A Review On Co-amorphous Technique Use For Solubility Enhancement

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Abstract - **The review article gives as a berif idea of the solubility and various parameters of solubility. It shows the importance of the process of solubility and dependence of dissolution process on the solubility. There are various factors enlisted which are affecting the solubity. It consist of the information regarding the dissolution apparatus and various technique to enhance the solubility.**

keywords - **Dissolution apparatus, Solubility enchance**

General Introduction:

The oral route is the most preferable route of drug delivery to the patient. The oral drug delivery is being increase around the world due to its ease of administration and better patient compliance. Solid dosage forms such as tablets are more popular to use due to advantages in safety and convenience in its administration. The administered drug must therefore be dissolved and released in the gastrointestinal (GI) fluid before it can get into the systemic circulation to reach the action site. However, many active pharmaceutical ingredients (API) belong to the Biopharmaceutical Classification System (BCS) class II group which means they are poorly soluble but having high permeability. [1]

The significant drug absorption and appropriate drug delivery are prerequisites for successful oral treatment of diseases. Low aqueous solubility is indeed one of the major reasons behind failures in the development of oral drug delivery system There is a significant increase in insoluble new chemical entities (NCE) in the research portfolio, in recent past. According to recent studies showed that 75% of the drug development candidates had low solubility and belonged to biopharmaceutical classification system (BCS) classes II and IV. A number of novel approaches for enhancing low aqueous solubility of drugs have been attempted and continued to evolve over a period. Micronization, nanonization, chemical modification, PH adjustment, solid dispersion, solubilization of drug in co-solvents or micellar solutions, complexation, salt formation, self emulsification.

Drug safety and therapeutic efficacy are critical concerns of the bioavailability of drugs. Thus, poor solubility and subsequently poor oral bioavailability of a drug have become a major challenge in the formulation industry. Current scenario reveals abundant research carried out on the amorphization of a drugs, a state which possesses the high thermodynamic energy and the apparent solubility is improve significantly .However, the structurally disordered metastable form causes the free molecular mobility and chemical reactivity is enhanced too. Therefore, the stabilization of the amorphous form is a vital issue as the thermodynamic drive is preordained towards the devitrification of a drug during the process of manufacturing and shelf life of the drug product.

Solubility:

The Solubility is defined as the amount of a substance that passes into the solution to achieve a saturated solution at the constant temperature and the pressure. The Solubility are expressed in terms of the maximum volume or mass of a solute that dissolve in a given volume or mass of the solvent. Pharmacopoeias give the solubility in terms of a number of parts by volume of solvent required to dissolve the one part by weight of a solid, or one part by volume of a liquid. If the solubility is increase the bioavailability is also increases.

Solubility is a property of the solid, liquid, or gaseous chemical substance are called as *solute* to dissolve in a liquid, solid or gaseous solvent to form the homogeneous solution of a solute in the solvent. The substance fundamentally depends on solvent used as well as on the temperature and the pressure. The extent of solubility of a drug in the specific solvent is measured as the saturation concentration where adding more solute does not increases its concentration in a solution. [2]

Solvent is generally a liquid, which is a pure substance or the mixture of two liquids. One may also speak of a solid solution, but rarely of a solution in a gas. The extent of a solubility ranges widely, from the infinitely soluble (fully miscible) such as ethanol in the water, to poorly soluble, such as silver chloride in the water. The *insoluble* term is often applied to a poorly or very poorly soluble substances.

The Solubility occurs under the dynamic equilibrium, which means that the solubility results from the simultaneous and opposing processes of a dissolution and joining phase (e.g., precipitation of solids). The Solubility equilibrium occurs when the two process proceed at athe constant rate. Under the certain conditions equilibrium solubility may be exceeded to give a so-called supersaturated solution, which is metastable.

Solubility is not to be confused with the ability to dissolve or liquefy a substance, since these processes may occur not only because of dissolution but also because of a chemical reaction. For example, the zinc is insoluble in hydrochloric acid, but does dissolve in it by chemically reacting into the zinc chloride and the hydrogen, where zinc chloride is soluble in a hydrochloric acid. Solubility not also depend on thr particle size or the other *kinetic* factors; given enough time, even the large particles will eventually dissolve.

The solubility as a analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. The solubility is stated in units of concentration, the molality, mole fraction, mole ratio, and the other units. Extensive use of a solubility from different perspective has led to the solubility being expressed in a various manners. .

Table No 1.1 Solubility terms given by USP 23

Descriptive Term	Parts of Solvent Required for 1 part of the Solute
Very soluble	≤1
Freely soluble	1 to 10
Soluble	10 to 30
Sparingly soluble	30 to 100
Slightly soluble	100 to 1000
Very slightly soluble	1000 to 10,000
Practically insoluble, or Insoluble	≥10,000

Biopharmaceutics classification system

It is a scientific framework to classify the drug substances based on their aqueous solubility and the intestinal permeability. It is a drug - development tool that allows the estimation of the contributions of three major factors such as the dissolution, solubility and the intestinal permeability that affect the oral drug absorption from IR solid oral dosage forms. It was first introduced into regulatory decision-making process in the guidance document on the immediate release solid oral dosage forms: Scale-up and the post approval changes. The drugs are divided into high/low-solubility and high/low permeability classes. [3]

