Solubility enhancement techniques of poorly soluble drugs with special emphasis on amorphous solid dispersion

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Abstract : **The solubility of active pharmaceutical ingredients (APIs) plays a critical role in drug development, affecting bioavailability and therapeutic effectiveness. A significant number of new chemical entities (NCEs) exhibit poor water solubility, limiting their absorption and efficacy. This review focuses on various solubility enhancement techniques, with a special emphasis on amorphous solid dispersions (ASDs). ASDs, achieved through solid dispersion technology, enhance drug dissolution rates by preventing recrystallization and maintaining a high-energy amorphous state. The selection of appropriate polymers, such as PVP, HPMC, and Eudragit, is crucial for stabilizing ASDs. Different manufacturing methods, including spray drying, hot-melt extrusion, electrospraying, and supercritical fluid technology, are explored, highlighting their advantages and limitations. The article also discusses the stability challenges of ASDs and characterization techniques such as DSC, XRPD, and FTIR. The advancements in ASDs offer promising solutions for improving drug solubility and bioavailability, contributing to the effective formulation of poorly soluble drugs.**

Keywords : Amorphous solid dispersions, Glass transition temperature, Recrystallization, Hot-melt extrusion, Spray drying

1. INTRODUCTION

New chemical entities (NCEs) are novel drugs or Active pharmaceutical ingredients (APIs) arriving the drug discovery pipeline because of technological improvement and pressure of competition'. NCEs are initiated in the mid-1990s by an arrangement of combinatorial chemistry and high throughput screening as opposed to wet chemistry. The resulting NCEs are mainly characterized as lipophilic with high molecular weight suitable for biological targets, which consequently exhibit poor water solubility. Both patients and the pharmaceutical industry are plagued with limited aqueous solubility of active pharmaceutical ingredients [1].

1.1 Solubility

Solubility is the phenomenon of dissolving a solute in a solvent, which is essential to produce a homogenous system. In quantitative terms, solubility may be defined as the required strength of the solute dissolved in a solution at a given pH, temperature, and pressure. In contrast, in qualitative terms, solubility is the material's ability to be melted in a saturated solution at a specific temperature. Solubility is presented with numerous terminologies such as molality, volume fraction, parts of solvent, percentage, molarity, mole fraction, and so forth. US Pharmacopoeias define solubility as the milliliters of solvent necessary to dissolve one gram of solute The varying degrees of solubility from very soluble to practically insoluble are defined and listed in **Table 1.** High solubility according to BCS is 85% within 30 minutes from pH 1 to 7.5. [2].

Drugs administered via the oral route in a solid dosage form are first disintegrated into smaller parts or even primary particles, from which the drug molecules are freer to dissolve in the gastrointestinal tract (GIT) fluids than from an intact tablet; the molecular dissolution of the drug is then followed by its penetration through the intestinal barrier, as displayed in **Fig. 1** [3]. Given that all bodily fluids are water-based solutions, aqueous solubility is an essential criterion to achieve the appropriate concentrations of the drug molecules in the systemic circulation to elicit the required therapeutic efficacy.

If a drug molecule has very low solubility, it cannot be dissolved in the GIT fluids, which hinders its permeability and, thus, bioavailability because it is directly related to the drug solubility. Low bioavailability observed with poorly soluble drugs make the final formulation expensive because high doses are needed to obtain therapeutic benefits and, sometimes, they might cause toxicity.

1.2 Biopharmaceutical classification system

Biopharmaceutics classification system was introduced by US Food and Drug Administration (FDA) and it classify the drug in to four classes according to permeability and solubility as shown **Fig. 2.** Solubility impediment are faced in the Class II and Class IV of the system facing dissolution as the rate limiting step for the absorption of drug due to low solubility.[1]

1.3 Process of solublisation

The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute [8], the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion are depicted in **Fig. 3**[4].

1.4 Need of Solubility Enhancement

Advancements in drug development are increasingly driven by better characterization of biochemical targets, which are often cell-based and easily accessible in these models. However, many highly active compounds exhibit poor physicochemical properties for whole-organism delivery, with low water solubility being a primary concern.

Recent estimates indicate that nearly 40% of new chemical entities are rejected due to poor solubility and biopharmaceutical limitations. Solubility plays a crucial role in achieving the required drug concentration in systemic circulation to elicit a pharmacological response. Ultimately, the therapeutic effectiveness of a drug is determined by its bioavailability, which is directly influenced by its solubility[5]

TECHNIQUES TO OVERCOME POOR SOLUBILITY [1 ,2,4-6]

I. Chemical Modifications:

1) Salt Formation

2) Co-crystallization

3) Co-solvency

4) Hydrotropy

5) Use of novel solubilizer

6) Nanotechnology

II. Physical Modifications:

1. Particle size reduction

a) Conventional method

b) Micronization

c) Nanosuspension

2. Modification of the crystal habit

a) Polymorphs

b) Pseudopolymorphs

3. Complexation

a) Physical mixture

b) Kneading method

c) Co-precipitate method

4. Inclusion Complex Formulation Based Techniques

a) Kneading method

b) Lyophilization/ Freeze- drying Technique

c) Microwave irradiation method

5. Solubilization by surfactants

a) Microemulsions

b) Self microemulsifying drug delivery system

6. Drug dispersion in carriers

a) Solid solutions

b) Solid dispersion

i. Fusion Process

ii. Solvent Method

iii. Fusion solvent method

iv. Spray drying

v. Lyophilization (Freeze Drying Method)

vi. Hot melt Extrusion

vii. Dropping Method

2. AMORPHOUS SOLID DISPERSIONS (ASDS) FOR ORAL DRUG DELIVERY

An amorphous solid dispersion (ASD) is a type of solid dispersion in which the active drug is distributed within an excipient matrix in a predominantly amorphous state. This amorphous form plays a crucial role in enhancing drug solubility. Since the drug is not in a crystalline state, no energy is needed to break a crystal lattice, allowing for significantly higher apparent solubility and much faster dissolution compared to its crystalline counterpart.

Additionally, ASDs promote greater membrane flux due to their high supersaturation levels, leading to improved bioavailability. The presence of hydrophilic polymers in ASDs further enhances drug wettability, contributing to better solubility and absorption.[7]

SDs are classified into four generations based on the carrier materials used.

First-generation SDs exhibit excellent thermodynamic stability but release drugs at a slower rate.

Second-generation SDs utilize polymers to create amorphous solid dispersions (ASDs), which thermodynamically unstable, making them prone to crystallization under high temperature and humidity conditions. While the incorporation of surfactants or polymeric materials can help prevent recrystallization and improve wettability and stability, long-term storage remains a challenge. As a result, solid dispersion formulations on the market tend to have limited shelf lives.

