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Influence of solid-state chemistry in drug substances in pharmaceutical products. A review

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Abstract
Most of Active pharmaceutical ingredients exhibits in different crystalline forms such as polymorphs, salts, solvates and hydrates and amorphous. Each forms exhibit polymorphism except amorphous. Crystal engineering approach presents a number of routes such as co-crystallization, polymorphism and salt formation to improve physico-chemical properties of drugs, which can be implemented through an in detail knowledge of crystallization processes and the molecular properties of drugs. Various polymorphs usually have different physic chemical, mechanical and thermal properties that can extremely affect the bioavailability, stability and other characteristics of the active pharmaceutical ingredients. Co-crystal is a binding of two molecules for enhancing drug pharmaceutical properties. All this solids form may affect Chemical and Physical Stability, Apparent Solubility, Dissolution, Bioavailability and Bioequivalence and Manufacturability of drug product, which require special attention during product development as it affects the quality, safety and efficacy of drug product.

Keywords: Polymorphisms, solvates and hydrates, salts, co-crystals and amorphous

Introduction
Solid-state chemistry is referred as a material chemistry; it is the study of synthesis, structure and properties of solid phase materials. Solid-state chemistry gives idea about packing of molecules, elements and atoms in solid form. This branch of chemistry is important in all industries like metals, polymer, rubber, fine chemicals and pharmaceuticals. In last 30 years, after highlighting Ritonavir case in 1989, view of pharmaceutical section towards crystal chemistry gets change. Active pharmaceutical ingredients (API) or drug substances is exists in various solid forms like polymorphs, solvates and hydrates, salts, co-crystals and amorphous. Fig.1.

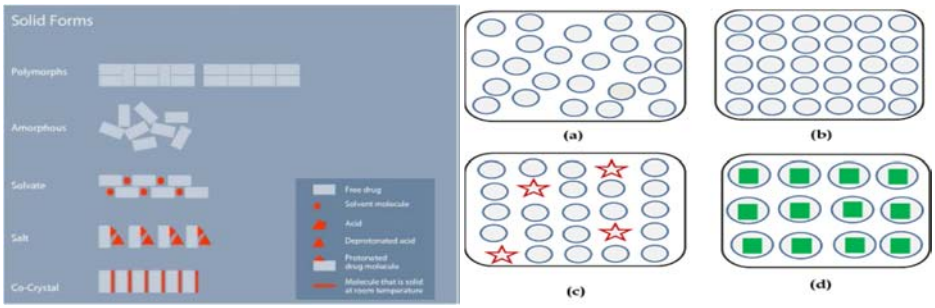

Fig 1: Various Types of Solid Forms (Pictorial representation (a) Amorphous form (b) Crystalline form (c) Hydrates and Solvates (d) Clathrates of Drug molecule ∗ Solvent molecule)

Each and every form has its unique thermal, mechanical, physical and chemical properties that have impact on the solubility, dissolution rate, bio-availability, hygroscopicity, melting point, stability, compressibility and many more. This is reflected and mostly depends on the last stage of synthesis which is crystallization. Formation of these different forms can be controlled at the time of the crystallization by effective procedures. Hence, authentic understanding of the relationship between the particular solid form of an API and its crystallization process is critical to prepare the most suitable and stable polymorphs of drug substance in formulation. In this contribution, we will introduce the concepts, properties and perspectives of various solid forms of drug substances and some examples.

Polymorphs in Polymorphisms: Many drug solid are exhibits in different physical forms. Polymorphism is an ability of a drug substance to exist in two or more than two crystalline states that are possessing different and distinct arrangements and/or conformations of molecules in the crystal lattice. In short, polymorphs have same chemical compositions with different lattice structure (different packing chemistry) and/or different molecular conformation. It is an wide spread phenomenon for the most drug substances, some of the pharmaceutical active substances are non-polymorphic form but theoretically there possibilities that can appears in polymorph. Different polymorphs of a drug molecule generally have different physical and chemical properties or physicochemical such as solubility, dissolution rate, stability, melting point and reactivity etc. Ritonavir is well known example of polymorphism, which is the drug, introduced and offer importance for polymorphism. History about it's that Ritonavir form-I first introduced in market which has less stability than Form-II. Change in temperature and humidity the form-I gets convert into stable Form-II, this stable Form-II has low solubility around 50% than Form-I. Paracetamol, it is used as antipyretic drug commonly as a pain reliever and fever reducer. It uses for many conditions like headache, muscle aches, arthritis, back ache, toothaches, in cold and fever. Paracetamol exist in three form most commonly available monoclinic form, orthorhombic form and third one is tri-hydrate. Both available form means monoclinic and orthorhombic form are easily differentiate by simple melting point technique. All the commercial Paracetamol samples which having monoclinic form (Form-I) are having melting point in the range 165–170 °C. While orthorhombic form having melting point about 155 °C. Thus the Form-II is meta-stable form and Form-I is stable form. Fig.2.