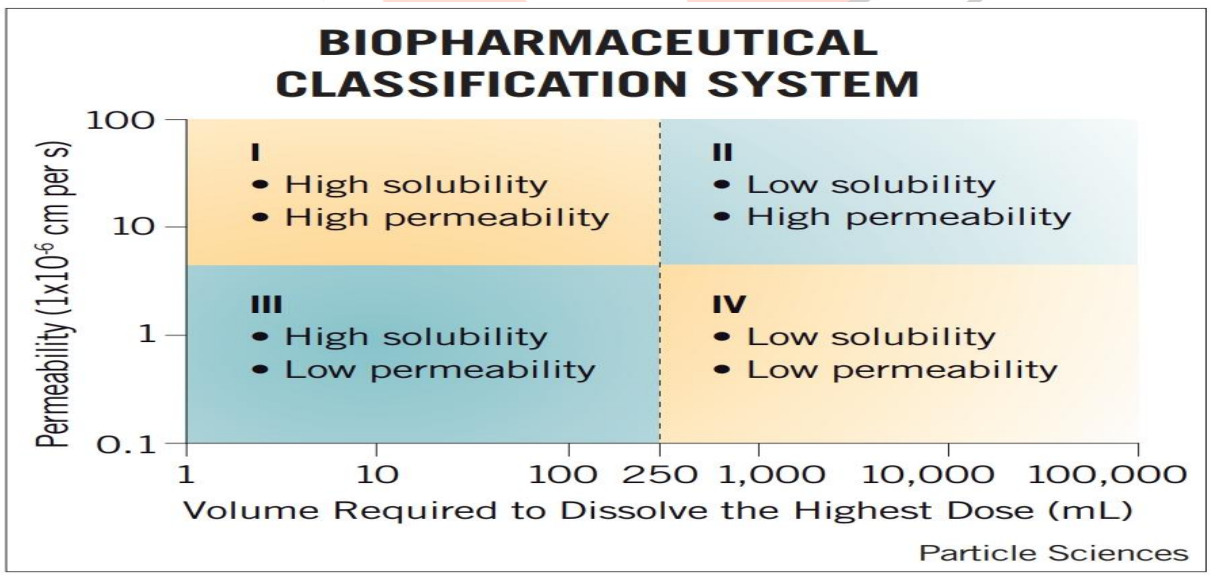


Fig 1.1 Biopharmaceutics classification system

Class I - High Permeability, High Solubility: Those compounds are well absorbed and their absorption rate is usually higher than excretion. The substance of this class exhibits the high absorption number and the high dissolution number. The rate-limiting step is drug dissolution, and if the dissolution is very rapid, then the gastric-emptying rate becomes a rate-determining step. They dissolve rapidly when presented in immediate release form, and are also transported across the gut wall.

Class II – High Permeability, Low Solubility: These drugs have a high absorption number but a low dissolution number. *In vivo* drug dissolution is then a rate limiting step for absorption except at a very high dose number. These drug exhibited a variable bioavailability and need the dissolution enhancement for increasing the bioavailability of a drug. These compounds are suitable for design the SR and CR formulations. The *In vitro and in vivo* correlation is usually expected for class II drugs.

Class III - Low Permeability, High Solubility: The absorption of a drug is limited by the permeation rate but the drug is solvated very fast. The permeability of a drug is rate-limiting step for the drug absorption, but the drug is solvated very quickly. This class of drugs exhibit a high variation in a rate and the extent of a drug absorption. Since the dissolution is rapid, and the variation is attributable to alteration of a physiology and the membrane permeability rather than dosage form factors.

Class IV - Low Permeability, Low Solubility: The compounds having a poor bioavailability. Usually they are not absorbed well over the intestinal mucosa and a high variability is expected. The class IV drug are problematic for effective oral administration. Fortunately, extreme examples of the Class IV drug are the exception rather than the rule, and these are rarely developed and marketed.

Table No. 1.2 Formulation approach

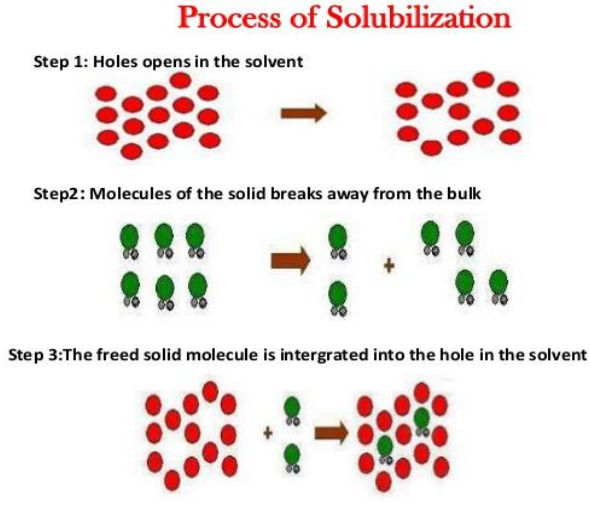
BCS Class	Solubility	Permeability	Oral Dosage Form Approach	Chances of Non-oral Dosage Form being Required
1	High	High	Simple solid oral dosage form	Increasing
2	Low	High	• Techniques to increase surface area like particle size reduction, solid solution, solid dispersion • Solutions using solvents and/ or surfactants	
3	High	Low	Incorporate permeability enhancers, maximize local lumenal concentration	
4	Low	Low	Combine 2 and 3	

1.2.2 Importance of Solubility

1. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecule
2. Solubility is one of the important tool to achieve the desired concentration of drug in systemic circulation for achieving required pharmacological response of the drug.
3. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration.
4. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development.
5. Solubility also plays a major role for other dosage forms like parenteral formulations as well
6. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. The water is a solvent of choice for the liquid pharmaceutical formulations. The most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility.
7. Currently only 8% new drug candidates having both high solubility and high permeability.
8. More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water. The poorly water solubility of a drugs having slow absorption of drug leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity.
9. For orally administered drugs solubility is a most important rate limiting tool to achieve their desired concentration in the systemic circulation for pharmacological response of the drug.
10. The compound having negative effect with low solubility include the poor absorption and bioavailability, insufficient solubility for dosing, development challenges leading to increasing the development cost and time, burden shifted to the patient (frequent high-dose administration.

1.1.1 Process of solubilization

The solubilization process involves the breaking of intermolecular or the inter-ionic bonds in a solute, the separation of a molecules of the solvent to provide space in the solvent for the solute, interaction between solvent and the solute molecule or ion. [4]



1.2.4 Factors Affecting Solubilization

The solubility of the drug is depends on the nature and the composition of solvent medium, the physical form of a solid as well as temperature and the pressure of system. Consider a lot of factors are as follow.