Third-generation SDs employ surfactants as carriers to prevent drug recrystallization, with commonly used surfactants including Poloxamer and Soluplus.

Lastly, fourth-generation SDs incorporate enteric-soluble or water-insoluble carriers to enable the sustained and controlled release of PWSDs. The successful development of SDs depends on drug properties, the types of polymers used, and the preparation techniques applied.[8]

3.1 Selection of Polymers in Amorphous Solid Dispersions (ASD)

Due to the limited availability of drugs in the early stages of development, selecting appropriate polymers is essential to characterize and correlate them with the physicochemical properties of the drug. These properties include melting enthalpy, glass transition temperature (Tg), molecular weight, solvent miscibility, solubility, structural flexibility, and viscosity both above and below the polymer's Tg. While some compounds exhibit good glass-forming ability and low crystallization tendencies, their amorphous forms remain thermodynamically unstable. However, despite this instability, these compounds are recognized as effective glass formers with reduced crystallization tendencies.

Amorphous solid dispersion (ASD) involves incorporating an amorphous drug into a polymer matrix, which influences the conversion kinetics between crystalline and supersaturated states. The selection of a suitable polymer is critical, as it significantly alters the physicochemical properties of the drug. An ideal polymer should meet the following criteria:

1. Stabilization of the Amorphous Form – It should maintain the drug in its amorphous state not only during manufacturing but also throughout storage and transportation.
2. Solubility and Supersaturation Maintenance – The polymer must be readily soluble in gastrointestinal (GI) conditions and sustain a supersaturated solution state, which is crucial for drug absorption.

3. Enhanced Bioavailability – It should facilitate improved bioavailability by enhancing the drug's permeation through GI membranes[9].

A viscous polymer matrix plays a crucial role in providing kinetic stabilization[10]. Since the glass transition temperature (Tg) of an amorphous drug is typically lower than that of the polymer, the Tg of an ASD system usually falls between the Tg values of the drug and the polymer. This increase in Tg raises the kinetic barrier to crystallization[11,3]. This principle also underlies the 'Tg - 50°C' rule, which states that the molecular mobility of an amorphous solid becomes negligible at temperatures 50°C below its Tg[12].

As a result, selecting a polymer with a high Tg is essential for ASD formulations. When the drug-polymer system is miscible and the drug concentration remains below its saturation solubility in the polymer, the ASD remains thermodynamically stable. The presence of a polymeric carrier is beneficial, as it stabilizes the amorphous form of the drug. Additionally, since most polymers used in ASD preparation are hydrophilic, they improve drug dissolution by enhancing the wettability of the formulation[13]. In some drug-loading regimens, the dissolution of the drug is controlled by the dissolution of the polymer.

Commonly used polymers for amorphous solid dispersions (ASDs) are employed across various manufacturing platforms. These include povidone derivatives such as polyvinylpyrrolidone (PVP) and polyvinylpyrrolidone/vinyl acetate (PVPVA)[14,15], polymethacrylate derivatives (Eudragit series)[16-18], hydroxypropyl methylcellulose (HPMC)[7], hydroxypropyl methylcellulose acetate succinate (HPMCAS)[19], and polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (Soluplus)[20]. Their glass transition temperature (Tg) and solubility in organic solvents are detailed in **Table 2.**

3.2 Manufacturing methods for preparing amorphous solid dispersions

An ideal manufacturing process should be able to produce homogenous ASDs which can retain their amorphous form for the required duration of time Amorphous solid dispersions (ASDs) can be produced using various techniques, all of which share a common fundamental principle. The process begins by disrupting the crystalline drug's lattice structure and transforming it into a liquid state, either by applying heat or dissolving it in a solvent. The system is then rapidly cooled (in heat-based methods) or dried (in solvent-based methods), pushing it out of equilibrium at the glass transition temperature (Tg). This results in the formation of the drug in an amorphous solid state. Achieving this state requires sufficiently fast cooling or drying of the liquefied drug.

ASD manufacturing techniques can be broadly categorized into solvent-based and melting (fusion) methods. Solvent evaporation techniques, such as spray drying (SD), electrospraying, and rotary evaporation, involve dissolving the drug and polymer in a solvent, which is subsequently evaporated to create the ASD[21]. These methods are particularly suitable for thermolabile drugs. In contrast, melting methods involve heating a physical mixture of the drug and polymer until it melts, followed by rapid solidification to generate the ASD.

ASD products with different physical and functional properties will generate by different manufacturing processes[20.21]. Therefore, an adequate understanding of manufacturing processes and their impact on product properties is important for obtaining a successful ASD product.

3.2.1 Solvent evaporation-based methods

The solvent evaporation method for preparing amorphous solid dispersions (ASDs) involves dissolving the drug and polymer in an organic solvent system, followed by rapid solvent removal. Aqueous solvents may be used alongside organic solvents to improve polymer solubility and/or minimize organic solvent usage. Amorphous drug-polymer dispersions are created by quickly evaporating the solvent from the solution. Since this process typically occurs at temperatures well below the drug's melting point, it is especially suitable for thermolabile formulations.

3.2.1.1 Spray drying

Spray drying is the most commonly used solvent-based method due to its high efficiency in solvent removal [22]. This continuous process is easily scalable from laboratory to industrial production. Polymers such as PVP and HPMCAS are frequently utilized in the manufacturing of ASDs via spray drying [23].

A key challenge in developing ASDs through spray drying is selecting an appropriate solvent that can adequately dissolve both the drug and polymer. Typically, a solubility of at least 50 mg/mL for both components is desirable to ensure efficient ASD production[24]. The schematic setup of the spray drying process is illustrated in **Fig. 4 a**. This process consists of several key steps. Initially, the feed solution or suspension—containing the drug, polymer, and potentially other additives—is pumped into the drying chamber through a spray nozzle.

Different types of commonly used nozzles are shown in **Fig. 4 (b, c, d)**. Among these, the two-fluid nozzle is the most frequently used for preparing spray-dried amorphous solid dispersions (ASDs)[25], particularly in laboratory-scale applications. In this type of

nozzle, atomization energy is primarily provided by a gas. The liquid, introduced at low pressure, can be mixed with the gas either internally or externally[26].

Another widely used nozzle in the pharmaceutical industry is the pressurized nozzle[27,28], which relies solely on the feed liquid's pressure for atomization. Within this category, the pressure-swirl nozzle converts the potential energy of the liquid into kinetic energy. However, this nozzle is not effective for atomizing highly viscous liquids. Higher solution viscosity reduces swirl intensity, leading to increased liquid throughput as the cross-sectional area of the liquid expands.