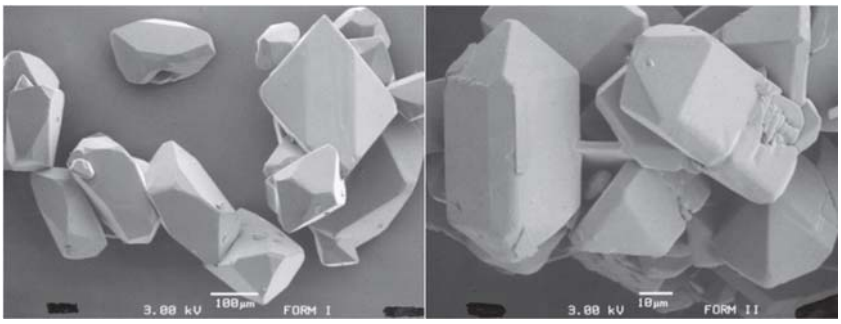

Fig 2: Paracetamol in monoclinic and orthorhombic form by scanning electron micrograph.

Similarly Nicergoline a potent blocking agent for α-1-adrenoreceptor, exist in two Triclinic Form (I) and orthorhombic Form (II). Triclinic form I is stable up to its melting point 134°C, while orthorhombic Form (II) melts about 120-122°C and then Form II gets convert into stable Form-I by recrystallized using low heating rate. Hygroscopicity nature mostly depends on polymorphs packing example of this Stavudine Thymidine nucleoside, it having two forms. Monoclinic form (I) is less hygroscopic than Triclinic form (II). Hygroscopicity of Fluoroquinolone F orm I and Form III with impact on solubility is given below in Fig.3.

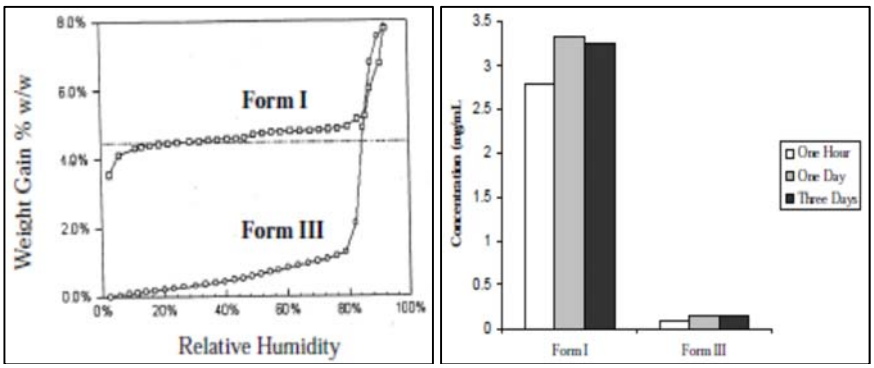

Fig 3: a. Hygroscopicity of fluoroquinone **b.** Solubility of fluoroquinone

Solvates and Hydrates: It is a Pseudo- polymorphism crystalline form of compound in which solvent molecules involved as an integral part of the crystals. Some compounds while crystallize they entrap solvent in the crystal. Crystals that contain solvent in the crystallization are called crystal solvates. When water used as a solvent for crystallization then it gives Hydrates form. Crystallization occurs in water without forming hydrates are called anhydrous form or anhydrates. Theses solvates exhibit a wide range of behavior depending on the interaction between the solvent and crystal structure. Some solvents are utilized for holding the crystal lattice together. Solvates and Hydrates may have different solubility, dissolution rate, mechanical properties, stability and bio-availability from their non solvates counter parts. They are stoichiometric or non-stoichiometric in nature. Cephaloridine is a first generation semi synthetic derivative of Cephalosporin C. Cephaloridine exists in six forms of solvates or hydrates. These different solvates and hydrates have variable dissolution rate. Following tables show dissolution rate of Oxyphenbutazone. (Table No.1)