- **Particle Size:** The size of a solid particle influences the solubility because if the particle becomes smaller, the surface area to volume ratio increases of the particle. The larger surface area of particle allows a greater interaction with a solvent.
- **Temperature:** As the temperature is increased than the solution process absorbs energy and the solubility will be increased but if the solution process releases energy then the solubility will decrease with increasing temperature. A some solid solutes are having less solubility in warm solutions. For examples The solubility of all gases decreases as the temperature of the solution increases.
- **Pressure:** For solids and liquid solutes, if the changes in pressure have practically no effect on the solubility but for gaseous solutes, an increase in the pressure, increases solubility and a decrease in pressure, decrease the solubility.
- **Nature of the solute and solvent:** Only 1 g of lead chloride can be dissolved in 100 gr of the water at room temperature while 200 g of the zinc chloride can be dissolved. The great difference in a solubility's of these two substances is the result of the differences in their natures.
- **Molecular size:** The solubility of a drug is decreased when the molecules have high molecular weight and high molecular size because the larger molecules are more difficult to surround with the solvent molecules in order to solvate the substance. In the case of a organic compounds the amount of carbon branching will be increase the solubility since more branching will reduce the size (or volume) of a molecule and make it easier to solvate the molecules with solvent.
- **Polarity:** The Polarity of the solute and solvent molecules will affect the solubility. Generally like dissolves like means non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules having the positive and the negative end to the molecule. If solvent molecule is also polar then the positive ends of solvent molecules will attract the negative ends of solute molecules. This is the type of intermolecular force known as dipole-dipole interaction. The other forces called london dispersion forces where the positive nuclei of a atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives nonpolar solvent a chance to solvate the solute molecules.
- **Polymorphs:** Polymorphs can vary in melting point. Since the melting point of a solid is related to the solubility, so polymorphs will have different solubility's. Generally the range of a solubility differences between the different polymorphs is only 2-3 folds due to the relatively small differences in a free energy.
- **Rate of solution:** The rate of a solution is a measure of how fast substances dissolve in the solvents. A various factors that affecting rate of solution like-

(a) Size of the particles: Breaking of a solute into smaller pieces increases its surface area, when the total surface area of a solute particles is increased; the solute dissolves more rapidly because the action takes place only at the surface of a each particle and hence increases in its rate of solution.

(b) Temperature: For liquids and solid solutes, increasing the temperature not only increases the amountof solute that will dissolve but also increases the rate at which the solute will dissolve. For the gases reverse is true.

(c) Amount of solute already dissolved: When there is a little solute already in solution, dissolution takes place relatively rapidly. As the solution approaches the point where no solute can be dissolved, dissolution will be takes place more slowly.

(d) Stirring: With liquid and solid solutes, stirring brings fresh portions of the solvent in contact with the solute, thereby increasing the rate of solution.

1.3 Dissolution: The rate and extend in which the amount of drug substance dissolved over a period of time is called dissolution. It is expressed as the percentage release of a drug substances present dosage forms like Tablets, Capsules, oral suspensions and ointments. In our present study dissolution method development for various kinds of tablets such as immediate release or instant release, modified release dosage form.

Dissolution is a process in which the substance forms a solution in a solvent. For the dissolution of a solid, the dissolution process can be explained as the breakdown of the crystal lattice into individual ion, atom or the molecules and their transport into the solvent.

When the dosage form is swallowed, the rate at which it release the active ingredient is critical to ensure that the drug is delivered properly. The rate at which the drug is released is called the dissolution . [5]

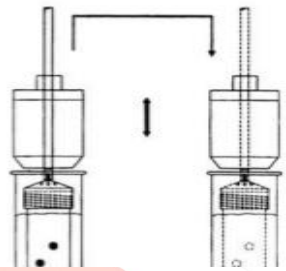
Table No 1.3 Dissolution test apparatus

	I.P	U.S.P	B.P	E.P
TYPE 1	Paddle apparatus	Basket apparatus	Basket apparatus	Basket apparatus
TYPE 2	Basket apparatus	Paddle apparatus	Paddle apparatus	Paddle apparatus
TYPE 3		Reciprocating cylinder	Flow through cell	Flow through cell
TYPE 4		Flow through cell		
TYPE 5		Paddle over disk		
TYPE 6		Rotating cylinder		
TYPE 7		Reciprocating disk		

Dissolution test apparatus

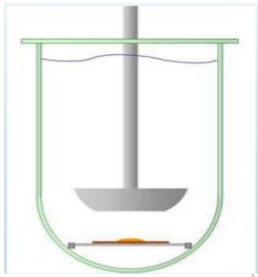
Type 1

Type 2



Type 3

Type 4



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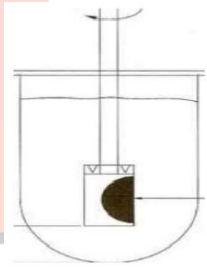
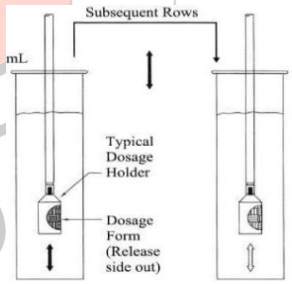


Type 6



Type 7

1.3.1 Importance of dissolution

1. Important tool during development of more efficacious and therapeutically optical dosage forms.
2. Ensure the quqlity and stability of the product.
3. It is used in in-vivo bioavailability and bioequivalence studies.
4. Batch to batch drug release uniformity.
5. In-vitro dissolution is also used to assess drug product quality with respect to stability shelf life.
6. It is also useful for assessing the impact of pre or post approval changes to drug product such as change to formulation or manufacturing process. Thus the in-vitro comparability assessment is a critical to ensure the continued performance equivalency and product similarity.
7. Dissolution testing is widely used in the pharmaceutical industry for optimization of formulation and quality control. [6]