Pressurized nozzles offer advantages such as the ability to produce larger particles with better flow properties and ease of scale-up. This is particularly beneficial for downstream processing, as it enhances powder flow, die filling, compression, and tablet uniformity.

The choice of feed pump depends on factors such as the viscosity of the feed material, the type of atomization nozzle, and the drying capacity.[29] Once the droplets are atomized by the nozzle, they come into contact with heated gas inside the drying chamber, which facilitates solvent evaporation and completes the drying process.

Industrial spray dryers are designed to handle a gas flow rate of up to 5000 kg/h, enabling a solvent evaporation capacity of up to 400 kg/h.[30]Once the drying process is complete, the dried material is transported to a cyclone separator, where heavier particles are separated from the drying gas and collected. Meanwhile, finer particles are carried away with the exhaust gases and are later captured using a filter system[28].

In some cases, particle deposition occurs at the bottom of the drying chamber. These deposits may be removed using scraping techniques, which can involve vibratory devices and/or compressed air. Although mechanical brushes can also be used, they may introduce additional mechanical stress, potentially affecting product quality. An operating and processing space for generating stable ASDs is shown in **Fig. 5**

The evaporation rate plays a crucial role in the drying process. Slower evaporation rates allow more time for molecular rearrangement, which can lead to phase separation or crystallization. Additionally, an increase in feed solution temperature can enhance the solubility of the drug and excipients, influencing the final product characteristics.[31]

Despite its advantages, spray drying has certain limitations. One major challenge in spray-dried amorphous solid dispersions (ASDs) is the presence of solvent residue, which can impact product stability and safety. Another concern is the adhesion of material to equipment walls, which reduces product yield. This issue is particularly critical in early-stage development when the availability of the active ingredient is limited, especially for expensive drugs. To improve product recovery and bulk density, researchers have found that incorporating silicon dioxide into the feed solution can significantly enhance the yield of ASD products[32].

3.2.1.2 Electrospraying

Electrospraying utilizes electrical forces to atomize the feed solution—containing the drug and other additives—into nanometer- to micrometer-sized droplets. Similar to spray drying, the rapid solvent evaporation promotes the formation of an amorphous drug state within the ASD.

However, one of the key advantages of electrospraying over spray drying and many other techniques is its capability to produce small particles, with a narrow particle size distribution[33]

A standard electrospraying setup consists of four key components: a siphoning system (typically a pump), a spray nozzle assembly with adjustable high voltage, and a grounded substrate[34]. In this process, an electrically conductive feed is gradually delivered to the spray nozzle, where an electrical potential difference is applied.

Electrospraying functions under precisely controlled conditions, ensuring that electrostatic repulsion exceeds the solution's kinetic energy and surface tension. This allows the jet to break into fine droplets. However, when the kinetic energy within the Taylor cone and the surface tension exceed the electrostatic repulsion—often due to the presence of high molecular weight polymers—the charged solution jet does not fragment into droplets Instead, it forms fine polymeric fibers with diameters ranging from a few nanometers to several micrometers [35]. This fiber formation process is referred to as electrospinning.

3.2.1.3 Fluidized Bed Technology

Fluidized bed technology is widely utilized in pharmaceutical processes, including granulation (fluidized bed granulator), coating (fluidized bed coater), drying (fluidized bed dryer), and cooling [36]. Similarly, fluidized bed coaters and granulators play a role in the production of amorphous solid dispersions (ASDs) [37,38].

In ASD manufacturing, drug-polymer solutions are sprayed onto inert excipient cores, where solvent evaporation and ASD layering occur simultaneously. Additionally, the organic solvent used in the process can be recovered and recycled [39]. This technique has been successfully applied to develop both controlled-release and immediate-release solid dispersions [40,41].

3.2.1.4 Supercritical fluids (SCFs)

Supercritical fluids (SCFs) have also been utilized in the production of amorphous solid dispersions (ASDs). SCFs are gases that exhibit both liquid and gaseous properties under specific temperature and pressure conditions. The liquid-like characteristics of SCFs facilitate drug-polymer solubilization, while their gaseous nature supports solid diffusion and solvent evaporation. Although, in theory, most gases can become SCFs, only a few are commonly used due to the constraints of achievable temperature and pressure. Notably, over 98% of SCF applications involve carbon dioxide (CO_2) because of its low critical temperature (31°C) and pressure (7.4 MPa), making it easier to establish suitable SCF conditions. Additionally, CO_2 is non-flammable, non-toxic, reusable, cost-effective, and environmentally friendly[42-44].

A schematic for the selection of an appropriate SCF-based process for ASD preparation is shown in **Fig. 6**[45].

Advantages of SCF-Based Methods:

1. Eco-Friendly – These methods are considered greener compared to conventional solvent evaporation techniques.
2. Cost-Effective – Lower production costs make them more economical.
3. Controlled Solvent Evaporation – Temperature and pressure adjustments allow better control over the process.
4. High Diffusivity – The low viscosity of SCFs enhances diffusivity.
5. Rapid Solvent Evaporation – Leads to faster processing and higher yields[46].

Drawbacks of SCF-Based Methods:

1. Residual Solvent Removal – It can be challenging to eliminate residual organic solvents when used.
2. High Initial Investment – Requires significant capital investment for setup[42].

3.2.1.5 Spray-Freeze-Drying (SFD) for ASD Preparation

Spray-freeze-drying (SFD) is a cryogenic technology used to produce amorphous solid dispersions (ASDs) **Fig. 7.** The process involves atomizing a drug-polymer solution into a cryogenic liquid, freezing the droplets, and then freeze-drying them to create a porous, flowable powder.

Advantages:

- Produces amorphous, porous powders with high surface area and enhanced dissolution rates.
- Offers better particle size control, higher excipient compatibility, and reduced thermal stress compared to spray drying.
- Achieves higher yield and better bioavailability of poorly soluble drugs (e.g., carbamazepine, danazol, baicalein).[47-50]

Considerations:

- Requires low organic solvent content due to freeze-drying limitations.
- The porous, low-density nature of the powder may cause fragility, posing challenges for secondary processing.[51,47]

3.2.2 Melting-Based Methods

Melting-based methods involve heating formulation components to create dispersions, followed by a cooling process. One of the key advantages of these techniques is the elimination of solvents, making them a cleaner and more environmentally friendly approach. However, these methods also present challenges:

- Potential Drug Degradation: Exposure to high temperatures can lead to thermal degradation of the drug.
- Solubility/Miscibility Constraints: Successful dispersion requires adequate solubility or miscibility of the drug in the polymer melt, which may be difficult to achieve for certain compounds.

