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# AMORPHOUS DRUG SYSTEMS: INNOVATIVE STRATEGIES FOR SOLUBILITY AND DISSOLUTION ENHANCEMENT

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**ABSTRACT**
Co-amorphous drug delivery systems have recently gained considerable interest in the pharmaceutical field because of their potential to improve the oral bioavailability of poorly water-soluble drugs through drug dissolution enhancement due to the amorphous nature of the material. It is a system. It is characterized by only low molecular weight components that are mixed into a homogeneous single-phase co-amorphous blend. The use of only low molecular weight co-formers approach is desirable, as the amount of amorphous stabilizer can be significantly reduced compared with other amorphous stabilization. These formulations of solid dispersions describe their formation and mechanism of stabilization, study their impact on dissolution and in vivo performance.

**KEYWORD:** Solubility, Dissolution, Bioavailability, Co-amorphous, Crystalline drug.

## 1. INTRODUCTION

### 1.1 Role of solubility in formulation development

Oral ingestion is the most convenient and commonly used route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, most minor sterility constraints, and flexibility in the design of dosage form. As a result, many drug companies are inclined more to produce oral drug products.[2] A significant challenge with the design of oral dosage forms is their poor bioavailability. The oral bioavailability depends on several factors, including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism.[3] Solubility is the most critical parameter for orally administered drugs to achieve their desired concentration in systemic circulation for a pharmacological response. The problem of solubility is a significant challenge for formulation scientists.[4] The poor solubility and low dissolution rate of poorly water-soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. The Biopharmaceutical classification system, especially for class II drugs (low solubility and high permeability) substances. The bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids.[1,2,5] 90% of the drugs under development show poor water solubility, resulting in poor and variable oral absorption, low bioavailability. Therefore, for stability reasons, a drug's low solubility crystalline form is used in formulations.[6,7] The amorphous solid-state offers improved apparent solubility and dissolution rate due to the lower energy barrier required to dissolve the molecules. Hence, a transformation of the crystalline drug into amorphous is widely employed for increasing solubility. However, thermodynamic instability due to the recrystallization tendency during processing, storage, and contact with the biological fluids limits the potential application of amorphous systems.[8] Co-amorphous systems are a new formulation approach where a low molecular co-former stabilizes the amorphous drug through solid intermolecular interactions.

## 2. APPROACHES FOR DELIVERY OF POORLY SOLUBLE DRUG

**2.1. Cyclodextrin inclusion**
**2.2. Microemulsion**
**2.3. Cocrystals**
**2.4. Amorphous dispersion**

### 2.1 Cyclodextrin inclusion

Cyclodextrins (CD) were discovered approximately 100 years ago, and the first patent o-n C.D.s and their complexes were registered in 1953. Cyclodextrin is used as a complexing agent to increase the aqueous solubility of poorly soluble drugs and increase their bioavailability and stability. Studies in both humans and animals have shown that Cyclodextrins can be used to improve drug delivery from almost any type of drug formulation. There are approximately 30 different pharmaceutical products

worldwide containing drug and cyclodextrin complexes in the market. However, their large-scale commercial utilization was prevented mainly due to their high cost and concerns regarding their safety. Cyclodextrins have been used to prevent gastrointestinal or ocular irritation, eliminate unpleasant smells or tastes, prevent drug-drug or drug-additive interactions, or convert oils and liquid drugs into microcrystalline or amorphous powders.[9]

Enhancement of solubility Cyclodextrins increases the aqueous solubility of many poorly soluble drugs by forming inclusion complexes with their polar molecules or functional groups.[10] Enhancement of bioavailability Cyclodextrins possesses a unique ability to complex with drugs, increasing solubility, reducing bitterness, enhancing stability, and decreasing tissue irritation upon dosing. It reduces the hydrophobicity of drugs by CD complexation and improves their percutaneous or rectal absorption. In addition to improving solubility, CDs also prevent the crystallization of active ingredients by complexing individual drug molecules so that they can no longer self-assemble into a crystal lattice.[11]

