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Review Article

Advances in Solid Dispersion Technology: Method-Dependent Solubility Enhancement Approaches

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A B S T R A C T

Solid dispersion technology is widely recognized as an effective approach for enhancing the solubility and oral bioavailability of poorly water-soluble drugs. A large number of newly developed pharmaceutical compounds belong to Biopharmaceutics Classification System (BCS) Class II and IV categories, where poor aqueous solubility limits dissolution and gastrointestinal absorption, resulting in reduced therapeutic efficacy. Solid dispersions improve drug dissolution through mechanisms such as particle size reduction, enhanced wettability, amorphization, reduced crystallinity, and increased surface area. This review highlights the fundamental concepts, mechanisms, classification, carriers, preparation methods, characterization techniques, recent advances, applications, and future prospects of solid dispersion technology. Various hydrophilic carriers including polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and Soluplus® are extensively used to enhance dissolution behavior and maintain supersaturation. Conventional techniques such as fusion and solvent evaporation, along with advanced technologies including hot-melt extrusion, spray drying, freeze drying, electrospinning, and supercritical fluid processing, are discussed in terms of their advantages, limitations, and industrial applicability. Recent innovations such as ternary solid dispersions, nanostructured systems, lipid-based formulations, artificial intelligence-assisted optimization, and continuous manufacturing have significantly improved formulation efficiency and scalability. Commercially available products demonstrate the successful industrial application of solid dispersions in oral drug delivery. However, challenges including physical instability, recrystallization, moisture sensitivity, and scale-up difficulties continue to affect formulation development. Future advancements in smart polymers, green manufacturing technologies, and personalized medicine are expected to further expand the potential of solid dispersion systems in modern pharmaceutical research and industry.

Keywords: Solid dispersion, solubility enhancement, bioavailability, amorphous systems, hot-melt extrusion, spray drying,

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INTRODUCTION

The first problem that can be noted in modern pharmaceutical formulation is a lack of aqueous solubility. Around 40% to 70% of recently found compounds and nearly 90% of those in the developmental stage have low aqueous solubility, which affects their ability to dissolve and get orally absorbed [1,2]. Compounds with poor aqueous solubility typically fall under either BCS Class II or BCS Class IV drugs, where the limiting factor in the absorption process is dissolution [3]. Poor dissolution can lead to low bioavailability, altered pharmacokinetics, delayed action, and low efficiency of treatment [4].

The oral route of drug administration continues to be the most favored one due to its ease of administration, patient compliance, economical nature, and versatility of dosage form development [5]. Nevertheless, the oral delivery of hydrophobic drugs often suffers from poor gastrointestinal dissolution rates and absorption profiles [6]. Several methods have been explored to tackle the issues including particle size reduction, micronization, salt formation, inclusion complex formation, use of lipids and nanoparticles, and solid dispersion formulations [7]. Solid dispersion formulation technique has been regarded as one of the most efficient methods for enhancing the dissolution properties of hydrophobic drugs [8].

A solid dispersion can be described as the molecular dispersion of one or more drug substances into a carrier matrix in a solid form [9]. In such systems, the drug can be present in crystalline, amorphous, or molecular form depending on the preparation technique and the properties of the matrix [10]. The use of hydrophilic polymers and surfactants as carriers has been common to increase the wettability, minimize aggregation, increase surface area, and reduce the degree of crystallinity of the drug substances [11]. All these alterations contribute significantly to the increase in dissolution rate and saturation solubility of insoluble drugs [12]. Amorphization of the drug in the carrier matrix is regarded as one of the main ways by which solid dispersion increases the release rate of a drug substance [13].

The demand for solubility enhancement techniques has been significantly amplified due to advances in combinatorial chemistry and high throughput screening methods, which commonly produce very hydrophobic drug molecules [14]. While these drugs might have excellent pharmacodynamic properties, their therapeutic efficacy is often hindered by low solubility and dissolution rates [15]. Other problems associated with poorly water-soluble drugs include food effect, dose dependency, poor wetting ability, incomplete absorption in the GI tract, and susceptibility to degradation during the production and storage processes [16]. This could lead to an increase in the drug dose required to attain therapeutic levels in plasma, thus risking toxicity [17].

The solid dispersion technique has made a significant contribution towards increasing the oral bioavailability of medications by virtue of their increased dissolution properties [18]. The faster dissolution property of the drug attained using solid dispersions can be attributed to smaller particle sizes, better wettability, greater porosity, molecular dispersion of drug particles, and lower crystallinity [19]. Moreover, amorphous solid dispersions can achieve supersaturation of drug concentration in gastrointestinal fluids, thus allowing for better absorption of the drug [20]. A number of poorly soluble drugs, including itraconazole, celecoxib, curcumin, fenofibrate, and ritonavir, have shown increased bioavailability due to solid dispersion systems [21].

Solid dispersion technology was originally coined in 1961 by Sekiguchi and Obi who developed eutectic blends of sulfathiazole and urea to enhance the dissolution of poorly water-soluble drugs [22]. It was in this early research that the basis of solid dispersions was laid. The initial generation of solid dispersions made use of crystalline carriers such as sugars and urea but subsequent generations of solid dispersions utilized amorphous carriers such as polymers as well as surfactants that offered enhanced dissolution and physical stability [23]. Continuous developments in the field of polymer chemistry and pharmaceutical engineering contributed to the emergence of innovative preparation methods of solid dispersions, which include hot melt extrusion, spray drying, freeze drying, electro spinning, supercritical fluid technology, and KinetiSol® technology [24, 25].

The recent developments in solid dispersion technology include enhancing physical stability, avoiding drug recrystallization, and scaling up production [26]. The emerging techniques for solid dispersions, including ternary solid dispersions, nano-solid dispersions, lipid solid dispersions, and machine learning algorithms for optimizing formulations, are attracting considerable interest in pharmaceutical science [27]. Moreover, the use of continuous processing methods and innovative carriers is further increasing the commercial viability of solid dispersion formulations [28]. Solid dispersion systems remain an essential part of contemporary oral dosage forms owing to their capability to overcome solubility issues [29].