Despite these limitations, melting-based methods remain widely used for drug formulation due to their solvent-free nature[52].

3.2.2.1 Hot-melt extrusion (HME)

Hot-melt extrusion (HME) is a well-established melting technique that has garnered significant interest in the manufacturing of amorphous solid dispersions (ASDs) [53]. Compared to solvent-based methods, HME offers the advantage of being a solvent-free process [50], making it a more environmentally friendly, "green" technology with reduced safety and ecological concerns. Additionally, HME enables the continuous production of ASDs, facilitating large-scale manufacturing.

More recently, the nanoextrusion process has emerged as an advanced technique for incorporating drug nanoparticles into polymeric carriers using conventional HME equipment [54,52]. Li et al. employed the nanoextrusion method to develop griseofulvin nanocomposites. Initially, a nanocrystal suspension was created through wet milling with the stabilizers hydroxypropyl cellulose (HPC) and Soluplus®. This drug suspension was then used as a feed in the nanoextrusion process, combined with additional polymer (HPC/Soluplus®) to effectively disperse drug nanoparticles within the polymeric matrix, ultimately forming nanocomposite extrudates[54].

3.2.2.2. Kinetisol® Technology in Pharmaceutical Processing

Kinetisol® is an advanced fusion-based technology adapted from the plastics industry to enhance the solubility of poorly soluble active pharmaceutical ingredients (APIs). This innovative process uses frictional and shear energies to rapidly transition drug-polymer blends into a molten state, ensuring thorough molecular-level mixing to form a single-phase amorphous solid dispersion (ASD).

Key Features of Kinetisol® Technology

1. **Mechanism of Action**

- Friction and shear forces generate heat, melting the drug-polymer blend.
- API and excipients mix thoroughly at a molecular level to achieve ASD formation[55].

2. **Polymer Compatibility**

- Commonly used polymers include Carbopol, Eudragit, HPMC, HPMCAS, co-povidone, PVA, PVP, and Soluplus®.

3. **Processing Steps**

- Blending: Powdered API and polymer blend is loaded into a sealed chamber.
- Heating & Melting: Blade rotation generates heat through friction, converting the blend into a molten mass.
- Quenching & Solidification: The molten mass is ejected into a quenching zone, forming amorphous flat disks.
- Milling: The solidified disks are milled into fine granules of the desired size.
- Final Drug Product: Granules are either compressed into tablets or filled into capsules[56].

4. **Processing Efficiency**

- Total processing time within the chamber is under 20 seconds.
- Elevated temperatures are sustained for less than 5 seconds before discharge and cooling.

5. **Advantages**

- Operates without heating elements, allowing processing below the melting point of APIs, beneficial for thermolabile drugs.
- No torque limitations, enabling the processing of high molecular weight and high-melting-point compounds.
- Suitable for both batch (lab-scale) and semi-continuous (commercial) operations.
- High product throughput, reaching up to 1000 kg/h in commercial settings.

This technology provides a rapid, efficient, and solvent-free approach to improving the bioavailability of poorly soluble drugs while maintaining the integrity of thermosensitive compounds [57].

3.2.2.3. Three-dimensional (3D) printing

Three-dimensional (3D) printing is an advanced technology that converts digital 3D models into physical objects through additive manufacturing . It is also among the fastest-growing technologies in pharmaceutical manufacturing [58].

In pharmaceutical applications, 3D printing is frequently combined with hot melt extrusion (HME) to produce amorphous solid dispersions (ASD). For successful processing, the polymer must exhibit both stability and appropriate viscosity [7]. Several carrier materials suitable for 3D printing have been identified in the literature, including polyvinyl alcohol (PVA), poly(lactic acid) (PLA), Eudragit® E PO, and Soluplus® [7,58,59].

There are several techniques and variations in 3DP, such as material jetting, binder jetting, and material extrusion. The most widely used technology in the pharmaceutical sector is material extrusion and fused deposition modeling (FDM).

It is a technique to manufacture customized medicines for patients by delivering multiple drugs with varying print settings, allowing for better control over the drug dissolution kinetics[59].These novel, single-step technologies could be advantageous for the preparation of ASDs for preclinical studies where the quantity of drugs is limited or the use of traditional HME is challenging.

3.2.2.4. Microwave Heating in In Situ Amorphization

Microwave-induced in situ amorphization is a novel approach where crystalline drugs within the final dosage form are amorphized using microwave heating. Studies have demonstrated its feasibility, such as Doreth et al.'s work on indomethacin-PVP ASDs, which showed no drug degradation and a six fold increase in dissolution rate[60].

The process involves three main steps:

1. Preparing the drug-polymer mixture
2. Inducing amorphization through microwave heating
3. Cooling, with possible further processing.

Successful amorphization depends on optimizing formulations where drugs have high solubility in the polymer, and polymers melt at low temperatures. PVP K12 has been the primary polymer studied, but further research is needed to identify more suitable carriers.[61]

Since polymers and drugs weakly absorb microwaves, two heating techniques are used:

(1) convective heating via a microwave-absorbing reactor or sample holder and[62]

(2) using microwave-absorbing solvents, which evaporate upon heating. The heating time is typically under 15 minutes, minimizing drug degradation.[63]

A key advantage is the ability to amorphize drugs directly within the final dosage form without additional processing. However, absorbed moisture can influence amorphization and potentially lead to hydrolysis. More systematic studies are required to assess drug stability during and after microwave-induced amorphization[62].

3.3 Characterization of ASD

A comprehensive understanding of the recrystallization process in ASD is essential for evaluating its characterization and stability. Quality by Design principles emphasize the need for an in-depth understanding of molecular and particle-level processes. Since no single characterization technique can provide a complete picture of ASD, various methods have been explored[20]. A selection of key studies is summarized in **Table 3**.

3.4 Stability of amorphous solid dispersion

Amorphous solids exhibit short-range molecular arrangement compared to crystalline solids, which possess a well-defined three-dimensional structure. Despite this, amorphous solids offer significant pharmaceutical advantages, including enhanced solubility and higher kinetic solubility compared to their crystalline counterparts. In vivo, a well-developed amorphous system can maintain a supersaturated state, thereby improving drug exposure[9].

However, a major challenge associated with amorphous solid dispersions (ASD) is their poor physical and chemical stability, which poses significant obstacles to commercialization.

The primary reasons for this instability include:

1. Limited availability of reliable technologies for predicting formulation stability.
2. Incomplete understanding of the physicochemical properties of active pharmaceutical ingredients (API), excipients, and polymers.
3. Insufficient technological advancements in manufacturing processes.