**2.2. Micro and Nano emulsion**

A microemulsion is defined as a system of water, oil, and amphiphile, which is a single optically isotropic and thermodynamically stable liquid solution with a droplet size usually in the range 20 to 200 nm.[12][13][14] Microemulsions are thermodynamically stable transparent Newtonian non-viscous liquids. However, unlike microemulsions, nanoemulsions are thermodynamically unstable systems, even though the long-term physical stability of nanoemulsions usually makes them unique.[15] Moreover, the Easy formation of microemulsions makes them more acceptable for exemplification in the industry than conventional emulsions. Self-emulsifying oil formulations, which are isotropic mixtures of oils, surfactants, solvents, and co-solvents/ surfactants, can be used to design microemulsions in order to improve the oral absorption of highly lipophilic drug compounds.[16-19] These systems are emulsifiable rapidly under mild agitation and in the presence of aqueous media such as gastrointestinal tract fluids to generate fine emulsion droplets, ranging in size from 100 nm to less than 100 nm for self-micro emulsifying drug delivery systems. However, the use of self-emulsifying drug delivery systems is limited because of their drug loading capacities and the use of excipients; therefore, the selection of excipients is significant.[20-21]

**2.2.1 Drug loading capacity**

Lipid excipients can solubilize hydrophobic drugs within their matrix. However, all excipients have different solubilization capacities. For example, medium-chain triglycerides generally have a higher solubilizing capacity on a weight basis than long-chain triglycerides.[22]

**2.2.2 Selection of excipients**

**2.2.2.1 Oily phase**

The selection of oil depends on the nature of the drug and the administration route. The chosen oil must have solubilization potential for the dissolution of the selected drug. For intravenous drug delivery, the selection of organic solvents should be biocompatible, sterilizable. The oils commonly used for intravenous delivery include long-chain triglycerides, for example, soybean oil, castor oils, etc.[23] Medium-chain triglycerides, medium-chain mono- and di-glycerides, vitamin E, and unsaturated fatty acid and its ester, for example, oleic acid, cholesteryl oleate. More excipients are available as the oil for transdermal drug delivery, and some of them also act as a penetration enhancer, for example, oleic acid. Several factors affect our choice of excipients, including excipient properties, such as irritancy, toxicity, solvent capacity, miscibility, melting point, digestibility, purity, chemical stability, the cost, and so on, affect our choice of excipient.

**2.2.2.2 Aqueous phase**

The pH of the aqueous phase always needs to be adjusted as it has a considerable influence on the phase behavior of the microemulsions. For parenteral microemulsions, the aqueous phase should be isosmotic to the blood, which can be achieved with the addition of agents such as sodium chloride, glycerol, dextrose, and sorbitol.[24]

**2.2.2.3 Emulsifying agent**

Microemulsions are classified into three types

a. oil-in-water

b. water-in-oil

c. bi-continuous systems

This microemulsion formation is dependent on the emulsifying agent type.[25-26]

**2.3. Cocrystal**

It is single crystalline phase material composed of two compounds via noncovalent interactions in specific stoichiometric ratios. They are typically formed via solid hydrogen bonds between carboxylic acids, amides, carbohydrates, alcohols, and amino acids. In addition to the advantages of cocrystals, co-amorphous or amorphous cocrystals can improve the stability of amorphous forms of drugs. Amorphous systems are a valuable way of improving solubility and dissolution rate. They are thermodynamically unstable. Excipients such as polymers or amino acids stabilize the amorphous system. An overview of cocrystals and co-amorphous pharmaceuticals, preparation and characterization methods, solubility, and dissolution properties. Co crystal defines as indicates the practical difference between cocrystals and its other sub-category of cocrystal. Kinetic or thermodynamic solubility approaches usually determine cocrystal solubility. Kinetic solubility shows cocrystals dissolution rate and indicates non- equilibrium solubility due to the cocrystal instability in solution. The solubility of equilibrium solubility of a cocrystal depends on the drug and co-

former concentration in the solution phase.[27] It can be calculated using the proposed method by Rodríguez-Hornedo and coworkers, where the transition point of each component is determined at the three-phase equilibrium. These three phases are drug, cocrystal, and solution phase. The concentrations at the eutectic point give cocrystal stability, which is directly related to cocrystal solubility.[28-29]

### 2.4. Amorphous dispersion (Solid Dispersion)

Solid dispersion is a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The most used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols (P.E.G.s), Plasdone-S630. Surfactants like Tween-80, docusate sodium, and sodium lauryl sulphate (S.L.S.) also find a place in solid dispersion formulation. Solid dispersions represent a useful pharmaceutical technique for increasing drug dissolution, absorption, and therapeutic efficacy in dosage forms. For example, the solubility of celecoxib, halofantrine, and ritonavir can be improved by solid dispersion using suitable hydrophilic carriers like celecoxib with povidone (PVP) ritonavir with a glacier. Various techniques to prepare the solid dispersion of hydrophobic drugs to improve their aqueous solubility are listed here.