Biopharmaceutical Background of Poor Solubility

Biopharmaceutical Classification System (BCS)

Biopharmaceutical Classification System (BCS) is a scientific system used for categorizing drug substances based on the aqueous solubility and intestinal permeability profiles. BCS has been proposed by Gordon L. Amidon and coworkers for predicting oral drug absorption and formulation design of drug products [1-5]. BCS classifies drugs into four classes: Class I drugs are highly soluble and highly permeable; Class II drugs are poorly soluble but highly permeable; Class III drugs are highly soluble but poorly permeable; while Class IV drugs are both poorly soluble and poorly permeable [1,2]. However, it should be noted that BCS Classes II and IV pose serious formulation difficulties due to the low aqueous solubility resulting in poor dissolution and absorption [3]. Many new drug products are members of BCS Class II because of their highly hydrophobic and lipophilic nature [4]. Hence, BCS classification becomes essential for selecting suitable solubility enhancement strategies and predicting drug behavior in vivo [5].

Impact of Poor Solubility on Absorption and Bioavailability

Low aqueous solubility greatly influences the absorption and bioavailability of drug substances when administrated orally. Any drug administrated orally needs to be dissolved in digestive fluids in order to pass through biological membranes and enter the systemic circulation [6-10]. For poorly soluble drug substances, slow dissolution results in insufficient amount of the drug substance available for absorption, thus limiting the degree and rate of absorption [6]. Poorly soluble drugs may display limited and varying bioavailability, prolonged time of onset, absorption depending on food intake, and unpredictable pharmacological effect [7]. High doses of drugs need to be taken in order to achieve adequate drug levels in the bloodstream, increasing the possibility of developing side effects [8]. Some new pharmaceutical drug molecules synthesized using combinatorial chemistry have high lipophilicity and low aqueous solubility; hence it is necessary to enhance the solubility of such drug substances [9,10].

Dissolution Rate Limitations

The process of dissolution is regarded as an essential phase in regulating oral drug absorption of lipophilic compounds. Based on the dissolution-rate controlled drug absorption principle, a drug will not absorb unless it dissolves in the body fluid [11-15]. Hence, drugs with low dissolution rates have low absorption and bioavailability properties [11]. Dissolution rate depends on the physicochemical factors of

particle size, surface area, wettability, diffusion constant, and saturation solubility [12]. The connection between dissolution rate and the above factors can be mathematically expressed using the Noyes-Whitney equation. According to the formula, dissolution rate increases with an increase in surface area and saturation solubility [13]. Lipophilic drugs in crystalline form may experience slow dissolution and poor surface wettability, resulting in low drug absorption [14]. For this reason, it is crucial to use formulation techniques that increase the dissolution rate in enhancing the effectiveness of BCS class II and IV drugs [15].

Factors Affecting Drug Solubility

The solubility of a drug can be affected by several physical and chemical parameters such as particle size, crystal habit, pH, temperature, lipophilicity, and wettability [16-20]. Smaller particles have more surfaces available for dissolution; hence, solubility increases [16]. Crystal form is another important factor since amorphous drugs are highly soluble compared to crystalline drugs due to higher free energy and molecular mobility [17]. pH of the dissolution medium affects the ionization process of weak acids and bases, thus affecting drug solubility [18]. Wettability refers to the ability of the dissolution medium to cover the drug's surface, whereas lipophilic substances are less soluble in water due to their hydrophobic nature [19,20].

Need for Advanced Formulation Strategies

An increase in the number of poorly soluble drugs has led to a need for novel formulation strategies that can improve dissolution and oral bioavailability [21–25]. Classical methods are sometimes inadequate in boosting the efficiency of hydrophobic drugs [21]. Modern drug formulation research has concentrated on developing novel strategies including solid dispersions, nanocrystals, lipids, self-emulsifying drug delivery systems, complexation, and amorphous drugs [22]. Among all these novel methods, the formation of solid dispersions is increasingly being used due to their ability to boost wetting, decrease crystallization, sustain supersaturation, and dissolution rates [23]. Cutting-edge technologies, including hot melt extrusion, spray drying, electrospinning, and supercritical fluid technology, have increased the industrial application of solubility boosting systems [24]. As a result, advanced formulation approaches are crucial for developing contemporary oral drug delivery systems and commercializing poorly soluble drug molecules [25].

Fundamentals and Mechanism of Solid Dispersion

Solid dispersion technique is considered one of the most efficient and well-studied methods for increasing the solubility, dissolution rate, and oral bioavailability of poorly water-soluble drugs [26–35]. A solid dispersion can be described as a solid-phase system wherein one or several active substances are incorporated into an inert hydrophilic polymer matrix [26]. Depending on the formulation method used as well as physical and chemical characteristics of the drug and carrier, the drug can be present in crystalline, amorphous, eutectic, or molecularly dispersed state within the matrix [27]. The fundamental idea of solid dispersion technology lies in the ability to increase the drug dissolution rate through improving its wettability, increasing its surface area, decreasing crystallinity, creating an amorphous state, and achieving molecular dispersion of hydrophobic drugs [28]. Hydrophilic polymers like PEG, PVP, HPMC, poloxamers, and Soluplus® have frequently been used as matrices due to high efficacy in dissolving and stabilizing poorly water-soluble drugs [29]. Solid dispersions provide great benefits for BCS Class II and IV drugs, in which dissolution is the limiting factor for absorption and bioavailability [30].

Drug–polymer interactions are key in influencing the stability, effectiveness, and dissolution characteristics of solid dispersions [31]. Drug–polymer interactions such as hydrogen bonds, Van der Waals interaction, ionic interaction, and hydrophobic interaction keep the drug stable in its amorphous form while preventing crystallization [32]. Hydrogen bonding of drugs to hydrophilic polymers decreases molecular mobility and increases the physical stability of the amorphous dispersions [33]. Some specific types of polymers like PVP and HPMC work well due to their ability to perform hydrogen bonding, making the mixture more soluble and maintaining supersaturation during dissolution [34]. Adequate miscibility of the drug with the polymer is required for proper dispersing of molecular drugs and dissolution, or otherwise there may be phase separation leading to recrystallization of the drug [35].

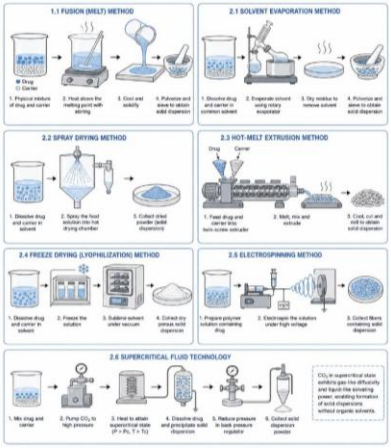

Figure 01: Mechanisms of Solubility Enhancement in Solid Dispersion Systems

There are a number of physicochemical processes that contribute to the increase in solubility and dissolution rate in solid dispersions. Among these, the most significant is the process of decreasing particle size [36]. The drug particles in the majority of cases are distributed on a colloidal or molecular level in solid dispersions, leading to fine particle sizes and increased surface area for dissolution [37]. This can be demonstrated by the Noyes Whitney equation:

$$\frac{dC}{dt} = \frac{DA(C_s - C)}{h}$$

Where:

$\frac{dC}{dt}$= dissolution rate

D= diffusion coefficient

A= surface area

C_s= saturation solubility

C= drug concentration in bulk solution

h= thickness of diffusion layer

Therefore, reduction in particle size greatly improves drug dissolution and absorption [38].