1.3.2 Process of dissolution

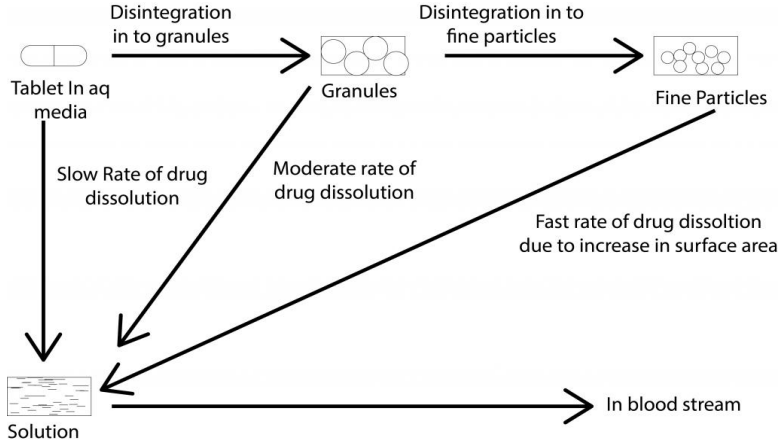


Fig 1.4 Dissolution of solid dosage form

1.4 Technologies improving the solubility and dissolution rate of poorly water soluble drugs

solubility and dissolution rate improving technique can be categorized into physical modification, chemical modification of drug substance and other technique. [7]

1. **Physical modifications**

A. Particle size reduction
- Micronization
- Nanosuspension
- Sonocrystallization
- Supercritical fluid process

B. Modification of the crystal habits
- Polymorphs
- Pseudopolymorph

C. Drug dispersion in carriers
- Eutectic mixtures
- Solid dispertion
- Solid solutions
- Cryogenic technique

D. Complexation
- Use of complexing agents

E. Solubilization by surfectants
- Microemulsion

2. Chemical modification

A. Change in PH
B. Use of buffers
C. Derivatization
D. Complexation
E. Salt formation

3. Miscellaneous method

A. Use o adjuvant
- Surfactants
- Solubilizers
- Co solvency
- Hydrotrophy
- Novel excipient

1.5 Solid Dispersions—Glass Solutions

Solid dispersion (SD) was defined as the "dispersion of one or more active substances in an inert carrier prepared by melting, dissolution or melting-dissolution. They can be classified according to the solid phase and physical state as eutectic mixtures, solid solutions, glass solutions and glass suspensions. Glass solutions are single-phase amorphous systems. They are considered as supersaturated drug delivery systems, capable of maintaining elevated supersaturation drug levels in the gastrointestinal fluids thus, increasing absorption rate and bioavailability. Amorphous SDs are further divided into polymeric and non-polymeric according to the stabilizers used.

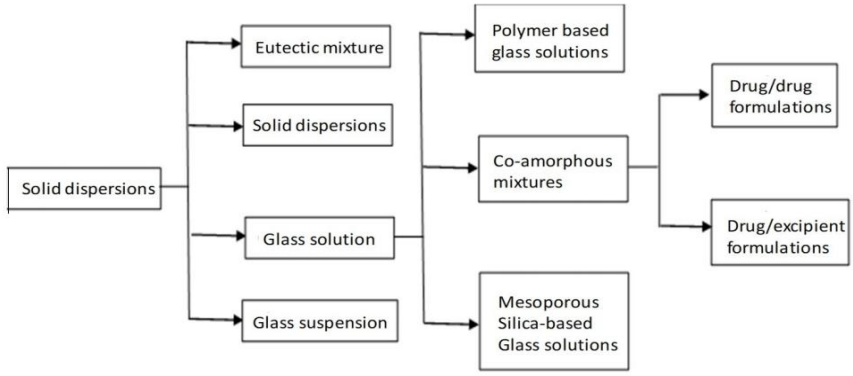


Fig 1.5 Classification chart of solid dispersions [8]

In a polymeric SDs, the drug is incorporated as the molecular dispersion in the glass polymeric matrix, stabilized by physical separation of the molecules inside the polymer chains. Most polymeric carriers have high glass transition temperature (Tg), and thus increase the Tg of the amorphous drug. The polymers act as a stabilizers by decreasing the molecular mobility, and hence inhibit the nucleation and crystal growth, while molecular drug-polymer interactions can further inhibit the recrystallization. Nonetheless, there are problems related to polymeric SDs such as low miscibility, necessitating large polymer/drug ratios which in the case of high dosing lead to oversize dosage units. Furthermore, sensitivity to heat and humidity due to hygroscopicity of a polymers can be an issue, since the moisture reduces the Tg with the possible phase separation and the recrystallization. Also, since the relaxation of a amorphous material and recrystallization is possible below the Tg, storage at the low temperatures 50 K less than Tg has been suggested. The other challenges of a solid drug-polymer glass solutions have a poor processing ability due to their sticky nature. Hence, due to the possible stability problems and formulation difficulties, only the few polymeric ASDs have reached the market.

1.5.1 Polymer-based glass solutions: Polymeric carriers are used to stabilize the amorphous drug and improve its solubility and dissolution rate. Below its limit of solubility, the drug is molecularly dispersed in the amorphous polymer and stabilized by physical separation of the molecules between the polymer chains.

Drawback-

1. Polymeric carrier have high glass transition temperature (Tg) and thus increasing Tg of drug in glass solution compared to its pure amorphous form.
2. 2.Intermolecular interaction between drug and polymer found play role in the stabilization mechanism. Limited drug solubility in large polymeric excipients and formulation is not stable .
3. Hygroscopic nature of many polymeric carriers which results in absorption of moisture.The absorbed moisture acts as plasticizer, thus reducing the Tg and increasing mobility,which result in phase separation.