Samples	Dissolution rate(mg/min)
Solvate C	21.05 ± 0.02
Solvate B	18.54 ± 0.47
Anhydrate	14.91 ± 0.47
Hemihydrates	17.01 ± 0.78
Monohydrate	9.13 ± 0.23

In the solvates and hydrates there are transition of forms occurs like polymorphs e.g. L-phehylalanine monohydrate will transform into its stable anhydrate form, when the temperature is above transition point 35.4 °C. Formation of solvated or non solvated form is totally depends upon drug products properties. Similarly dihydrate form of Frovatriptan Succinate on heating loses water molecule and convert into anhydrous form. Different form of FS can differentiate by DSC (Differential scanning calorimetry). Fig.4.

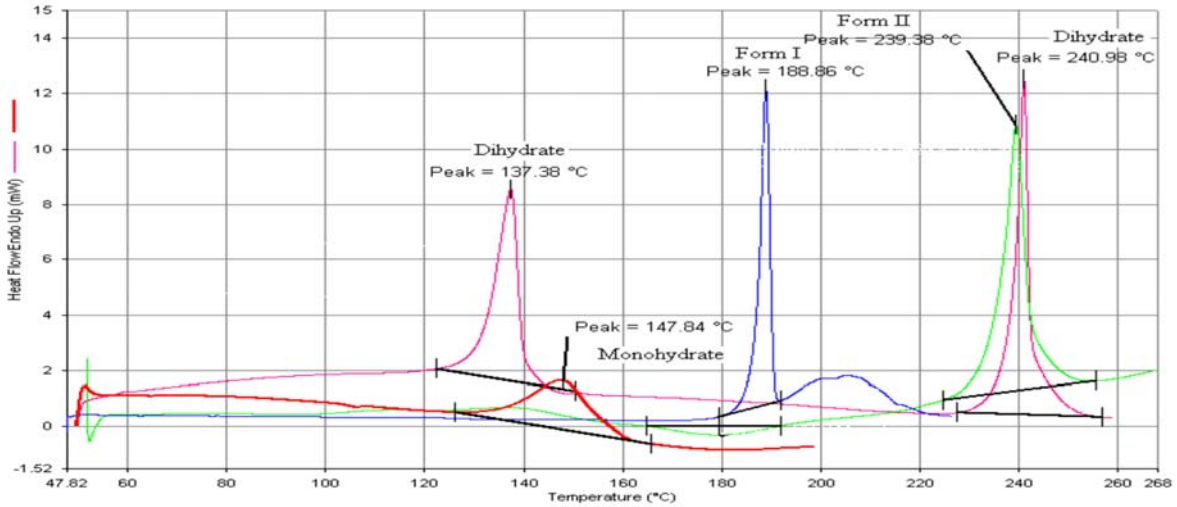

Fig 4: DSC of Frovatriptan Succinate hydrate and polymorphs.

Pharmaceutical Salts: Salts formation is generally possible when drug substance having ability of ionization. Only ionizable drug can take part in salt formation. Reason behind this is enhancing the solubility of drug substances in aqueous solution. Thus salts form drug have impact on solubility, stability, dissolution rate and bio-availability. Now more than 50% drugs are incorporated in form of salts. Salts formation occurs by giving treatment of acid or base to the drug molecule. The presence of ions strongly influences the physicochemical properties of the crystals formed salts. In presence of these ions drugs improved their pharmaceutical properties such as solubility, dissolution rate, stability, crystal habit, crystallinity, and hygroscopicity etc. These salts form also exhibits in different polymorphs like their counter parts. Highly polymorphic and prone to solvate formation is Sertraline Hydrochloride, which has been found to have 28 totall forms, like 17-polymorphs,4 solvates, 6hydrates and amorphous.