Wettability is another crucial factor responsible for the improvement of dissolution through solid dispersions [39]. Drugs having poor solubility usually have hydrophobic surfaces that are not easily wetted by the dissolution medium. The addition of hydrophilic carriers and surfactants in solid dispersions reduces the surface tension between the medium and drug particles, thus facilitating rapid diffusion of the medium into the drug particles [40]. This process increases the rate of drug dissolution and release. PEG, PVP, and HPMC are some examples of carriers that can easily absorb water.[41]

Amorphization has been recognized as one of the key factors that contribute to the increase in solubility of solid dispersion systems [42]. The reason behind the poor solubility and slow dissolution of crystalline compounds is that they have high Gibbs free energy and intermolecular interaction forces, which reduce their solubility and dissolution rates [43]. However, by making crystals amorphous, Gibbs free energy increases; hence, the rate of dissolution and solubility of amorphous systems is higher [44]. Being more thermodynamically active than crystalline form, amorphous systems dissolve quickly with enhanced bioavailability [45].

Lowering crystallinity is another factor responsible for enhancing the solubility profile of solid dispersions [46]. The tight packing of molecules in a crystalline form requires high energy to dissolve compared to partial crystalline and amorphous forms which have low lattice energy [47]. In a solid dispersion system, the presence of hydrophilic polymers prevents the formation of crystals and keeps the drug in a lower crystalline and amorphous form to enhance its solubility [48]. DSC and PXRD are standard techniques for evaluating lowered crystallinity and amorphization of the drug in solid dispersions [49].

An equally important approach would be the availability of greater surface area for dissolution [50]. Molecular dispersion along with the distribution of drug particles in polymer matrices results in an increase in the area of contact with the dissolution medium, leading to increased kinetics of dissolution. Moreover, porous systems developed by means of spray drying and freeze drying also ensure quick penetration of the dissolution medium and increased drug release [51]. Thus, through solid dispersion technique, several approaches are effectively combined.[52]

Classification of Solid Dispersions

Solid dispersion systems may be classified based on the nature of carriers used, molecular orientation of the drug molecules inside the carrier matrix, and degree of advancement of the formulation technology [36–45]. It is crucial to classify the solid dispersions owing to the differences in their physical and chemical behavior, dissolution rate, stability, and application in industry [36].

Classification Based on Carrier Type

Solid dispersions can be classified according to the nature of the carrier employed in the formulation system. The carrier significantly influences drug dissolution, wettability, stability, and release behavior [37].

Solid dispersions may be categorized on the basis of the carrier type used, namely crystalline carrier-based solid dispersions, polymeric carrier-based solid dispersions, and surfactant-based solid dispersions. One of the early types of carriers used in solid dispersions includes crystalline carriers like urea, mannitol, and sorbitol which help to increase drug dissolution by decreasing particle size and improving wettability [38,39]. Such dispersions have easy methods of preparation and good physical stability but have a very low solubility enhancement effect and are prone to phase separation [40]. Solid dispersions based on polymeric carriers are one of the most common techniques being used today in drug formulations because hydrophilic polymers like polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), Soluplus®, and poloxamers improve drug dissolution by increasing wettability, lowering crystallinity, maintaining the amorphous form of the drug, and creating supersaturation [41–43].However, these systems may be susceptible to moisture, may be physically unstable during storage, and might suffer from thermal degradation during processing [44]. Solid dispersions using surfactants contain surface-active agents like Tween 80, poloxamers, Cremophor®, and sodium lauryl sulfate, which help in lowering the interfacial tension, increasing wettability, enhancing dissolution rate, and preventing precipitation of the drug [45]. Despite the effectiveness of these systems in improving the dissolution of poorly soluble drugs, these systems have limitations due to their toxicity at high concentrations, hygroscopic nature, and instability over time [36]. Generally, the choice of carrier is dependent on the physicochemical properties of the drug, among other factors; however, polymeric carriers are the most commonly used because of their higher solubility and bioavailability [41-45].

Classification Based on Molecular Arrangement

Solid dispersions can also be classified according to molecular arrangement and physical state of drug within the carrier matrix [37].

Eutectic Mixtures

Eutectic systems consist of homogeneous systems made up of two crystalline substances that are perfectly soluble at the liquid phase but poorly soluble at the solid phase [38]. In the dissolution process, the dissolving agent will dissolve quickly to release fine drug particles that have more surface areas.

Solid Solutions

Solid solution is one of the examples of homogeneous solid-state dispersion wherein drug molecules are molecularly dispersed within the matrix of the carrier to form a one-phase system where there is uniform dispersion of the drug. Based on the degree of miscibility of the drug within the matrix, solid solutions can be categorized as either continuous or discontinuous. Due to the molecular dispersion of the drug, solid solutions offer increased solubility, wettability, and oral bioavailability relative to conventional preparations. The formation of solid solutions requires complicated preparation procedures, and there is a tendency for the amorphous form of the drug to recrystallize during storage [41].

Glass Solutions and Suspensions

Glass solution and glass suspension are both amorphous solid dispersion systems where the drug is dispersed into a glassy carrier matrix system. In glass solution, the drug molecules are dispersed in molecular form in an amorphous carrier while in glass suspension, fine dispersed particles of drug are dispersed in glassy carrier [42]. Amorphous nature of such systems improves the solubility and dissolution of drugs by avoiding crystalline lattice hence providing rapid drug release and supersaturation. However, one major disadvantage of glassy solid dispersions is that such formulations are thermodynamically unstable and very sensitive to moisture which causes recrystallization of the drug [43].

Generations of Solid Dispersions

Advancement in polymer science and formulation technologies has led to the development of different generations of solid dispersions [44].