To mitigate the risks of physical instability, these factors must be carefully considered. Several approaches have been developed to analyze the mechanistic insights and instability of ASD prepared by various techniques. Traditionally, stability prediction is conducted under stress conditions following ICH guidelines. Long-term stability studies provide a comprehensive understanding of the solid-state properties and the physical and chemical integrity of ASD formulations. **Table 4**[7]

According to ICH Q1 guidelines, standard stress conditions include storage at 2–8 °C (refrigerated), 25 °C/60% RH, 30 °C/65% RH, 30 °C/75% RH, and 40 °C/75% RH, with evaluation time points ranging from one day to six months or up to two years. At each interval, the samples undergo analysis using techniques such as X-ray Powder Diffraction (XRPD), Differential Scanning Calorimetry (DSC), and Fourier-Transform Infrared Spectroscopy (FTIR). During the late stages of drug development, long-term stability studies extending over several years are conducted using PXRD or DSC to determine the final shelf life of the formulation.[24]

4. CONCLUSION

Enhancing the solubility of poorly water-soluble drugs is crucial for improving their bioavailability and therapeutic efficacy. Among various solubility enhancement methods, amorphous solid dispersions (ASDs) have proven to be a highly effective approach. The selection of an appropriate polymer and manufacturing technique plays a vital role in stabilizing the amorphous state and preventing recrystallization. While ASDs offer significant advantages, challenges such as long-term stability and scale-up persist. Continued research in formulation strategies, polymer chemistry, and advanced processing techniques will be essential in overcoming these limitations. The development of innovative ASD-based drug delivery systems is expected to enhance patient compliance and optimize therapeutic outcomes in the pharmaceutical industry.

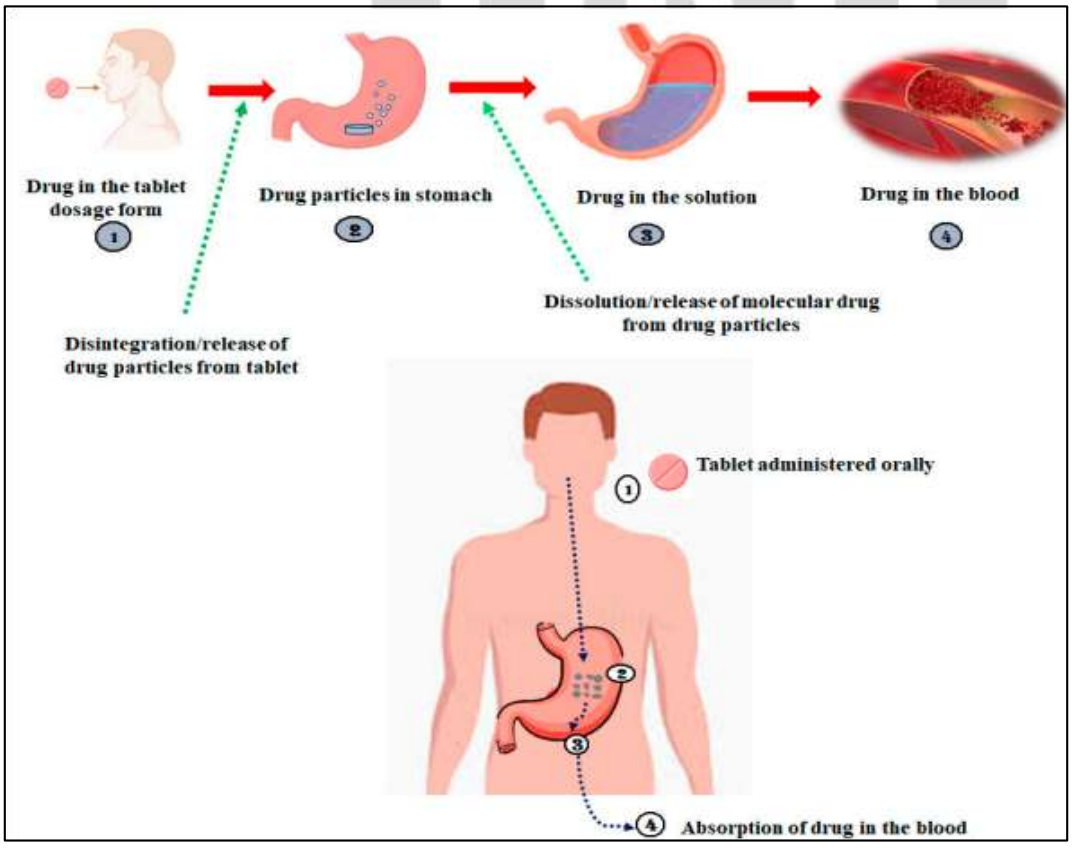

Figure 1 : Fate of drug molecule after administering via oral route[3].

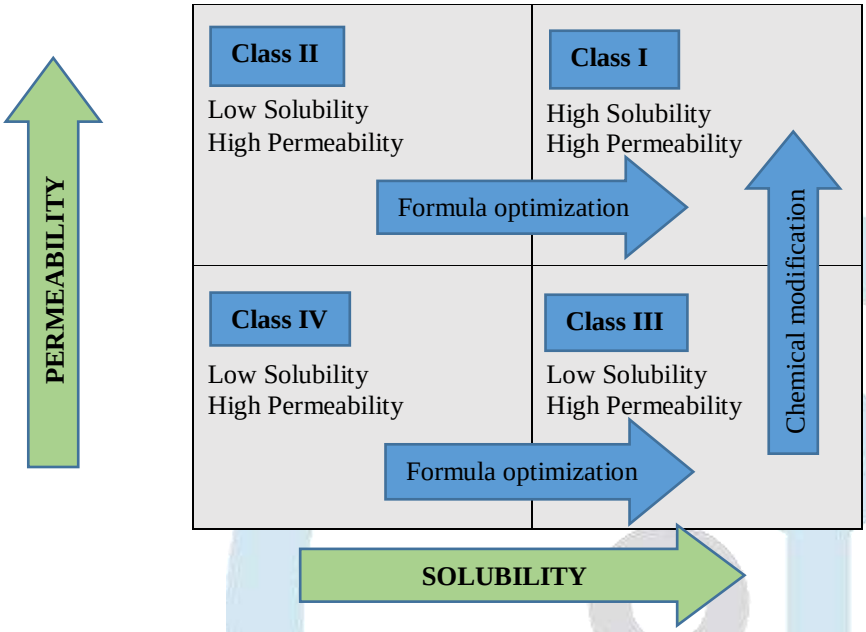

Figure 2 : Biopharmaceutical classification system[1]