#### 2.4.1 Hot-melt method (Fusion Method)

The main advantages of this direct melting method are its simplicity and economy. Sekiguchi and Obi first proposed the melting or fusion method to prepare fast-release solid dispersion dosage forms. In this method, the physical mixture of a drug and a water-soluble carrier is heated directly until the two melt. The melted mixture cooled and solidified rapidly in an ice bath with vigorous stirring. The final solid mass is then crushed, pulverized, and sieved, which can be compressed into tablets with the help of tableting agents.[30] The melting point of a binary system depends on its composition, that is, the selection of the carrier and the weight fraction of the drug in the system. Most important of solid dispersion by the hot-melt method is the miscibility of the drug and the carrier in the molten form. Another important is the thermostability of both the drug and the carrier.

#### 2.4.2 Solvent evaporation method

The drug and the carrier in a common solvent then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic β-carotene in the highly water-soluble carrier povidone. In addition, many investigators studied solid dispersion of meloxicam and naproxen using the solvent evaporation technique. These findings suggest that the technique mentioned above can successfully improve and stabilize solid dispersions of poorly water-soluble drugs.

#### 2.4.3 Media milling

It is prepared by using high-shear media mills. The milling chamber charged with milling media, water, drug, and stabilizer is rotated at a very high-shear rate under controlled temperatures for several days (at least 2–7 days). The milling medium is glass, Zirconium oxide, or highly cross-linked polystyrene resin. High energy shear forces are generated due to the impact of the milling media with the drug, resulting in the breaking of a microparticulate drug into nanosized particles.

#### 2.4.4 High-pressure homogenization

High-pressure homogenization has been used to prepare nanosuspension of many poorly water-soluble drugs. In this method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high-pressure homogenizer. The principle of this method is based on cavitation in the aqueous phase. The cavitation forces within the particles are sufficiently high to convert the drug microparticles into nanoparticles. Concern with this method is the need for small sample particles before loading and the fact that many homogenization cycles are required. Nevertheless, dissolution rate and bioavailability of poorly soluble drugs such as spironolactone, budesonide, and omeprazole have been improved by reducing their particle size by high-pressure homogenization.

#### 2.4.5 Combined precipitation and homogenization

The precipitated drug nanoparticles tend to continue crystal growth to the size of microcrystals. Therefore, they need to be processed with high-energy forces (homogenization). They are in entirely amorphous, partially amorphous or completely crystalline forms, which create problems in long-term stability and bioavailability, so the precipitated particle suspension is subsequently homogenized, preserving the particle size obtained after the precipitation.

## 3. COAMORPHOUS

Co-amorphous systems are a new formulation approach where a low molecular co-former stabilizes the amorphous drug through solid intermolecular interactions. Pharmaceutical co-amorphous, a kind of single-phase amorphous binary system, is formed between an active pharmaceutical ingredient and another small molecular compound that can be active pharmaceutical ingredients or excipients.[31] As a newly defined solid form, pharmaceutical co-amorphous has been a new approach for drug research and development due to its great potential in improving solubility, dissolution, stability, or even bioavailability.[32]

