.
[36] Hatanaka, Y., Uchiyama, H., Kadota, K., & Tozuka, Y. Improved solubility and permeability of both nifedipine and ketoconazole based on coamorphous formation with simultaneous dissolution behavior. Journal of Drug Delivery Science and Technology. 2021; 65, 102715.
[37] Phan, C., Shen, J., Yu, K., Liu, J., & Tang, G. Hydrogen bonds, topologies, energy frameworks and solubilities of five Sorafenib salts. International Journal of Molecular Sciences. 2021;22(13): 1-12.
[38] Wu, Y., Hao, X., Li, J., Guan, A., Zhou, Z., & Guo, F. New insight into improving the solubility of poorly soluble drugs by preventing the formation of their hydrogen-bonds: A case of dapsone salts with camphorsulfonic and 5-sulfosalicylic acid. CrystEngComm. 2021;23(35), 6191-6198.
[39] Trombino, S., Siciliano, C., Procopio, D., Curcio, F., Laganà, A. S., Di Gioia, M. L., & Cassano, R. Deep eutectic solvents for improving the solubilization and delivery of dapsone. Pharmaceutics.2022; 14(2), 333.
[40] Hatanaka, Y., Uchiyama, H., Furukawa, S., Takase, M., Yamanaka, S., Kadota, K., & Tozuka, Y. Effect of Solubility Improvement via Formation of an Amorphous Composite of Indomethacin and Sulindac on Membrane Permeability. Chemical and Pharmaceutical Bulletin.2023; 71(3), 257-261.