Solid dispersions have undergone a development process in four stages depending on the carrier type and formulation approach. The first generation solid dispersion uses crystalline carriers such as urea and sugars and is made mostly as eutectic mixture with the help of fusion technique. The advantages of these systems include increased wettability of the drug and good physical stability, but they do not provide sufficient amorphization, dissolution enhancement, maintenance of supersaturation, and are prone to phase separation [45,36]. Second generation solid dispersions use amorphous hydrophilic polymers like polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), and hydroxypropyl methylcellulose (HPMC) that increase drug dissolution by changing crystalline structure of the drug into an amorphous one. These systems increase supersaturation, solubility, bioavailability, and industrial application of the system. However, these solid dispersions show moisture susceptibility and physical instability of amorphous phase during storage [37,38]. Third generation solid dispersions use surfactants or self-emulsifying carriers together with polymers that increase wettability, supersaturation, inhibit drug recrystallization, and increase dissolution rate. These systems demonstrate excellent dissolution enhancement, stability, and less precipitation tendency, but the formulations may be difficult to develop and surfactant toxicity is a problem [39,40].

The third generation of solid dispersions involves the use of surfactants or self-emulsifiable systems together with polymers, with the aim of improving wettability, supersaturation, inhibition of drug recrystallization and dissolution rate. The fourth generation of solid dispersions is currently being used as controlled or targeted drug delivery systems where solubility and modified drug release is achieved through the use of highly sophisticated polymers and new techniques of preparation [39,40]. These drugs have the ability to increase the efficacy of treatment, patient compliance and site-specific delivery but at a higher cost of production.[41,42].

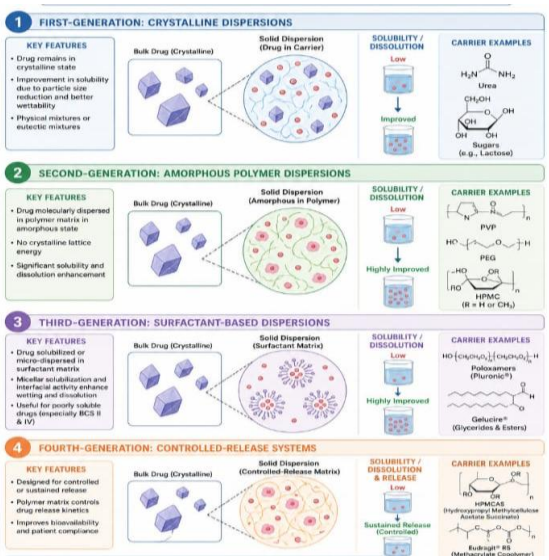

Figure 02: Classification and Generations of Solid Dispersions

Comparative Advantages and Limitations of Solid Dispersion Types

Type	Advantages	Limitations
Crystalline carrier systems	Good stability, simple preparation	Lower dissolution enhancement
Polymeric systems	Excellent solubility enhancement	Moisture sensitivity
Surfactant systems	Improved wettability and supersaturation	Stability and toxicity concerns
First generation	Physically stable	Limited amorphization
Second generation	High dissolution improvement	Recrystallization risk
Third generation	Better supersaturation maintenance	Complex formulation
Fourth generation	Controlled release and targeting	Expensive processing

Overall, classification of solid dispersions helps in selecting suitable carriers, preparation methods, and stabilization strategies according to physicochemical properties of the drug and desired therapeutic performance [43–45].

Carriers and Excipients Used in Solid Dispersion

Carriers and excipients have a significant influence on the properties of solid dispersion systems, including their performance, stability, dissolution profile, and bioavailability [46-55]. The choice of proper hydrophilic polymers, surfactants, and solubilizers is important for improving the drug delivery properties and maintaining drug supersaturation. Ideally, carriers should be highly soluble in water, thermally stable, non-toxic, easily miscible with the drug, and should inhibit drug recrystallization upon storage and dissolution [46]. Hydrophilic polymers are the most common type of materials used in current solid dispersion systems [47].

Hydrophilic Polymers Used in Solid Dispersions

Polyethylene Glycol (PEG)

One of the most commonly employed hydrophilic carriers in solid dispersion systems is polyethylene glycol (PEG), attributed to its high water solubility, biocompatibility, and low toxicity [48]. PEG exists in various molecular weights, usually from PEG 4000 to PEG 20000, and demonstrates good solvating ability and low melting point, thus being highly favorable for formation through such techniques as melt fusion and solvent evaporation [49]. Using PEG helps to improve dissolution due to its impact on the increase of wettability, decrease of particle agglomeration, and formation of uniform molecular dispersion within the carrier matrix, consequently increasing the rate and extent of drug absorption from the formulation [50]. However, there are some drawbacks of PEG-based solid dispersions that include hygroscopicity, thermal instability, and the risk of drug recrystallization or phase separation during storage [51].

Polyvinylpyrrolidone (PVP)

Polyvinylpyrrolidone (PVP) is a water-soluble synthetic polymer that has been widely utilized in amorphous solid dispersions due to its hydrogen bonding capability and good solubility characteristics [52]. The presence of PVP enhances the drug dissolution process by stabilizing it in an amorphous form and prevents the re-crystallization process [53]. Types of PVP include PVP K30 and PVP K90 and have been used mainly in spray drying and solvent evaporation methods. [54]

Hydroxypropyl Methylcellulose (HPMC)

HPMC (hydroxypropyl methylcellulose) is a partially synthesized polymer derived from cellulose that is commonly used as a matrix in solid dispersion systems [55]. The benefits of HPMC include enhanced solubility due to improved wettability, reduction in crystallinity, and maintenance of supersaturation while the drug is being released. Precipitation inhibition capacity of HPMC is high since it forms hydrogen bonds with the drug molecules [56][57].

Soluplus®

Soluplus® is a graft copolymer, which was specially designed for use in the field of solid dispersions and hot-melt extrusion [58]. It displays amphiphilic behavior that favors an increase in solubilizing and stabilizing capacities of hydrophobic drugs. It improves dissolution through its ability to form micelles and maintain supersaturation throughout dissolution. It has great miscibility with many drugs having poor solubility, thus making it an ideal option for amorphous solid dispersions [59].

Surfactants and Solubilizers

The addition of surfactant in solid dispersion is very common, since it improves the wettability, decreases interfacial tension, and increases dissolution rate of lipophilic drugs [46]. Moreover, surfactant helps in maintaining supersaturation of drug by preventing its precipitation.