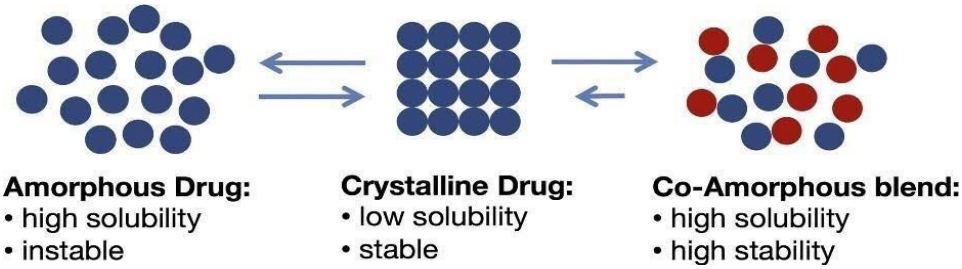


**Figure 1: Different properties of between amorphous drug, crystalline drug and co-amorphous blend.**

**Table 1: Comparison between amorphous drugs, crystalline drugs, and co-amorphous blends.**

| Property | Amorphous Drug | Crystalline Drug | Co-Amorphous Blend |
|---|---|---|---|
| Molecular Arrangement | Disordered and random | Ordered, repeating lattice | Disordered mixture of two or more components |
| Thermodynamic Stability | Metastable (less stable) | Highly stable | Intermediate stability (more stable than pure amorphous, less than crystalline) |
| Solubility | High solubility due to high free energy | Lower solubility | Improved solubility compared to crystalline form |
| Dissolution Rate | Fast due to high surface free energy | Slow | Faster than crystalline; may be similar or better than single amorphous form |
| Bioavailability | Enhanced | Often limited | Enhanced or optimized |
| Physical Stability | Poor (prone to recrystallization) | Excellent | Improved stability due to molecular interactions (e.g., hydrogen bonding) |
| Manufacturing Difficulty | Requires special techniques to maintain amorphous state | Easy to manufacture and store | More complex; requires precise control of component ratios and processing conditions |
| Glass Transition Temperature (Tg) | Present and measurable | Not applicable | Present and can be modified depending on components |
| Storage Conditions | Requires moisture and temperature control | Stable under normal conditions | Needs controlled conditions but more stable than pure amorphous form |
| Interactions Between Components | Not applicable | Not applicable | Strong molecular interactions (e.g., salt formation, hydrogen bonding) |

**3.1 Various techniques to prepare co-amorphous**

The preparation techniques of amorphous systems are.

1. Quenching cooling
2. Milling media

a. ball milling

b. Cry milling

3. Solvent evaporation method

a. Rotary evaporation method

b. Spray drying

They can be divided into thermodynamic and kinetic. The former has as starting point a thermodynamically stable non-crystalline form, i.e., the drug in melt or in solution and co-amorphous is obtained by quenching.[33] On the other hand, the kinetic pathway involves direct conversion of the solid crystalline into its amorphous state. This is possible during milling due to the continuous introduction of crystalline defects and disturbances through shearing, crushing and impact, and the overall mechanical activation. Therefore, selection of the preparation method depends on the thermal stability, melting temperature and the crystallization tendency of the drug and excipients, and it is very important for the quality and stability.

**1. Quench cooling**

The physical mixtures of the components are melted in a heated vessel under agitation and the melt is rapidly cooled on a plate top of ice. Quench cooling has the ability to quickly evolute critical physicochemical parameters such as miscibility and recrystallization, as co-amorphous can be prepared and analyzed. Ritonavir-indomethacin could not be formed as a co-amorphous system with the solvent evaporation technique, but it was possible by quench cooling.[34]

**2. Vibrational ball milling**

This is the main preparation method for co-amorphous. The add in mechanical activation causes twisting of the crystal and leads to transitions from crystalline to

amorphous state, co-amorphization, and salt formation. An advantage of this method is small chemical degradation and high recovery compared to other methods. Vibration ball mill can be time consuming while selection of the co-former is made by trial and error. The ability of mechanical activation to produce amorphous transitions depends on the vibration frequency, milling time and temperature. Process of milling and co-amorphous formation, the Tg is monitored as an index and in case of the drug or the co-former is first converted and produced the amorphous phase. The influence of the milling process co-amorphous salt dispersion by two methods: Dry ball milling (D.B.M.) and solvent grinding, where a drop of solvent is added during milling, increased molecular diffusion. The results of dry milling led to the formation of a fully co-amorphous salt, when water was added a crystalline synthesis than evidenced by the appearance.[37]

**3. Cry Milling**

This is usually performed in a vibrational ball mill. The milling bowls with components and grinding spheres are immersed in liquid nitrogen to ensure cryogenic conditions. After milling, they are placed in a desiccator and allowed to reach room temperature. Milling temperature is important for solid-state.[38] Cryo milling is more effective than conventional dry milling for producing co- amorphous S.D.s. Solid-state characterization appears that 1:1 molar combination of simvastatin-lysine, Glibenclamide-serine and Glibenclamide-threonine and 1:1:1 combination glibenclamide-serine-threonine formed co-amorphous Solid dispersion by weak intermolecular interactions.