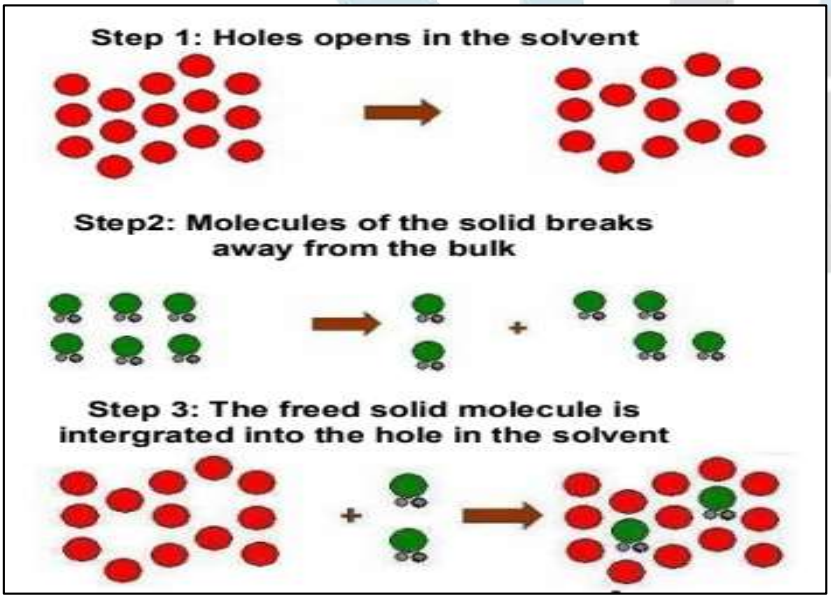

Figure 3: Process of Solublisation[5]

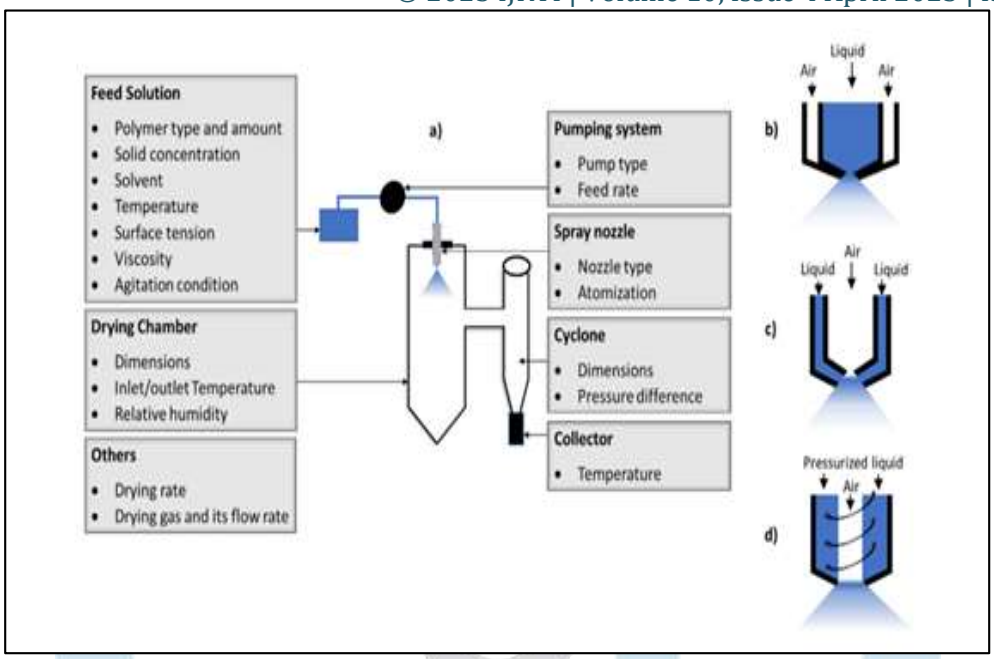

Figure 4 : A schematic of (a) spray dryer set-up and the manufacturing variables affecting product properties and performance; (b) external mixing two-fluid nozzle; (c) internal mixing two-fluid nozzle; (d) pressure-swirl nozzle[31]

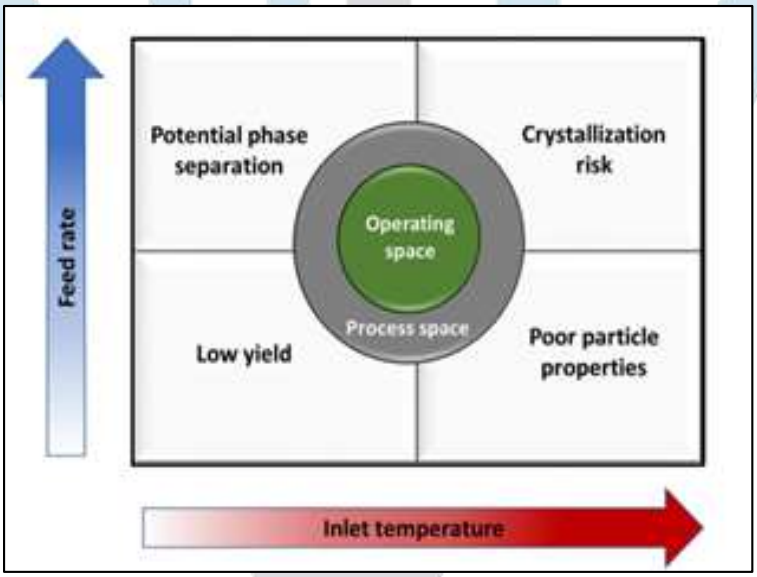

Figure 5 : Spray drying design space for generating stable ASDs[32]

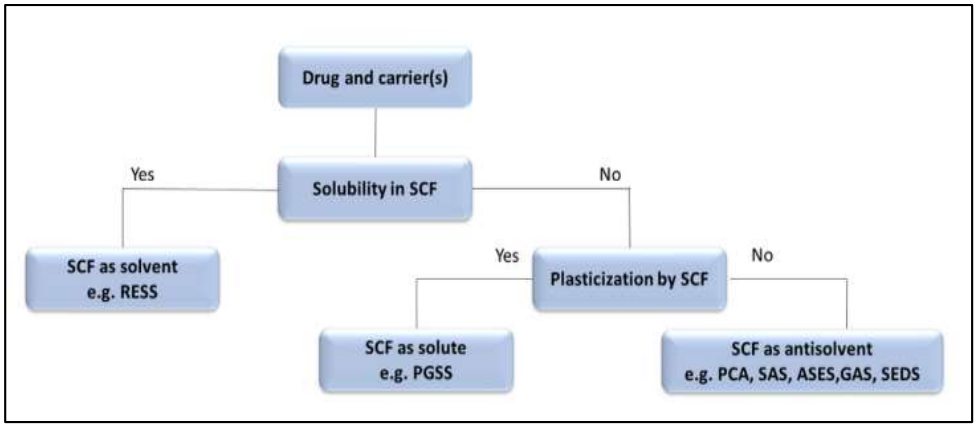

Figure 6 : Schematic for selection of SCF-based process for ASD preparation.