Commonly used surfactants include:

- Tween 80
- Poloxamers
- Sodium lauryl sulfate (SLS)
- Cremophor® EL
- Span surfactants

Surfactants increase the drug release rate by enhancing the penetration of the dissolution medium through the drug particles as well as facilitating micellar solubilization [47]. Solid dispersion formulations of third generation generally involve the use of surfactants in addition to hydrophilic polymers for better dissolution enhancement and prevention of precipitation [48]. Cyclodextrins and other solubilizers like lipid based additives are used to enhance the solubility of lipophilic drugs [49].

Selection Criteria for Carriers

The selection of the appropriate carrier is considered to be one of the most crucial aspects of developing solid

dispersions [51]. This is because the carrier should have physicochemical characteristics that will enhance the solubility of the drug while retaining its stability.

Important selection criteria include:

The choice of a proper carrier is one of the crucial aspects of the development of solid dispersions, since it affects the drug's solubility, stability, and bioavailability. The optimal carrier should have sufficient aqueous solubility, thus increasing wettability and dissolution rate of hydrophobic drugs [52]. In addition, it should demonstrate sufficient thermal stability, thus being resistant to processing methods, including hot melt extrusion, and fusion processes [53]. Moreover, a proper drug-polymer interaction and miscibility is of great importance for the achievement of uniform molecular dispersion and for the prevention of phase separation [54]. It is important that the carrier should have a sufficiently high Tg value, which contributes to the stabilization of the amorphous state of the drug by decreasing the molecular mobility and preventing its crystallization process [55].

Role of Polymer–Drug Compatibility

Compatibility between the polymer and the drug has a significant effect on physical stability, solubility, and bioavailability of solid dispersion systems [47]. The interaction between the drug molecules and the polymers helps to stabilize the amorphous form and prevent recrystallization. Hydrogen bonding is one of the key interactions that help promote compatibility [48]. Hydrophilic polymers such as polyvinylpyrrolidone and hydroxypropyl methylcellulose have functional groups that help to develop hydrogen bonds with drug molecules [49].

The compatibility between drug and polymer is commonly evaluated using analytical techniques such as:

- Fourier-transform infrared spectroscopy (FTIR)
- Differential scanning calorimetry (DSC)
- Powder X-ray diffraction (PXRD)
- Raman spectroscopy [50]

Incompatibilities could cause phase separation, precipitation, and poor dissolution properties [51]. Hence, adequate knowledge about the interaction between the polymer and drug molecules is important for the successful formation of solid dispersions.

Method-Dependent Preparation Techniques

The mode of preparation is considered to be the most important factor which determines the physicochemical properties, dissolution profile, stability, and scale-up potential of solid dispersion systems [56–65]. The variation in the mode of preparation leads to the differences in the particle structure, crystalline nature, miscibility, and amorphous stabilization of the solid dispersion systems. The selection of the proper mode of preparation can depend on many physicochemical factors such as the drug-carrier compatibility, thermal stability, solvent affinity, dissolution profile, and manufacturing capability on the large scale [56].

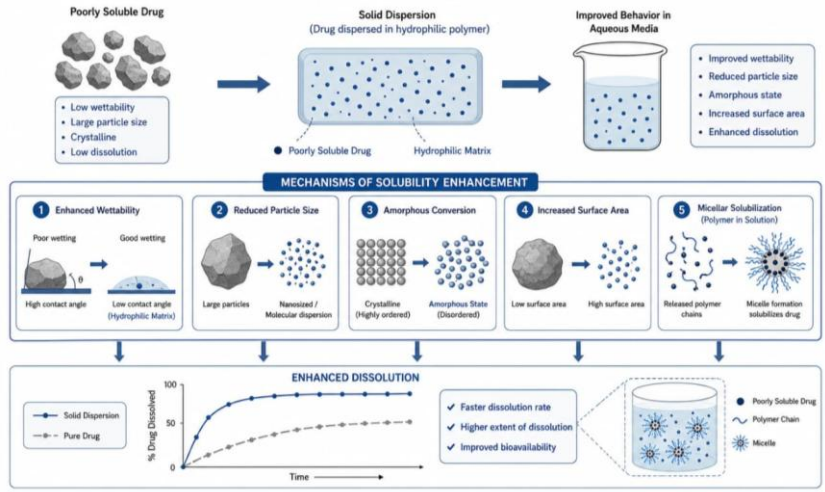

Figure 03: Conventional and Advanced Preparation Techniques of Solid Dispersions

Conventional Methods

Fusion/Melting Method

The fusion/melting technique is among the simplest and earliest techniques used to prepare solid dispersions [57]. Under this technique, the active ingredient and hydrophilic carriers are melted at temperatures above their respective melting points to form a homogeneous mixture [58]. After this step, the melt is cooled to solidify and the resulting mixture is then ground and sieved. Solid dispersions prepared via the fusion technique are characterized by enhanced dissolution rate owing to reduced crystallinity and formation of amorphous forms [59].

Solvent Evaporation Method

Solvent evaporation is a technique whereby both the drug and the carrier are mixed using a single volatile solvent and then subjected to evaporation under low pressure or heating. Solid dispersions are formed after removal of the solvent.

Common solvents include:

- Ethanol

- Methanol
- Acetone
- Dichloromethane

This method is particularly useful for thermolabile drugs because it avoids exposure to high temperatures [62].

Kneading Method

Kneading technique requires mixing the drug along with the polymer to create a paste-like consistency using minimal solvent and then proceeding further with the process of kneading, drying, and powdering. The hydrophilic polymer absorbs the solvent, allowing the drug to get uniformly distributed in the matrix.This method is commonly employed for cyclodextrin complexes and low-dose formulations.

Advanced Methods

Hot-Melt Extrusion (HME)

The hot melt extrusion technique is considered to be the most technologically and commercially advanced method of creating solid dispersion formulations [66]. This technique involves melting and blending of drugs with polymers using extrusion technology.

The process promotes molecular dispersion and amorphization of poorly soluble drugs within polymer matrices [67]. Common carriers include:

- Soluplus®
- HPMC
- PVP
- PEG

Spray Drying

Spray drying is a solvent-dependent method that is commonly employed in the development of amorphous solid dispersions [69]. The drug and polymer are dissolved in suitable volatile solvents and then converted to fine dry particles by spray drying.Dry particles produced by spray drying have high porosity and faster dissolution rate [70].

Freeze Drying (Lyophilization)

Freeze drying involves freezing a drug-polymer solution followed by sublimation of solvent under reduced pressure [72]. The process produces highly porous and amorphous structures with improved dissolution characteristics.

Supercritical Fluid Technology

Supercritical fluid technology employs supercritical CO2 as a solvent or nonsolvent in solid dispersion preparation [74]. This technique produces fine particles with uniform particle size distribution and enhanced solubility characteristics.