**4. Solvent evaporation**

This is a common method for preparing co-amorphous S.D.s, placed by crystalline components that are dissolved in a common organic solvent which is evaporated under vacuum or heating. Extra solvent is completely removed by drying for at least 24 hours.[39] Due to the rapid removal of the solvent, the molecules have no time to rearrange crystal. eg. atenolol-hydrochlorothiazide (ATE-HCT), where the method failed due to crystallization evaporation. Co-amorphous LH-SAC showed superior physical stability than amorphous L.H., improved pH-independence solubility, enhanced intrinsic dissolution rate and supersaturated dissolution.[40]

**5. Spray drying**

This is the first large-scale production method of co-amorphous drug-amino acids S.D.s with comparable properties to those prepared by milling.[41] It is easy to produce stable glass solutions and solid dispersions. A solution of the components is sprayed into a hot air stream than the droplets are formed and dried by evaporation method resulting in spherical, narrow size distribution co-amorphous particles. Inlet temperature and feed rate are the most critical parameters. The product should be dried, any extra solvent can reduce Tg and increase solvate formation. Thermal exposure during spray drying should be kept below the Tg of the materials to avoid crystallization.[42]

**6. Hot melt extrusion (H.M.E.)**

This is a continuous solvent-free process and has been applied in the pharmaceutical industry for the production of crystalline or amorphous. It is monitoring detection of co-amorphization, degradation and intermolecular interactions by the application of Process Analytical Technology. Application of H.M.E. requires consideration of the process and materials, which significantly affect the type of produced dispersion.[43] P.E.O. (polyethylene oxide) reduced the melt viscosity, prevented phase separation and resulted in a ternary amorphous S.D. where P.E.O. acted as co-solvent for both drugs. H.M.E. has not been applied extensively to drug-amino acid co-amorphization, because amino acid co amorphization degrades above 200 ◦C and because the mechanical and thermal energy (short residence time) may be inadequate to overcome. Although the co-amorphous dispersion that result increased dissolution, phase separation was found. Proposed the use of phase diagrams based on the melting behavior of physical mixtures for the development of co- amorphous S.D.s with high crystalline drug content. This is because in this case the minimum H.M.E. processing temperature is controlled by the melting of crystalline solids.[44]

**4. APPLICATION OF AMORPHOUS SYSTEM**

**4.1 Drug-drug combinations**

Cimetidine is sometimes co-administered with naproxen for the treatment of NSAID-induced gastrointestinal disorders. prepared co-amorphous naproxen- cimetidine with increased Tg by milling. The IDR of naproxen and cimetidine in the co-amorphous Solid dispersion was respectively four-fold and two-fold higher than the individual crystalline forms.[45] While the dissolution rate of amorphous cimetidine was found to recrystallization upon contact with the dissolution medium, the dissolution of co-amorphous Ritonavir. A protease inhibitor was stabilized with indomethacin in co-amorphous prepared by solvent evaporation. These were stable for 90 days, while the solubility of both drugs was about three-fold greater compared to the corresponding crystalline analogs.co-administration of the two drugs improved the efficiency of antiretroviral therapy and the reduction of ritonavir side effects. Co-amorphous naproxen–indomethacin prepared by spray drying. The influence of the process conditions on the resulting initial sample crystallinity and the recrystallization of the drugs was studied. Recrystallization was affected by the total and individual recrystallization rates of the co-amorphous components, the formation of indomethacin polymorphs and by the inlet temperature and feed rate of the spray dryer.[46] Combined oral therapy of hypoglycemic agents may assist side effects and costs. Co-amorphous dispersions of Nate-glinide and metformin hydrochloride give therapeutic doses and

increased release rate of N.T. They also action in patients with type 2 diabetes that could not be controlled with monotherapy.[47] Co-administration did not affect pharmacokinetics.

### 4.2 Drug excipients

#### 4.2.1 Drug carboxylic acids

Carboxylic acids are prepared by cooling or solvent evaporation of drug solutions in various solvents. Acyclovir formed cocrystal with tartaric acid but co-amorphous mixture with citric acid.[48] The amorphized mixture prepared stable clozapine (C.Z.) co-amorphous systems with low M.W./low Tg carboxylic acids such as citrate and d-Tartrate by rapid solvent evaporation in vacuum via formation of H- bonds. The co-amorphous mixture with tartaric acid had the highest dissolution rates than pure crystalline. Solvent evaporation was also applied to prepare co-amorphous S.D.s of olanzapine (O.L.) using Polycarboxylic acids as co-formers. The mixtures were incorporated into rapidly dissolving oral polymer films containing added HPMC, glycerin, PEG 400, citric acid, saccharin, menthol as an easy and simple way of administration. Co-amorphization of olanzapine ascorbic acid was achieved at 1:2 molar ratio through H-bonding and showed a more than 600-fold increase in O.L. solubility. The films showed a high dissolution rate.[49]