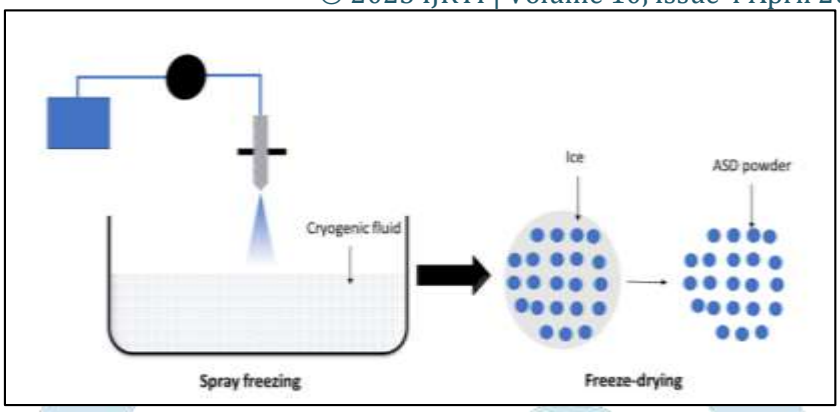

Figure 7 : Preparation of ASDs by spray-freeze-drying. The feed solution is atomized and sprayed directly into a cryogenic liquid and the frozen particles are subsequently transferred to a freeze-dryer to generate dried ASD powder.

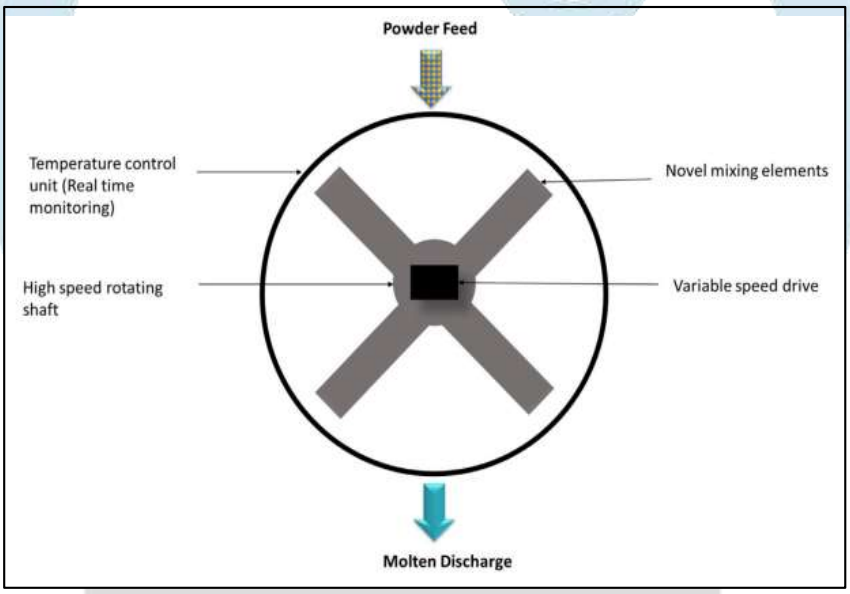

Figure 8 : Schematic of KinetiSol technology. Mechanical forces involved in the process result in a rapid temperature increase. This creates a molten mass which is immediately quenched to generate ASDs.

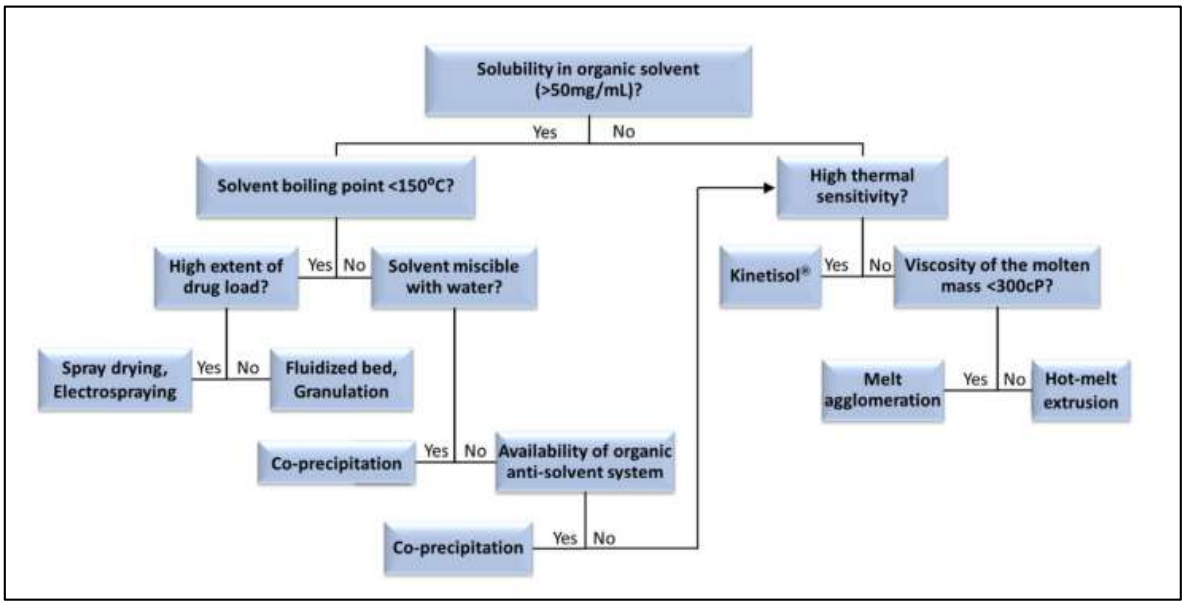

Figure 9 : A method selection decision tree with the commonly used manufacturing processes for preparing ASDs

Definition	Parts of solvent required for one part of solute	Solubility range (ml/ml)	Solubility assign (mg/ml)
Very soluble	Less than 1	Greater than 1000	1000
Freely soluble	From 1-10	100 - 1000	100
Soluble	From 10 -30	33 - 100	33
Sparingly soluble	From 30-100	10 - 33	10
Slightly soluble	From 100-1000	1 - 10	1
Very slightly soluble	From 1000 -10,000	0.1 – 1	0.1
Insoluble	Greater than 10,000	< 0.1	0.01