1.5.2 Co-amorphous systems: Co-amorphous systems consisting of two excipients, co-amorphous systems consisting of two suitable drugs or API plus excipient.Poor water solubility of many drugs has emerged as one of the major challenges in pharmaceutical world. Polymer-based amorphous solid dispersions have been considered as the major advancement in overcoming limited aqueous solubility and oral absorption issues.

Advantages of co amorphous formulation-

1. Solubility and dissolution of BCS class 2 drug increases.
2. Stability of poorly water soluble drug is increases.
3. It has better patient compliance. .

Draback-

1. Polymer based glass transition temperature causes problem.
2. It has tendency to uptake a moisture.
3. Down streaming of the formulation in to final dosage form yet not done.

1.5.3 Mesoporous silica-based glass solutions.

The drugs are amorphized by adsorption onto the surface of the silica particles, which consists of a matrix of pores with diameter between 2 and 50 nm.15 On the one hand, stabilization of the amorphous drug is achieved through molecular interactions between the drug and the functional groups of the silica matrix.16, 17 On the other hand, crystallization is inhibited physically by the pore diameter of the materials,which may be smaller than the size of a crystal nucleus of the drug.

Drawback

Drawback of mesoporous silica-based glass solution are their production, which predominantly involves the use of organic solvents for drug loading and often limited capacity of only 20-30%.

1.6 Co-Amorphous

1.6.1 History of Co-Amorphous

Amorphous systems using small molecules like urea, citric acid, tartaric acid as amorphous stabilizers have been reported since long (Ford and Rubinstein, 1981; Liu et al., 2004; McGinity
et al., 1984).However, the term “co amorphous” was coined by Chieng et al. (2009). This term was introduced to differentiate amorphous mixture containing two small molecules from the term PASD. CAM is defined as “a multi-component single phase amorphous solid system which lacks periodicity in lattice and is associated by weak and discrete intermolecular

interactions between the components" (Suresh et al., 2014). They possess short-range interactions such as hydrogen bonding of carboxylic acids, phenols/alcohols and carboxamides similar to amorphous system of single component systems. However, this system differs from cocrystal, salt or eutectic primarily by its amorphous nature which is characterized by presence of broad hump ('amorphous halo') in the X-ray diffractogram (Grohganz et al., 2013). Yamamura et al., developed the first drug-drug CAM by combining cimetidine with naproxen, (Yamamura et al., 2000. [9]

1.6.2 What is Co-amorphous

Co-amorphous systems consisting of two excipients, co-amorphous systems consisting of two suitable drugs or API plus excipient.Poor water solubility of many drugs has emerged as one of the major challenges in pharmaceutical world. Polymer-based amorphous solid dispersions have been considered as the major advancement in overcoming limited aqueous solubility and oral absorption issues.

Co-amorphous systems are one of the attractive strategies used to enhance the dissolution rates and solubility of poorly soluble drugs. This strategy has an additional advantage as it has the ability to overcome stability issues that may arise from the conversion of a crystalline drug into its amorphous. [10]

In the last years a new strategy, alternative to amorphous polymeric, is co-amorphous solid dispersions with solubility and stability improvements over the corresponding amorphous and crystalline drugs. They combine two or more low molecular weight (MW) ingredients into a homogenous amorphous single-phase and have been used to stabilize amorphous forms of low solubility drugs. Due to the low MW components, low amount of stabilizer (coformer) is required, and thus oversized dose units and hygroscopicity problems inherent to polymeric amorphous SDs are avoided. [9]

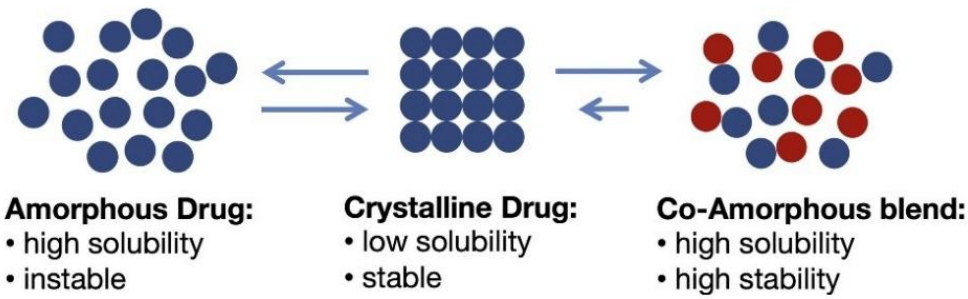


Figure 1.6 Advantages of co-amorphous dispersions over the corresponding amorphous and crystalline drugs.

1.6.3 The advantages of co-amorphous over polymeric dispersions

1. Co-amorphous SDs provide high drug solubility due to the high energy of the amorphous state and because no energy is needed for the rearrangement of the crystal lattice during dissolution. .
2. Additionally, they may exhibit high stability and improved dissolution not only compared to their crystalline homologues but also to the individual amorphous forms.
3. Significant increase of Cmax (1.3 to 30 times) and area under the curve (AUC) (1 to 5 times), as well as a decrease of Tmax have been achieved by many co-amorphous systems.
4. The main reason for these improvements is the strong solid-state interactions between the components.
5. In addition, the stability of co-amorphous mixtures is due to the increase of Tg and to the homogeneous molecular-level dispersions achieved by high energy mixing.
6. Impregnation with small molecules, e.g., amino acids, are considered critical for preventing recrystallization. In the majority of the studies the physical stability of such systems is attributed to intermolecular interactions such as hydrogen bonds or even ionic interactions. [11]