#### 4.2.2 Drug amino acids

Prepared co-amorphous systems of Amino acids system in combination with carbamazepine (C.B.Z.) and indomethacin (IND) by milling. The selection of Amino acid was based on the binding site at the biological receptor's arginine (A.R.G.) and tyrosine (Tyr) for IND binding to cyclooxygenase 2, and receptors phenylalanine (P.H.E.), tryptophan (T.R.P.) for C.B.Z. binding to neural Na+ channels. Specific hydrogen bonding and π–π interactions were found in all co-amorphous dispersions that contained at least one binding Amino acid from the biological target site of the drug.[50] Arginine was found to form co-amorphous salts with weak acids such as NSAIDs and was used successfully as a co-former for indomethacin. Additionally, it can make π–π interactions with molecules having aromatic rings, e.g., naproxen-arginine co-amorphous mixture compared to crystalline drug. On the basis of the ability of arginine for co-amorphization, it was thought that the structurally similar citrulline (CTL) could also show similar behavior, so drugs reduced their crystallinity, fully co-amorphous mixture was obtained only with furosemide (FUR-CTL) and nitrofurantoin (NIT-CTL). The receptor binding amino acids of simvastatin (S.V.S.): aspartic acid, lysine and serine, the drug formed co-amorphous only with L.Y.S.[51]

## 5. CONCLUSION

The various properties of co amorphous mixtures of API and small molecule conformers with those exhibited by API-polymer amorphous solid dispersions. Various techniques are successfully used to prepare solid dispersion in the lab-scale and can also be used at industrial scale. The solid dispersion method is an effective approach to achieving a goal of solubility enhancement of poorly water-soluble drugs. Solubility enhancement of poorly water-soluble drugs remains one of most challenging aspects of drug development.

## ABBREVIATIONS

CD- Cyclodextrin
P.E.G.s- Polyethylene glycols S.L.S.- Sodium lauryl sulphate PVP- Povidone
D.B.M.- Dry ball milling
ATE-HCT- Atenolol hydrochlorothiazide HME- Hot melt extrusion
P.E.O.- Polyethylene oxide C.Z.- Clozapine
O.L.- Olanzapine
CBZ- Carbamazepine IND- Indomethacin ARG- Arginine
T.Y.R.- Tyrosine
P.H.E.- Phenylalanine T.R.P.- Tryptophan
CTL Citrulline
FUR- Furosemide
N.I.T.- Nitrofurantoin

## REFERENCES

1. Ketan T. Savjani, Anuradha K. Gajjar, and Jignasa K. Savjani Drug Solubility: Importance and Enhancement Techniques International Scholarly Research Network, I.S.R.N. Pharmaceutics, 2012; Page No 1-10.
2. S. R. K. Yellela, "Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs," Journal of Bioequivalence& Bioavailability, 2010; 2(2): 28–36.
3. K. H. Edward and D. Li, "Solubility," in Drug Like Properties: Concept, Structure, Design and Methods, from ADME to Toxicity Optimization, p. 56, Elsevier, 2008.
4. D. Sharma, M. Soni, S. Kumar, and G. D. Gupta, "Solubility enhancement— eminent role in poorly soluble drugs, "Research Journal of Pharmacy and Technology, 2009; 2(2): 220–224.
5. A. Kumar, S. K. Sahoo, K. Padhee, P. S. Kochar, A. Sathapathy, and N. Pathak, "Review on solubility enhancement techniques for hydrophobic drugs," PharmacieGlobale, 2011; 3(3): 001–007.
6. Hauss, D.J. Oral lipid-based formulations. Adv. Drug Deliv. Rev, 1995; 59: 667–676.
7. Williams, H.D.; Trevaskis, N.L.; Charman, S.A.; Shanker, R.M.; Charman, W.N.; Pouton, C.W.; Porter, C.J.Strategies to address low drug solubility in discovery and development. Pharmacol. Rev, 2013; 65: 315–499.
8. Yu, L. Amorphous pharmaceutical solids: preparation, characterization and stabilization. Adv. Drug Deliv. Rev, 2001; 48: 27–42.
9. Agu RU, Vu Dang H, Jorissen M, Willems T, Kinget R, Verbeke N. Nasal absorption enhancement strategies for therapeutic peptides: an