Co-Crystals: Structurally homogenous crystalline materials containing two or more components present in the standard stoichiometric amounts and it is a neutral molecule, at ambient temperature in solid form. While co- crystal formed it is partnership between main drug and co crystal former. When one form is in liquid form at room temperature then their prone to form solvates while both are solid form then result in co-crystal. In salts form transformation occurs while in co-crystal this will not happen. Co-crystal phenomenon enhanced drug solubility, dissolution rate, stability and bio availability. This co crystal former is might be another drug or inactive pharmaceutical ingredients (excipients). In Combivir, Lamivudine and Zidovudine are used, its use as a medicine for HIV treatment. Both are active pharmaceutical agent, one is act as a co crystal former. Some acid(citric acid, malonic acid, glutaric acid, maleic acid, P-Amino benzoic acid etc.), amide (pyridine) and polymer (Poly vinyl butyrate) used as an exciepient are actually acts as a co crystal former. Co- crystal is occure due to van-der waals force, π- π stacking, hydrogen bonding and halogen bonding between two molecules. Thses co-crystal is possible between molecule contains group like –COOH,-N<, pyridine mostly. Most common examples are norfloxacin saccharinate dihydrate and its co-crystal, norfloxacin saccharinate–saccharin dehydrate, carbamazepine-nicotinamide, carbamazepine-saccharin, and caffeine or theophylline with dicarboxylic acid ligands etc. A typical hydrogen bonds existing in pharmaceutical co-crystals as shown in Fig.5.

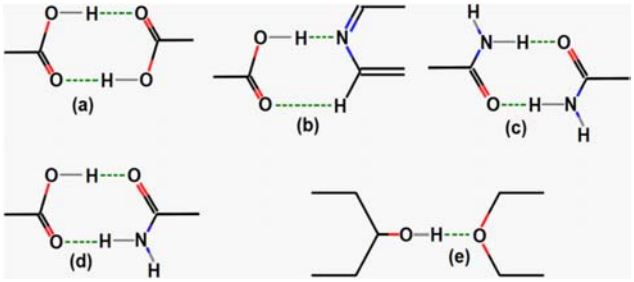

Fig 5a: Typical hydrogen bonds existing in pharmaceutical co-crystals.

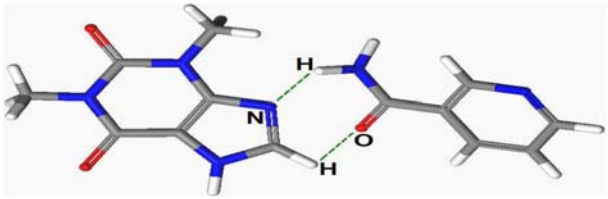

Fig 5b: A Co-crystal of Theophylline and Nicotinamide in a molar ratio of 1:1.

Theophylline has low solubility than its co crystal Theophylline- Nicotinamide. Techniques apply for co-crystallization are neat co grinding, solvent drop cogrinding, melt crystallization and slow evaporation from solution. Co-crystals can also form solvates and exhibits polymorphism.

Amorphous solids: This form has non uniform arrangement of atoms in molecules. Differentiation of this lattice is not easy. Amorphous form having normally desirable pharmaceutical properties than their crystalline counter parts. The difference in solubility of amorphous and crystalline form has been reported to be between 1.1 and 1000 fold. Even though amorphous form have high dissolution rate and high solution concentration than their crystalline counter parts it's bio- availability is low as compare to crystalline form. Thus amorphous form have limited use in pharmaceutical region. This due to difficulty in preventing recystallization from amorphous form during In-vitro study. When they are present in to dissolution medium their prone to crystallize through form transition. If this transition takes immediately the supersaturation will be much less than predicted or theoretically assumed. No supersaturation occurs when their crystallization is rapid. For achieving this super-saturation and recystallization some stabilizer are use. Here also there are possibilities of transition occurs due to mechanical stress or by using some process. While formulation if the drug use which is meta-stable form then small change in temperature and humidity, this form gets change into stable form. This possibility at the time of stability conditions mostly accelerated (40°C/75%RH).