Table1: Descriptive terms for Solubility and their values as per USP[1]

Polymers	Tg (°C)	Solubility in solvents
Hydroxypropyl methylcellulose	175-185	Water, ethanol : dichloromethane (1:1, 2:1), methyl acetate : methanol (1:1)
Hydroxypropyl methylcellulose acetate succinate	100-110	Caustic water, acetone, methanol, dichloromethane, chloroform
Hydroxypropyl methylcellulose phthalate	133-137	Water, acetone, ethyl acetate, methyl ethyl ketone, ethanol : dichloromethane(1:1), methanol, dichloromethane, tetrahydrofuran
Polyvinylpyrrolidone	175-180	Water, acetone, ethanol, methanol, ethyl acetate, methyl ethyl ketone, dichloromethane, tetrahydrofuran
Polyvinylpyrrolidone/vinyl acetate	70-110	Water, acetone, ethanol, methanol, ethylacetate, methyl ethyl ketone, dichloromethane, tetrahydrofuran
Polymethacrylates derivatives (Eudragit-L100, S100)	>150	Water (only L100), acetone, ethanol, methanol, ethanol: dichloromethane (1:1)
Cellulose acetate phthalate	160-170	Acetone, ethyl acetate, methyl ethyl ketone
Solplus		water, acetone, ethanol, methanol, dichloromethane

Table 2 : Commonly used polymers for ASD preparation[7]

Table 3 : Characterization of amorphous solid dispersion

Techniques	Principle	Advantage	Limitations	Ref. No.
Thermal/ Calorimetric Analysis Differential scanning calorimetry	When a sample undergoes a physical transformation, like a phase transition, more or less heat will need to flow to it than the reference material to maintain both at the same temperature.	Suitable to measure melting, Experimental settings are simple and easily manageable	Less sensitive to heat capacity measurement	[64]
Modulated Differential scanning calorimetry	Uses two simultaneous heating rates - a linear heating rate that provides information similar to standard DSC, and a sinusoidal or modulated heating rate that permits the simultaneous measurement of the sample's heat capacity	Complex and overlapping of thermal events are differentiated, Study of phase separation, accurate quantification of amorphous phase	Strongly conditions dependent, Melting: Interpretation is abstruse, measurement is not precise	[65]
Dynamic mechanical thermal analysis	Measurement of resultant strain that comes from the applied oscillatory stress, and it builds a function of the strain determined versus frequency or temperature	Non sample destructive technique, viscoelastic properties of polymers are fetched by time-efficient technique	Not suitable for characterizing the low viscous materials, poor stress control capacity	[66]
Isothermal micro calorimetry	The constant assessment of the heat out flow and cumulative amount of heat consumed or produced at quite constant temperature by an instance	Highly sensitive, shelf life and non-destructive process	Tedious process takes hours to days to evaluate	[67]
Spectroscopic techniques Solid state Nuclear Magnetic Resonance	The excitation of nuclei when bombarded with pulses of broad radio frequency radiation induces spin in nuclei and when nuclei relaxes back to their equilibrium states the free induction decay results or produced as response.	Non-destructive, Minimal sample manipulation, Small sample size, Simple sample preparation	Non-destructive, Minimal sample manipulation, Small sample size, Simple sample preparation	[25]
Fourier transform Infrared technique	The chemical bonds and functional groups of a sample at atomic level undergoes constant rate of vibration. When IR with continuous wavelength strikes the sample, a particular wave number is absorbed by a specific bond and functional group of the sample and absorbed spectrum is produced by the detector.	Quantitative analysis, applied for all states of the matter, Nondestructive and Small sample size	less accurate results and moisture presence may give inaccurate results	[26]
Raman spectroscopy	It is based on Raman effect: the inelastic collisions of sample molecules when interacts with monochromatic laser beam generates the scattered light which is responsible for the construction of Raman spectrum.	Quantitative analysis, Nondestructive and Small sample size, not interfered by water, highly specific like a chemical fingerprint of a material.	The Raman effect is very weak. The detection needs a sensitive and highly optimized instrumentation; sample heating through the intense laser radiation can destroy the sample or cover the Raman spectrum.	[27]

Microscopic and macroscopical techniques X-ray Powder Diffraction	The filtered and collimated rays of cathode ray tube are directed towards the sample which produces constructive interference and diffracted rays which satisfies $n\lambda = 2d \sin\theta$ (Bragg's law).	Determine crystallinity of the compound, Best method for phase analysis, non-destructive	Less interaction with lighter elements, Relatively less sensitivity	[28]
Scanning electron microscopy	Accelerated electrons in an SEM carry significant amounts of kinetic energy, and this energy is dissipated as a variety of signals produced by electron-sample interactions when the incident electrons are decelerated in the solid sample.	Three-dimensional and topographical imaging consumes less time to complete SEI, BSE and EDS analyses.	Expensive, large and must be housed in an area free of any possible electric, magnetic or vibration interference	[30]
Polarized light microscopy	When polarized light hits the double refracting sample and produces ordinary and extraordinary light rays perpendicular to each other. These rays are combined using constructive and destructive interference through analyzer to produce high contrast image.	Non-destructive, easy to operate and reproducible	It is not suitable for agglomerates; sample recovery is little tedious	[29]
AFM	It works in three steps surface sensing, detecting and imaging, using a sharp tip cantilever to scan over the surface of a sample. The attractive and repulsive forces between the tip and the surface cause the cantilever to deflect towards or away from the surface respectively. Any of these slight deflections of cantilever are traced by deflections of laser beam which mounted on the cantilever are recorded by position sensitive photo diode and generates accurate tonographic image.	Highest lateral resolution up to 1 nm, it can identify the repeated lattices on crystal structure and good comprehensive understanding	Expensive, relatively slow scan time, which can lead to thermal drift on the sample	[68]

Table 4 : General factors impacting the stability of amorphous solid dispersions.

Factor (increase)	Stability	Cause
Glass transition temperature (Tg)	Increases	Antiplasticization effect by polymers
Molecular mobility	Decreases	Molecular mobility is directly responsible for drug recrystallization
Configurational entropy	Increases	Low configurational entropy will favor crystallization
Configurational enthalpy	Decreases	The greater thermodynamic driving force for crystallization causes an increased rate of nucleation
Drug chemical potential	Decreases	Systems with lower drug chemical potential are generally more stable
Humidity, mechanical stress, and temperature	Decreases	These factors can significantly increase molecular mobility and may plasticize the material
Polymer concentration	Increases	Kinetic stabilization
Surfactant concentration	Decreases	Enhance nucleation, accelerate solution mediated crystallization

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