*in vitro* study using cultured human nasal epithelium. *Int J Pharm*, 2002; 237: 179.
10. Archontaki HA, Vertzoni MV, Athanasiou Malaki MH. Study on the inclusion complexes of bromazepam with beta- and beta-hydroxypropyl-cyclodextrins. *J PharmBiomed Anal*, 2002; 28: 761–9.
11. Arima H, Yunomae K, Miyake K, Irie T, Hirayama F, Uekama K. Comparative studies of the enhancing effects of cyclodextrins on the solubility and oral bioavailability of tacrolimus in rats. *J Pharm Sci*, 2001; 90: 690–701.
12. Talegaonkar S AA, Ahmad FJ, Khar R.K., et al. Microemulsions: a novel approach to enhanced drug delivery. Recent Pat Drug DelivFormul, 2008; 2(3): 238-57.
13. Heuschkel S, Goebel A, NeubertRHH. Microemulsions- modern colloidal carrier for dermal and transdermal drug delivery. J Pharm Sci, 2008; 97(2): 603-31.
14. Spenrath A, Aserin A. Microemulsions as carriers for drugs and nutraceuticals.Adv Colloid Interface Sci, 2006; 128-130: 47-64.
15. Bouchemal K, Brianc¸on S, Perrier E,et al. NanoemulsionNanoemulsion formulation using spontaneous emulsification: solvent, oil and surfactant optimization. Int J Pharm, 2004; 280(1-2): 241-51.
16. Jadhav KR, Shaikh IM, Ambade KW, Kadam VJ. Applications of microemulsion based drug delivery system. Curr Drug Deliv, 2006; 3: 267-73.
17. Jayvadan Patel AS. Self-emulsifying delivery systems for poorly absorbed drugs. Int J Pharm Sci Nanotechnol, 2008; 1(3): 123-8.
18. Patel PA, Chaulang GM, Akolkotkar A, et al. Self emulsifying drug delivery system: a review research. J Pharm Tech, 2008; 1(4): 313-23.
19. Jing-ling T, Jin S, Zhong-Gui H. Self emulsifying drug delivery systems: strategy for improving oral delivery of poorly soluble drugs. Curr Drug Ther, 2007; 2: 85-93.
20. Pouton CW. Lipid formulations for oral administration of drugs: non- emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. Eur J Pharm Sci, 2000; 11(Suppl 2): S93-8
21. Shen H, Zhong M. Preparation and evaluation of self-micro emulsifying drug delivery systems (S.M.E.D.D.S.) containing atorvastatin. J PharmPharmacol, 2006; 58(9): 1183-91 22. Cao Y, Marra M, Anderson BD. Predictive relationships for the effects of triglyceride ester concentration and water uptake on solubility and partitioning of small molecules into lipid vehicles. J Pharm Sci., 2004; 93(11): 2768-79.
22. Date AA, Nagarsenker MS. Parenteral microemulsions: an overview. Int J Pharm, 2008; 355(1-2): 19-30.
23. Vandamme TF. Microemulsions as ocular drug delivery systems: recent developments and future challenges. Prog Retin Eye Res, 2002; 21(1): 15-34.
24. Yuan JS, Ansari M, Samaan M, et al. Linker-based lecithin microemulsions for transdermal delivery of lidocaine. Int J Pharm, 2008; 349(1-2): 130-43.
25. Lawrence MJ, Rees GD. Microemulsion-based media as novel drug delivery systems. Adv Drug Deliv Rev, 2000; 45(1): 89-121.
26. Sekiguchi K., Obi N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharm. Bull. (Tokyo), 1961; 9: 866–872.
27. Dengale, S.J.; Grohganz, H.; Rades, T.; Löbmann, K. Recent advances in co- amorphous drug formulations. Adv. Drug Deliv. Rev, 2016; 100: 116–125.
28. Suresh, K.; Mannava, M.K.C.; Nangia, A. A novel curcumin–artemisinin amorphous solid: Physical properties and pharmacokinetic profile. R.S.C. Adv, 2014; 4: 58357–58361.
29. Vasconcelos, T.; Marques, S.; das Neves, J.; Sarmento, B. Amorphous solid dispersions: Rational selection of a manufacturing process. Adv. Drug Deliv. Rev, 2016; 100: 85–101.
30. Bengali, S.J.; Ranjan, O.P.; Hussein, S.S.; Krishna, B.S.; Musmade, P.B.; Shenoy, G.G.; Bhat, K. Preparation and characterization of co-amorphous Ritonavir- Indomethacin systems by solvent evaporation technique: Improved dissolution behavior and physical stability without evidence of intermolecular interactions. Eur. J. Pharm. Sci, 2014; 62: 57–64.
31. Hancock, B.C.; Zografi, G. Characteristics and significance of the amorphous state in pharmaceutical systems. J. Pharm. Sci, 1997; 86: 1–12
32. Jensen, K.T.; Löbmann, K.; Rades, T.; Grohganz, H. Improving Co-Amorphous Drug Formulations by the Addition of the Highly Water Soluble Amino Acid, Proline. Pharmaceutics, 2014; 6: 416–435
33. Kasten, G.; Nouri, K.; Grohganz, H.; Rades, T.; Löbmann, K. Performance comparison between crystalline and co-amorphous salts of indomethacin-lysine. Int. J. Pharm, 2017; 533: 138–144.
34. Descamps, M.J.; Willart, F.; Dudognon, E.; Caron, V. Transformation of pharmaceutical compounds upon milling and compelling: The role of T(g). J. Pharm. Sci, 2007; 96: 1398–1407.
35. Löbmann, K.; Strachan, C.; Grohganz, H.; Rades, T.; Korhonen, O.; Laitinen, R. Co-amorphous simvastatin and glipizide combinations show improved physical stability without evidence of intermolecular interactions. Eur. J. Pharm. Biopharm, 2012; 81: 159–169.
36. Moinuddin, S.M.; Ruan, S.; Huang, Y.; Gao, Q.; Shi, Q.; Cai, B.; Cai, T. Facile formation of co-amorphous atenolol and hydrochlorothiazide mixtures via cryogenic- milling: Enhanced physical stability, dissolution and pharmacokinetic profile. Int. J. Pharm, 2017; 532: 393–400.
37. Jensen, K.T.; Larsen, F.H.; Cornett, C.; Löbmann, K.; Grohganz, H.; Rades, T. Formation Mechanism