Conclusion: The existence of polymorphs, solvates and hydrates, salts and Co-crystals may potentially be an important source of variation in pharmaceutical properties, which can cause problems concerning the stability, solubility and, consequently, efficacy and bioavailability of drug products. Co-crystals of drugs and drug candidates represent a new type of material for pharmaceutical development. Co-crystals are relatively new to pharmaceutical industry and pharmaceutical co-crystals have given a new direction to deal with problems of poorly soluble drugs.

References

1. Rahul P, Venugopalan P. Polymorphism – An overview. Resonance. 2009; 14(9):882-93.
2. Cesur S, Gokbel S. Crystallization of mefenamic acid and polymorphs. Crystal Research Technology. 2008; 43(7):720-8.
3. Harry G Brittain. Polymorphism in pharmaceutical solids, 2nd ed. New York: CRC Press, 2009, 3 & 13.
4. Hosokawa K, Goto J, Hirayama N. Predicition of solvents suitable for crystallization of small organic molecules. Chemical and Pharmaceutical Bulletin. 2005; 53(10):1296-9.
5. Manavalan R, Ramasamy C. Physical pharmaceutics, 2nd ed. Vignesh publisher, 2004, 20 & 43.
6. Bahl BS, Tuli GD, Arun Bahl. Essential of physical chemistry; twenty-fourth, Edition-1997, 565.
7. Panchagnula R, Sundramurthy P, Pillai O, Shrutidevi A, Yasvanth AR. Solid state characterization of mefenamic acid. Journal of Pharmaceutical Science. 2004; 93(4):1019-29.
8. Vrecer F, Srcic S, Smid-Korbar. Investigation of piroxicam polymorphism. International Journal of Pharmaceutics. 1991; 68:35-41.
9. Gary N, Christopher SF. Physico-chemical characterization of the orthorhombic polymorph of paracetamol crystallized from solution. Journal of Pharmaceutical Science. 1998; 87:684-693.
10. Bauer J, Spanton S, Henry R, Quick J, Dziki W, Porter W *et al.* Ritonavir: An extraordinary example of conformational polymorphism. Pharm. Res. 2001; 18:859-866.
11. U.S. Food and Drug Administration. Pharmaceutical Solid Polymorphism Chemistry, Manufacturing, and Controls Information. Available online: http://www.fda.gov/downloads/ Drugs/Guidances/UCM072866.pdf (accessed on 4 September 2014).
12. Threlfall TL. Analysis of organic polymorphs. A review. Analyst. 1995; 120:2435-2460.
13. Haleblian J, McCrone W. Pharmaceutical applications of polymorphism. J Pharm Sci. 1969; 58:911-929.
14. Stahly GP. Diversity in single- and multiple-component crystals. The search for and prevalence of polymorphs and cocrystals. Cryst. Growth Des. 2007; 7:1007-1026.
15. Taylor LS, Langkilde FW. Evaluation of solid-state forms present in tablets by raman spectroscopy. J Pharm Sci. 2000; 89:1342-1353.
16. Olimpia Maria Martins Santos, Polymorphism: an evaluation of the potential risk to the quality of drug products from the Famacia Popular Rede Propria, BJPS, ISSN 1984-8250201
17. Marco Farias and Renato Carneiro, Simultaneous Quantification of Three Polymorphic Forms of Carbamazepine in the Presence of Excipients Using Raman Spectroscopy, Molecules. 2014; 19:14128-14138. doi:10.3390/molecules190914128
18. Bashpa P, Bijudas K, Anjali Tom M, Archana PK, Murshida KP, Noufala Banu K *et al.* Polymorphism of paracetamol: A comparative study on commercial paracetamol samples, International Journal of Chemical Studies, ISSN: 2321-4902.
19. Ye Sun,3,6 Lei Zhu,4 Tian Wu,5 Ting Cai,1 Erica M. Gunn,1 and Lian Yu1,2,6, Stability of Amorphous Pharmaceutical Solids: Crystal Growth Mechanisms and Effect of Polymer Additives, The AAPS Journal. 2012, 14(3). (# 2012)DOI: 10.1208/s12248-012-9345-6.
20. Ethiraj Thiruvengadam, Ganeshan Vellaisamy. Polymorphism In Pharmaceutical Ingredients, World Journal Of Pharmacy And Pharmaceutical Sciences, ISSN 2278 – 4357