Electrospinning

Electrospinning is an advanced nanotechnology-based method used to prepare nanofibrous solid dispersions [76]. High voltage is applied to polymer-drug solutions to produce ultrafine fibers with extremely large surface area.

Microwave-Assisted Method

Microwave-assisted techniques utilize microwave energy to uniformly heat drug-polymer mixtures and facilitate molecular dispersion [78]. Microwave radiation accelerates solvent evaporation and promotes amorphization.

Comparative Analysis of Preparation Methods

Method	Advantages	Limitations	Industrial Applicability
Fusion/Melting	Simple, solvent-free	Thermal degradation	Widely used
Solvent Evaporation	Suitable for thermolabile drugs	Residual solvents	Moderate
Kneading	Economical	Poor scalability	Limited
Hot-Melt Extrusion	Continuous and scalable	High equipment cost	Excellent
Spray Drying	Excellent amorphization	Solvent concerns	Excellent
Freeze Drying	High porosity	Expensive and slow	Moderate
Supercritical Fluid	Eco-friendly	Complex processing	Emerging
Electrospinning	Nano-scale fibers	Scale-up issues	Research-focused
Microwave-Assisted	Fast and efficient	Uneven heating risk	Emerging

Generally, there is an increased preference for sophisticated technologies like hot-melt extrusion and spray drying for use in the pharmaceutical sector due to their excellent scalability, reproducibility, and stability of amorphous solid dispersion formed with higher bioavailability.

Characterization of Solid Dispersions

The characterization of solid dispersions is necessary in determining physicochemical properties, dissolution rate, amorphous stability, interactions between the drug and polymer, and other aspects regarding the performance of the solid dispersion system [81-90]. Characterization aids in understanding how effective the drug is in enhancing the solubility of the drug and ensuring consistency in its performance. Several techniques are used to characterize solid dispersion systems including analysis of drug content, crystallinity, etc.

Drug Content Analysis

The content analysis of the drug in the solid dispersion is done for quantifying the drug uniformly incorporated into the solid dispersion [82]. This helps in achieving uniform dosing and reproducibility of the formulation.

Generally, a weighed quantity of solid dispersion equivalent to a specific drug amount is dissolved in a suitable solvent and analyzed using:

- UV-visible spectrophotometry
- High-performance liquid chromatography (HPLC)
- Ultra-performance liquid chromatography (UPLC)

The percentage drug content is calculated using the following equation:

% Drug Content=Theoretical Drug Content / Practical Drug Content×100

Uniform drug distribution indicates successful preparation of the solid dispersion system [83].

Importance

- Confirms content uniformity
- Evaluates formulation reproducibility
- Detects drug loss during processing

Saturation Solubility Studies

Solubility increase by saturation solubility test is carried out to evaluate the improvement in apparent solubility achieved through the solid dispersion approach [85]. An excess quantity of the formulation is placed in the dissolution media, agitated until equilibrium is attained, filtered, and analyzed spectroscopically or chromatographically.

Common media used:

- Distilled water
- Simulated gastric fluid
- Phosphate buffer solutions

Enhanced saturation solubility indicates successful reduction in crystallinity and improved molecular dispersion of the drug [86].

Dissolution Testing

Dissolution testing determines the speed and extent of release of the drug from solid dispersions [88]. This test is among the most critical factors to determine the effectiveness of poorly water-soluble drugs since dissolution often limits oral absorption.

Common dissolution apparatus include:

- USP Type I (Basket apparatus)
- USP Type II (Paddle apparatus)

Dissolution studies are generally performed in simulated gastrointestinal fluids under controlled temperature and agitation conditions.

The percentage cumulative drug release is calculated as:

$$\%\ Cumulative\ Drug\ Release = \frac{Amount\ of\ Drug\ Released}{Total\ Drug\ Amount} \times 100$$

Solid dispersions generally exhibit significantly enhanced dissolution profiles compared to pure crystalline drugs because of improved wettability, reduced crystallinity, and increased surface area [89].

Thermal Analysis (Differential Scanning Calorimetry – DSC)

DSC technique is extensively utilized to study thermal behavior and crystallinity in solid dispersions [81]. The heat flows during phase transitions including melting, crystallization, and glass transition are measured using the DSC method.In solid dispersions, disappearance or reduction of drug melting endotherm indicates conversion of crystalline drug into amorphous form [82].

Parameters Evaluated

- Melting point
- Glass transition temperature (Tg)
- Crystallization behavior
- Drug-polymer miscibility

X-ray Diffraction (XRD)

The PXRD technique can be employed to determine the amorphous or crystalline nature of drugs in solid dispersion systems [84]. In crystalline substances, sharp diffraction peaks will be observed, while in amorphous systems, broad halos will be seen.The loss of sharp diffraction peaks suggests the amorphization of the drug [85].

Fourier Transform Infrared Spectroscopy (FTIR)

The Fourier Transform Infrared (FTIR) spectroscopy is one of the commonly employed techniques to study the interaction between molecules and to check the compatibility of drugs and polymers in solid dispersions [87]. The technique involves the measurement of absorption of infrared light by molecules or functional groups at certain specific frequency ranges, which result in distinct fingerprints for various chemicals. Any difference in peak positions, peak broadening, intensity change, and absence of distinctive absorption peaks would point to intermolecular interaction in the form of hydrogen bonds, ionic bonds, and van der Waals force interactions between the drug and polymer matrix. This method is quite important in terms of checking the compatibility of drug and polymer and for identifying the chemical stability of the formulations. However, this technique may have limitations in terms of overlapping absorption peaks and quantification [88].

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM)

SEM and TEM are commonly used methods for the characterization of morphology and structural characteristics of solid dispersion systems [89]. SEM makes it possible to obtain an image of the particle surface and analyze its size, roughness, porosity, and aggregate state. When compared to the corresponding crystalline drug, solid dispersions have an irregular and porous surface, which suggests lower crystallinity and better dispersion within the matrix. On the contrary, TEM allows visualizing the internal structure of particles, which makes it useful for the study of nanoscale solid dispersions and electrospun nanofibers [90]. These methods are critical for studying particle morphology, confirmation of particle size reduction, and analysis of structure changes affecting dissolution rate and bioavailability. Nonetheless, these techniques are not routinely used due to the high cost of the equipment,

complicated sample preparation, and sensitivity of some samples to vacuum.