of Coamorphous Drug-Amino Acid Mixtures. Mol. Pharm, 2015; 12: 2484–249.
38. Takeuchi, H.; Nagar, S.; Yamamoto, H.; Kawashima, Y. Solid dispersion particles of tolbutamide with fine silica particles by the spray-drying method. Powder Technol, 2004; 195: 141–187.
39. Hitzer, P.; Bäuerle, T.; Drieschner, T.; Ostertag, E.; Paulsen, K.; van Lishaut, H.; Lorenz, G.; Rebner, K. Process analytical techniques for hot-melt extrusion and their application to amorphous solid dispersions. Anal. Bioanal. Chem, 2017; 409: 4321–4333.
40. Martínez, L.M.; Video, M.; Sosa, N.G.; Ramírez, J.H.; Castro, S. Long-Term Stability of New Co-Amorphous Drug Binary Systems: Study of Glass Transitions as a Function of Composition and Shelf Time. Molecules, 2016; 21: 1712.
41. Allesø, M.; Chieng, N.; Rehder, S.; Rantanen, J.; Rades, T.; Aaltonen, J. Enhanced dissolution rate and synchronized release of drugs in binary systems through formulation: Amorphous naproxen–cimetidine mixtures prepared by mechanical activation. J. Control. Release, 2009; 136: 45–53.
42. Beyer, A.; Radi, L.; Grohganz, H.; Löbmann, K.; Rades, T.; Leopold, C.S. Preparation and recrystallization behavior of spray-dried co-amorphous naproxen- indomethacin. Eur. J. Pharm. Biopharm, 2016; 104: 72–81.
43. Wairkar, S.; Gaud, R. Co-Amorphous Combination of Nateglinide-Metformin Hydrochloride for Dissolution Enhancement. AAPS PharmSciTech, 2016; 17: 673–681.
44. Masuda, T.; Yoshihashi, Y.; Yonemochi, E.; Fujii, K.; Uekusa, H.; Terada, K. Cocrystallization and amorphization induced by drug-excipient interaction improves the physical properties of acyclovir. Int. J. Pharm, 2012; 422: 160–169.
45. Maher, E.M.; Ali, A.M.; Salem, H.F.; Abdelrahman, A.A. In vitro/in vivo evaluation of an optimized fast dissolving oral film containing olanzapine co-amorphous dispersion with selected carboxylic acids. Drug Deliv, 2016; 23: 3088–3100.
46. Löbmann, K.; Laitinen, R.; Strachan, C.; Rades, T.; Grohganz, H. Amino acids as amorphous stabilizers for poorly water-soluble drugs—Part 2: Molecular interactions. Eur. J. Pharm. Biopharm, 2013; 85: 882–888.
47. Wu, W.; Löbmann, K.; Rades, T.; Grohganz, H. On the role of salt formation and structural similarity of co-formers in co-amorphous drug delivery systems. Int. J. Pharm, 2017; 535: 86–94.