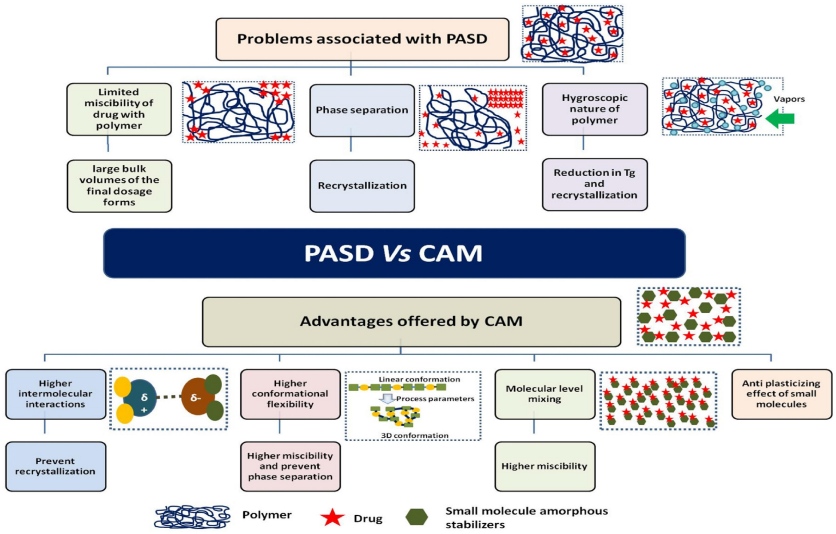


Figure 1.7 Advantages of co-amorphous systems (CAM) over polymeric amorphous solid dispersions (PASD)

1.6.4 Disadvantage of Co amorphous

1. Polymer based glass transition temperature causes problem.
2. It has tendency to uptake moisture, most of the stability studies of co amorphous mixtures have been conducted in dry conditions. Thus, it would be interesting to study the effect of water on the performance of co amorphous system.
3. With respect to co amorphous drug-drug formulation, it might be difficult to find a suitable partner molecule with specific pharmacological profile.
4. Down streaming of the formulation in to final dosage form yet not done.

1.6.5 Classification of Co-Amorphous Solid Dispersions [12]

1. Drug-Drug Compositions: In these systems, two pharmacologically-related drugs are stabilized. The simultaneous administration of a drugs in one dosage unit results in the better patient compliance and minimal excipients. Additionally, both the drugs gain improved solubility and dissolution rate, with synchronized release. For instance, tests with indomethacin/naproxen 1:1 molar ratio co-amorphous SD demonstrated similar dissolution profiles for two drugs with simultaneous release and also increased stability compared to the crystalline or amorphous IND, which was attributed to formation of heterodimers.

Examples of investigated co-amorphous systems were: naproxen-cimetidine and indomethacin-ranitidine hydrochloride for relief of pain and of the gastrointestinal side effects of NSAIDs, simvastatin-glipizide for hypercholesterolemia and diabetes in the metabolic disorders and tranilast-diphenhydramine hydrochloride as an anti-allergic/anti-inflammatory treatment.

The other studies showed that the co-amorphous SDs is increased the in vivo supersaturation and dissolution rate compared to individual amorphous or crystalline drugs but to a lesser extent than that expected from in vitro tests. However, the supersaturation depends on the dissolution factors like pH of the media and possible ionization, and the solubilizing effect of the bile salts among others. So only few studies have been reported in vivo evaluation of the drug-drug co-amorphous SDs.

Practically, co-amorphous drug-drug SDs have limited application, as it is difficult to combine pharmacologically related drugs that are also able to form glass solution in the required doses. Thus, the idea was extended to combinations of drugs with inert molecules such as amino acids, carboxylic acids (citrate, tartrate) weak bases (meglumine, flavonoids), saccharin or nicotinamide that are capable of hydrogen bonding and have low toxicity. [13]

2. Drug-Amino Acid Co-Amorphous Compositions and Co-Amorphous Salts: In these systems, amino acids (AAs) are used as biocompatible co-formers and act as anti-plasticizers by increasing the Tg, while blocking drug-drug interactions, delaying recrystallization. Due to the low MW, only small amounts are required compared with polymeric SDs. Selection of AAs is based on knowledge of possible drug-receptor interactions at biological binding site. The Dissolution rate and physical stability of co-amorphous drug-AA systems is more as compared to the amorphous drug have been reported, due to molecular interaction. However, the stable systems with non-interacting components are also possible .

For quick screening and suitability of A.A. co-formers, Kasten et al. examined degree of the co-amorphization following different milling times of a six model drugs combined with 20 AAs in the equimolar ratios. Selection of the AA was based on >90% crystallinity reduction after 15 minuted of milling. The results indicated that non-polar AA such as tryptophan, phenylalanine, leucine, isoleucine, methionine, valine and proline, are first-choice co-formers. Basic AAs appear to be suitable for amorphous salt formation with acidic drugs whereas acidic AAs are generally poor co-formers.

Higher stability has been found in mixtures where AAs form salts. Salts lead to increased Tg of the co-amorphous SD due to strong ionic interactions that resist crystallization and exert antiplasticizing effect.Furthermore, salt formation enhances dissolution because the dissolved ions make ion-dipole interactions with water molecules, which is energetically more favorable than hydrogen bonding between water and a non-ionized drug. However, the amorphous salt formation is limited to the pKa differences between components greater than 3, and hence they are applicable to a limited number of a drugs.

A. **Selection of Amino Acid Co-Formers:** The fact that certain AAs can be co-amorphisized successfully with one drug but not with another led to the need for systematic studies for co-former selection, using computational methods and theoretical approaches. Detection of intermolecular interactions with FTIR, Raman and NIR spectra is a good indication for the formation of stable co-amorphous SDs. Spectroscopic data can be aided by quantum mechanics. Using the density functional theory calculations (DFT), quantum molecular theory (QTAIM) and the natural bond orbital analysis (NBO), Russo et al. confirmed the used multiple variable analyses to study the effect of physicochemical properties of co-formers.