Stability Studies

Stability studies form an integral part of the characterization of solid dispersions since they provide information on physical, chemical, and dissolution stability of the formulations while in storage [82]. Due to the fact that amorphous solid dispersions are thermodynamically unstable, there is always a tendency for them to undergo recrystallization over time, thus leading to potential changes in the solubility and dissolution characteristics of the drug. Hence, stability studies are routinely done according to ICH guidelines using controlled storage conditions such as 25°C ± 2°C/60% RH ± 5% RH (long term) and 40°C ± 2°C/75% RH ± 5% RH (accelerated). During the stability studies, key quality parameters such as drug content, dissolution profile, crystallinity, water uptake, and appearance are routinely monitored to determine formulation stability. Stability studies are vital in assessing the shelf life of the formulation, checking for recrystallization, and the stability of the formulation under varying conditions. However, they tend to be time-consuming, especially due to moisture sensitivity of amorphous systems.Overall, characterization techniques provide comprehensive understanding of the physicochemical behavior, stability, and dissolution enhancement mechanisms of solid dispersion systems, thereby supporting successful formulation development and industrial application [84–90].

Recent Advances in Solid Dispersion Technology

Modern developments in solid dispersion technology have brought about great success in increasing the solubility, dissolution speed, stability, and bioavailability of poorly water-soluble compounds [91-100]. Traditional binary solid dispersions may suffer from certain drawbacks like poor physical stability, precipitation, and limited supersaturation levels. However, by adopting more advanced drug formulations like ternary systems, nanodispersions, lipid carriers, pH-dependent formulations, artificial intelligence-driven optimization techniques, and continuous manufacturing methods, researchers are able to achieve promising results [91].

Ternary Solid Dispersions

Ternary solid dispersions represent novel drug delivery platforms that contain three ingredients, including the drug itself, a hydrophilic polymer, and a surfactant or stabilizer [92]. Introduction of a third component greatly contributes to an increase in the dissolution profile and physical stability in comparison with binary solid dispersions. In ternary drug delivery systems, the third excipient can serve as a surfactant, plasticizer, inhibitor of precipitation, or crystallization of the active compound. Among the ternary mixtures, the following systems should be mentioned: drug-PVP-poloxamer, drug-HPMC-Tween 80, drug-Soluplus®-surfactant. Performance enhancement in ternary solid dispersions is mainly caused by synergetic effects that include increasing wettability, amorphization of the active compound, maintenance of supersaturation and prevention of drug recrystallization during dissolution. The presence of surfactants in ternary dispersions helps decrease interfacial tension and achieves homogenous distribution of the drug in the carrier matrix [93]. Overall, ternary systems provide superior dissolution and supersaturation, physical stability, recrystallization prevention, and bioavailability. On the other hand, ternary systems face numerous difficulties including formulation optimization, increased excipient compatibility, and more complicated preparation process [94].

Nanostructured Solid Dispersions

Nanostructured solid dispersion technology refers to novel drug delivery techniques where the particles are reduced to a nanometer size level, increasing the surface area and rate of dissolution of the poorly soluble drugs [95]. The systems can be prepared using methods like electrospinning, spray drying, nanoprecipitation, and supercritical fluid technologies. By reducing the system to a nano-size level, the drug performance is improved by increasing the saturated solubility, surface area, cell permeability, and dissolution rate [96]. The most important among them are the nanofibrous solid dispersions prepared using electrospinning technology due to their fast dissolution rate due to their high porosity and nano-sized morphological structure.

Lipid-Based Solid Dispersions

Lipid solid dispersions are novel drug delivery systems based on the use of lipids, surfactants, and lipid carriers in order to improve the solubility and gastrointestinal absorption of lipophilic drugs [98]. In other words, this technique combines the strengths of solid dispersions and lipid-based drug delivery systems and therefore ensures increased efficiency of the system as a whole. Examples of the most widely used lipid carriers include glyceryl monostearate, Compritol®, Gelucire® and phospholipids. Lipid-based delivery systems have multiple mechanisms of improving the solubility and dissolution of the drug which include micellar solubilization, lymphatic transport enhancement, membrane permeability improvement, and decreased first pass effect [99]. Thus, lipid solid dispersions are especially promising for the delivery of lipophilic BCS Class II drugs. Advantages of these systems include increased absorption of lipophilic drugs, improved permeability, maintenance of supersaturation, and reduced gastric irritation. However, the disadvantages include such factors as oxidative instability of lipids, complicated formulations and increased cost of manufacturing [100].

pH-Modulated Systems

pH-sensitive solid dispersions represent a highly sophisticated strategy of formulation that aims at improving the drug dissolution through pH modification of the immediate environment of drug particles [91]. Such systems are particularly suitable for weak acids and bases, whose solubility is pH-dependent. Through the incorporation of pH modifiers, buffers, alkalizers, or acidifiers, the pH of the system is optimized to facilitate the ionization of the drug and its better dissolution. Such pH-modifying substances can include citric acid, tartaric acid, sodium bicarbonate, and sodium carbonate. Increased drug dissolution in such systems is explained by the Henderson–Hasselbalch equation. Through increased ionization of the drug, the dissolution rate and the degree of supersaturation are increased significantly. The principal benefits of pH-sensitive solid dispersions

include the improvement of dissolution of ionizable drugs, increase in the stability of supersaturation, and decreased variability associated with the changes of gastrointestinal pH. However, the limitations of such systems can include instability problems, pH-dependent crystallization, and irritative effects on the gastrointestinal tract caused by pH modification.[92]

Artificial Intelligence (AI) and Machine Learning in Formulation Optimization

Artificial Intelligence (AI) and Machine Learning (ML) represent effective approaches in pharmaceutical formulations, especially in optimizing solid dispersion systems [93]. AI and ML allow analyzing large and complex datasets in order to forecast optimal formulation parameters like choosing the right polymer, drug-polymer compatibility, processing, dissolving behavior, and stability. Machine Learning models can assist in making an experiment more effective through minimizing the trials and errors and speeding up the screening of formulation factors [94]. Different predictive modeling methods like Artificial Neural Networks (ANN), Support Vector Machines (SVM), and others are frequently used for optimizing amorphous solid dispersions and enhancing the robustness of formulations. AI-assisted formulation technologies can facilitate the whole development process through increasing efficiency, making process optimization easier, applying Quality by Design approach (QbD), and predicting scale-up better. The major benefits of using AI and ML methodologies include faster formulation development, cost reduction of experiments, better predictive capabilities, and better process control. But AI/ML applications have certain limitations connected with the need for a huge number of high-quality data, computational difficulties, and lack of pharmaceutical databases [95].