They underlined the importance of crystallization tendency (Tg/melting temperature (Tm) ratio), molecular flexibility, reduced glass transition (Tg/Tm), number of hydrogen bond acceptors, topological polar surface area and polarizability in the formation of stable co-amorphous SDs. The importance of molecular size and flexibility was demonstrated by the suitability of the flexible tryptophan but not of the rigid proline and the high tendency of the last to be organised in a crystal lattice. Alhalaweh et al. developed the predictive computational tool based on two molecular markers, the number of hydrogen bond acceptors and the Huckel pi atomic charges that helped the screening of out of 131 drug molecules that formed the glass dispersions. Cimetidine, indapamide, quercetin and ritonavir were found to be potent glass-forming agents, capable of amorphous state stabilization. Further studies by Pajula et al. showed that miscibility in the coamorphous SD is the most important factor, while Tg increase, molecular mixing, interactions and stabilization follow in terms of importance. The Partial or non-miscibility can be dramatically influence the recrystallization tendency of stabilized co-amorphous drug after the phase separation. [14]

1.6.5 Methods used for preparation of co-amorphous blend

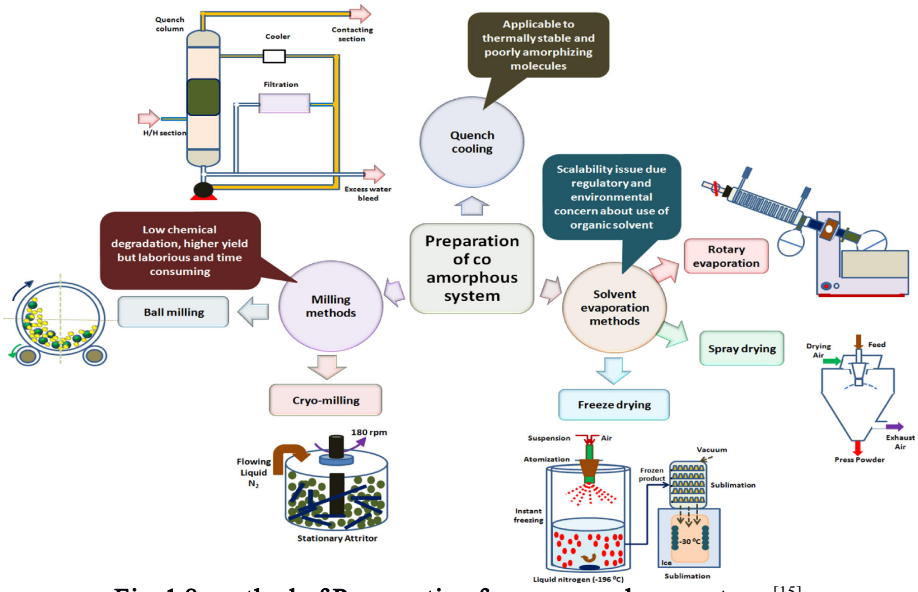


Fig. 1.8 method of Preparation for co amorphous system. [15]

1. Spray Drying: Mixtures of drug and AA were prepared at a molar ratio of 1 : 1. The mixtures were produced by dissolving the drug and AA in acetone and MilliQ water respectively. Subsequently, the drug and AA solutions were mixed together to give solutions (250 ml in volume) usable for Spray drying. Due to the differences in solubility of the components, different feed concentrations were Spray dried. All sample were prepared in triplicate. All samples were prepared at identical drying conditions.Analysis of the Spray dried powders was performed on the same day as preparation.[16]

2. Ball Milling: Pure drug and mixtures of drug and AA were subjected to vibrational Ball mill. The milled sam ples were produced by placing a total mass of 500 mg of the appropriate amount of drug and AA at molar ratios of 1 : 1 in 25 ml milling jars with two 12 mm stainless steel balls, and milling at 30 Hz for 90, 180, 270 and 360 min in an oscillatory ball mill . The Ball Mill powders were prepared in triplicate and analyzed the same day as prepared. [1]

3. Freez Drying- The FD cycle consisted of cooling the samples to 5°C from room temperature in 15 min, followed by an isothermal period at 5°C for 30 min and subsequently decreasing the temperature to −5°C, followed again by an isothermal period of 30 min. Temperature was then decreased to −40°C at 1 K/ min, followed by an isothermal period of 1 h. Then the temperature was increased to −15°C at 1 K/min with a vacuum of 0.200 mbar. Primary drying was carried out at −15°C for 15 h at 0.200 mbar. During secondary drying, the temperature was ramped at 0.1 K/min to 25°C and kept isothermal 4 h at 25°C. Samples were closed under vacuum in the freeze-dryer at the end of the cycle, and stored at 5°C prior to analysis.

4. Quench Cooling- Before the quench cooling of the molar ratio (1:1) physical mixture of drugs prepared by gentle mixing 100 mg drugs with mortar pestle for 60 s.

Amorphous sample of the drug 1:1 molar mixture of two drugs prepared by placing in aluminium dishes in preheated oven and quench cooling by pouring liquid Nitrogen onto sample. The sample dishes containing molten compound were placed in desiccator containing phosphorous pentaoxide followed by pouring liquid Nitrogen into dishes. Desiccator immediately close in order to avoid moisture sorption onto sample. The liquid Nitrogen allow to evaporate before IR measurement. [1]

5. Cryomilling- Some drugs were converted to co amorphous forms by Cryomilling because ball milling was not sufficient to produce co amorphous drug. It is produced by placing drug into milling chamber with three 9 mm stainless steel balls and milling done in oscillatory ball mill which was placed in cold room ($+4^0$). The milling chamber were immersed in liquid Nitrogen for 2 minutes prior to milling and at 10 minute intervals during milling to ensure cryogenic conditions. The chamber were allowed to reach ambient temperature in desiccator over phosphorus pentaoxide prior to opening. [17]. Sample were stored over phosphorous pentaoxide at -20^0c until further use.

6. Solvent evaporation technique: Co-amorphous system of drug-drug were prepared by solvent evaporation technique using methanol (ICH Class-2, Solvents to be limited) as a solvent. A total of 1000 mg in molar ratios of 1:1, 1:2, 2:1 were mixed homogeneously and then dissolved in 50 ml methanol. The solvent was evaporated under reduced pressure at 40 ^{0}C. The residual solvent left after evaporation was then removed completely by placing the sample under vacuum for 2 days inside desiccator containing CaCO3. The precipitates were stored in desiccator until its use in the experiment. [1]

1.6.6 Different Factors Affecting the Stability of Co-Amorphous Drug in Solid Dispersion

1) Glass transition temperature (Tg): Stability increases with increasing Tg. Polymers increase the kinetic stability of amorphous drugs (antiplasticization effect).

2) Structural relaxation/molecular mobility: Responsible for recrystallization. Rate of crystallization is higher at temperatures above Tg. Restriction of molecular mobility improves stability

3) Configurational entropy: Low configurational entropy favors crystallization. Lower crystallization tendency of erythromycin-free base, for example,can be explained by its lower thermodynamic driving force for crystallization.

4) Humidity, mechanical stress, and temperature: Temperature significantly affects molecular mobility, and moisture may plasticize the material by lowering its Tg near to storage temperature: increases crystallization rate and decreases crystallization temperature. Mechanical stress also causes significant differences in crystallization tendency

5) Preparation method (fusion or solvent evaporation method, freeze drying, supercritical fluid technology): Different preparation methods induce different thermal histories and mechanical stresses leading to different degrees of drug-polymer mixing and drug mobility in the dispersion. Hence, variable solid-state stability of the solid dispersion can be obtained.

6) Preparation conditions such as cooling rate, processing temperature, and time: Slow cooling of amorphous indomethacin increases its physical stability. Different inlet temperature used in the spraydrying of naproxen led to the difference in dissolution profile and drug stability. Different screw speed (residence time) in hot melt extrusion affected the stability of fenofibrate formulations in stressed conditions.

1.6.7 Physiochemical characteristics of coamorphous systems

For understanding the amorphous nature of coamorphous systems, a variety of conventional and emerging techniques have been used to qualitatively and quantitatively characterize their physiochemical properties. In this part, we will mainly focus on some of key physiochemical characteristics of coamorphous systems, including crystallinity, miscibility, molecular interactions and molecular mobility.

- **Crystallinity:** Coamorphous pharmaceutical solids have the tendency to crystallize during the processing or storage. Once the crystallization occurs, the performance of coamorphous formulations can be significantly altered. Therefore, how to determine the degree of crystallinity in a coamorphous formulation has attracted considerable attention in this field. A number of techniques have been utilized to determine the crystallinity of coamorphous formulations. For example, differential scanning calorimetry (DSC) is wildly used to analyze the thermal events associated with the transitions between amorphous and crystalline materials. One important parameter used to quantify crystallinity is the change in heat capacity at Tg. However, amorphous formulations prepared by milling methods sometimes lack the clear signals of glass transition. Powder X-ray diffraction (PXRD) is also the one of the well-established techniques to quantify the crystallinity of coamorphous formulations during processing and storage. The relative degree of crystallization (Dc) is determined on the basis of the obtained x-ray diffraction patterns. Here, the value of Dc is calculated as a ratio between the areas under the sharp diffraction peaks of the partially crystallized sample and the crystalline reference sample.
- **Miscibility:** Miscibility of multi-components in coamorphous formulation is one of the important aspects related to the physical stability. If components in coamorphous formulations are miscible with each other, the effects of stabilizers can be fully exploited and a good physical stability can be achieved. In general, a clear single Tg of a co-amorphous formulation indicates the miscibility of the components in the mixture. In addition, solubility parameters, considered as estimates of molecular similarities, can also be measured for evaluating the miscibility of components in coamorphous formulations. Hildebrand first put forward the concept of solubility parameter and defined it in the term of total cohesive energy. The major limitation of Hildebrand solubility parameter is its insufficient description of solubility behaviors in those systems with polar or specific interactions between components. Subsequently, Hansen proposed a modified approach to determine the total solubility parameter of polar compounds. In this approach, the total solubility parameter consists of the squares of contributions form dispersion, polar, hydrogen-bonding forces. Compared to Hildebrand solubility parameters, Hansen solubility parameters are more appropriate and widely applicable. Another alternative approach to investigate the miscibility of components in amorphous formulations is based on the Flory-Huggins theory combined with calculated solubility parameters from the melting point depression method, annealing method or in silico method. The Flory-Huggins interaction parameters (χ), which essentially determine the miscibility, can be used to characterize the interactions of components within the blend. A negative or slightly positive value of χ indicates a good miscibility, while a large positive value points to immiscibility. In recent years, several emerging techniques such as fluorescence-based techniques, Raman mapping and solid-state nuclear magnetic resonance (NMR) techniques have been introduced to investigate the miscibility of the various components in the amorphous formulations.
- **Molecular interactions:** Characterizing molecular interactions between drugs and co-formers are beneficial for understanding the physical stability of coamorphous systems at the molecular level. Molecular interactions in coamorphous formulations have been extensively investigated by several distinct techniques such as Fourier transform infrared spectroscopy (FT-IR)16 , Raman spectroscopy and nuclear magnetic resonance (NMR). With the aid of Raman spectroscopy,
- **Molecular mobility:** Molecular mobility is one of the most fundamental factors affecting the physical stability (crystallization) of amorphous systems. The Molecular mobility of amorphous API is mainly investigated by modulated DSC54 or dielectric spectroscopy.

1.6.8 Analytical Techniques Use For Characterization of Co amorphous:

- FT IR
- XRD
- DSC
- TGA
- Scanning Electron microscope
- UV Spectrometer
- FT Raman Spectrometer

CONCLUSION

- BCS class II drug shows low solubility in aqueous media which leads to poor dissolution and bioavailability. There are various techniques are available for solubility enhancement leading to enhanced solubility and dissolution a recent method which ensures good solubility and stability is co-amorphous technique.

- There is need to develop co-amorphous mixture blend for low solubility drugs that belong to BCS class II and to further reformulate the best composite co-amorphous blend into immediate release tablets.

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