Continuous Manufacturing Approaches

Continuous manufacturing is a recently developed advanced pharmaceutical manufacturing technology in case of solid dispersion systems which provides a transition from batch production technologies to a non-stop manufacturing process with better process control and product consistency. There are several different techniques of making solid dispersions, but hot-melt extrusion technology is the most popular technique for obtaining such dispersions in a continuous manufacturing system. The use of Process Analytical Technology allows for real-time monitoring of the quality attributes such as temperature, drug content, moisture content, crystallinity and dissolution behavior, thus providing the product consistency during production. Continuous manufacturing provides a number of industrial benefits, such as reduction of production time, increased quality consistency, reduced cost of manufacturing, increased scalability and less material waste [98]. USFDA and ICH regulatory agencies actively promote the implementation of continuous manufacturing processes owing to their efficiency, quality and regulation benefits [99]. The main advantages of continuous manufacturing include high industrial scalability, high reproducibility, real-time quality monitoring and reduction of batch-to-batch variability. The major disadvantages of the method are high initial capital investments, complexity of the process validation procedure and need of advanced instrumentation and technical skills [100].

Applications and Marketed Products of Solid Dispersion Technology

Among several other techniques that have been developed to improve solubility, dissolution and bioavailability of the poorly soluble compounds, which account for 40-70% of new chemical entities [101-110], the use of solid dispersions represents one of the most successful methods. It is especially relevant for class II and class IV of BCS drugs, where dissolution and/or permeation play critical roles for drug effectiveness. For oral drug delivery, solid dispersions help to increase absorption of the active substance using different strategies: increased wettability, amorphization, decreased crystallinity, increased surface area, maintaining of supersaturated state. Thus, they can be widely used in the form of immediate release, controlled release systems, fast dissolving, capsules, pellets, orodispersible dosage forms and others.

The efficiency of solid dispersions is seen in different poorly water-soluble compounds. Solid dispersions of itraconazole based on HPMC and cyclodextrin increase the dissolution and bioavailability properties of the compound, while solid dispersions of celecoxib based on PVP and HPMC increase the bioavailability and the efficacy of the drug [101-107]. Similar results have been obtained for curcumin, where PEG and Soluplus® solid dispersions have improved the solubility and pharmacokinetics of the compound.

Solid dispersion technologies have also been successfully commercialized, such as Sporanox® (itraconazole), Kaletra® (lopinavir/ritonavir), Cesamet® (nabilone), Prograf® (tacrolimus), and Intelence® (etravirine). Their significance in industry can be seen from the approval of several FDA and ICH guidelines regarding their production using QbD and PAT approaches, which include critical quality attributes such as crystallinity, stability, residual solvent levels, and dissolution profiles [108,109]. The technique is highly important in contemporary drug development despite issues with physical instability, hygroscopicity, and scale-up because of its practical applications, scalability, and capability of increasing bioavailability [101–103].

Product	Drug	Technology/Carrier	Therapeutic Use
Sporanox	Itraconazole	HPMC-based solid dispersion	Antifungal
Kaletra	Lopinavir/Ritonavir	Melt extrusion dispersion	Antiviral
Cesamet	Nabilone	PVP-based dispersion	Antiemetic
Prograf	Tacrolimus	Amorphous dispersion	Immunosuppressant
Intelence	Etravirine	Spray-dried dispersion	Antiretroviral

Challenges, Future Perspectives, and Conclusion

One of the most promising strategies to improve the solubility, dissolution, and oral bioavailability of poorly soluble compounds is solid dispersion technology [111-120]. In spite of the great advances made both from the scientific and technological point of view, there are several obstacles that prevent its large-scale use, especially concerning the physical instability, recrystallization, hygroscopicity, difficulties in scale up, and high manufacturing costs. Amorphous solid dispersions represent a thermodynamically unstable system which might undergo recrystallization during the storage due to the changes in temperature and humidity as well as insufficient polymer stabilization, which results in poor dissolution performance and oral bioavailability [113-115]. Moisture absorption reduces the glass transition temperature, causing agglomeration, phase separation, and possible drug degradation [116,117]. Besides, there are also several obstacles in industrial scale up because of the requirements of good process control and equipment, while more complex methods, such as spray drying and hot-melt extrusion, cause higher costs [118-120].

However, some progress is being made in the design of smart polymers, continuous manufacturing, green process technologies, and intelligent drug formulation using artificial intelligence. The use of new stimuli-responsive polymers, including pH-sensitive, thermoresponsive, and biodegradable polymers, is being explored to enhance the stability of drugs, maintain supersaturation, and provide controlled drug delivery [112,113]. In addition, modern technologies such as 3D printing, intelligent drug formulation using artificial intelligence, and on-demand manufacturing processes are leading the way for personalized medicines, providing individualized drug dosage form with better therapeutic effects [114,115]. Moreover, environmentally sustainable manufacturing processes, such as solvent-free hot-melt extrusion, supercritical fluid technology, and microwave technology, are being considered [116,117].

Solid dispersions will also experience major changes in the future due to the advancement of continuous manufacturing and automation, which will help improve process control, reproducibility, and real-time monitoring through Process Analytical Technology and AI-based tools [118,119]. Regulators like USFDA recommend the use of continuous manufacturing because of its efficiency and advantages related to quality [120]. Thus, the combination of advanced materials, digitalization, and green manufacturing will address current challenges and greatly increase the value of solid dispersions in the future.

CONCLUSION

The method of solid dispersion has emerged as one of the most efficient and widely adopted techniques for boosting solubility, dissolution rate, and bioavailability of low water-soluble drugs. Solid dispersions increase the effectiveness of BCS Classes II and IV drugs by minimizing crystallinity, boosting wettability, enlarging surface area, and stabilizing amorphous forms of drugs. Innovations in hydrophilic polymers, surfactants, nanotechnology, hot-melt extrusion, spray drying, and continuous processing have increased the potential applications and commercial viability of solid dispersion systems.

While much has been achieved, obstacles including problems relating to physicochemical stability, recrystallization tendency, susceptibility to moisture, scale-up concerns, and expensive manufacturing processes persist, making further commercialization difficult. New strategies using smart polymers, nanotechnology-based formulations, artificial intelligence, personalized medicine, and environmentally friendly manufacturing processes are anticipated to address these issues and ensure the production of stable and effective products that can improve patients' health outcomes. In summary, solid dispersion technology remains one of the most promising technologies for the development of future oral drug delivery systems.

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