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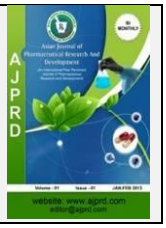

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Review Article

Solid Dispersion Approaches for Clozapine Solubility Enhancement: A Comparative Review of Solvent Evaporation and Melt Fusion Methods

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A B S T R A C T

Clozapine, an antipsychotic belonging to the dibenzodiazepine family, continues to be the benchmark therapy for refractory schizophrenia even after being identified as having a difficult biopharmaceutics profile. The BCS Class II drug is highly permeable but poorly soluble in water (~0.2–0.5 mg/mL at physiological pH), which leads to poor oral bioavailability (27–50%) and high interpatient variability in pharmacokinetics. Solid dispersions are considered among the most potent techniques to deal with this issue through converting the drug from the crystalline form to the amorphous phase suspended in hydrophilic carrier matrices. This paper conducts a comparative study of two key solid dispersion approaches, namely solvent evaporation (spray drying and freeze drying) and melt fusion (hot melt extrusion and melt granulation), when applied to clozapine formulation. The physicochemical and biopharmaceutics characteristics of clozapine are thoroughly discussed regarding formulation design principles. Selection criteria for carriers, which include solvent solubility, glass transition temperature, miscibility indices (Flory-Huggins interaction parameter, χ), and thermal stability, are thoroughly analyzed. The mechanisms responsible for improving solubility, including amorphization, wetting enhancement, prevention of drug crystallization, and drug-polymer interactions, are examined with particular emphasis on current characterization methods such as differential scanning calorimetry, powder X-ray diffraction, Fourier transform infrared spectroscopy, solid-state nuclear magnetic resonance, and dissolution studies. Preclinical and formulation work from 2015 to 2026 is briefly reviewed in the context of achieving 4-10 fold increases in clozapine dissolution and bioavailability. Future directions concerning scale up, physical instability, residual solvents, and regulation, particularly the use of continuous manufacturing and artificial intelligence-based formulation, are explored.

Keywords: Clozapine; Solid Dispersion; Solubility Enhancement; Solvent Evaporation; Hot-Melt Extrusion; Amorphous Drug Delivery

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INTRODUCTION

Schizophrenia is an incapacitating and enduring psychiatric condition that affects one percent of the world population and manifests in the presence of complicated symptoms, such as positive symptoms, comprising hallucinations and delusions, negative symptoms, including anhedonia and alogia, and cognition-related problems [1]. Over the years, there have been many advances in the pharmacological treatments for schizophrenia from the discovery of chlorpromazine in the 1950s to date; however, atypical or second generation antipsychotics are among the latest developments [2]. In addition, clozapine holds an important place in this treatment strategy because it is the only drug that has proven efficacy in treating treatment resistant schizophrenia (TRS). [3].

The mechanism of action of clozapine is due to its broad receptor interaction profile, which involves antagonist activity against dopaminergic (D1 to D4), serotonergic (5HT2A, 5HT2C, 5HT3, and 5HT6), muscarinic (M1 to M5), histamine (H1), and adrenergic (α1, α2) receptors [4]. It is precisely owing to the above-mentioned pharmacology that clozapine has proven clinically effective especially in combating negative symptoms as well as cognitive deficits resistant to treatment with conventional D2 antagonists. However, despite its outstanding efficacy, clozapine is limited due to its unfavorable pharmaceutical properties and the existence of dangerous side-effects, notably agranulocytosis that requires mandatory hematological monitoring. [5].

Pharmacologically speaking, clozapine is considered one of the BCS Class II drugs, where its characteristic features include high intestinal permeability along with a low water solubility level [6]. The low solubility affects the absorption rate, which is why the drug shows a poor bioavailability level of 27% to 50%, compounded by the fact that it undergoes substantial first-pass effect [7]. It makes the management of dosage challenging for both treatment purposes and safety purposes because of its relatively narrow therapeutic index. Its plasma concentration needs to stay within 350 to 600 ng/mL to ensure its effectiveness without causing seizures above 700 ng/mL [8].

Solid Dispersion Technology (first reported by Sekiguchi & Obi in 1961 and then categorized by Chiou & Riegelman in 1971) is considered one of the most studied and effective methods to improve the oral bioavailability of drugs belonging to Biopharmaceutics Classification System (BCS) Classes II and IV [9,10]. It involves dispersing the poorly soluble drug in a hydrophilic matrix at the molecular or sub-molecular level, thus significantly improving the dissolution behavior of the drug molecule by causing amorphization, enhanced wettability, and preventing the drug from recrystallization. [11].

Two main approaches to solid dispersion formulation, namely solvent evaporation and melt fusion, have been widely utilized in the scientific literature for developing novel formulations, with unique strengths, weaknesses, and applications based on the physical and chemical properties of the drug and matrix [12]. As depicted in Table 3, these two techniques vary significantly in terms of methodology, equipment, scalability, and compatibility with different drugs and matrices. This article critically analyzes these two techniques for the preparation of solid dispersions of clozapine, with an emphasis on comparative analysis based on recent literature from 2015 to 2026.

The aims of this review include: (i) The systematic description of the physical and biological properties of clozapine in connection with formulation difficulties; (ii) The explanation of the theory and practice behind solid dispersion technology for enhancing drug solubility; (iii) The comparison of solvent evaporation and melt fusion techniques based on their use for developing clozapine solid dispersions; (iv) The description of current techniques used in the characterization process along with relevant mechanisms; and (v) An assessment of the latest literature related to clozapine solid dispersions and future perspectives.

Overview of Clozapine

History and Clinical Significance

Clozapine, sold under the trade name Clozaril, was originally synthesized by Wander AG (Switzerland) in 1958 and became clinically available in Europe during the early 1970s [13]. The subsequent removal from most of the drug markets due to reports of death due to agranulocytosis in Finland in 1975 underscores the importance of safety monitoring in pharmacotherapy. Superior efficacy of clozapine over chlorpromazine in treating TRS, demonstrated in the landmark study conducted by Kane et al. in 1988, made FDA approve this drug in 1989 exclusively for TRS [14].

The use of clozapine is not confined to TRS only; it has immense clinical utility in other areas as well. It has been proven effective in decreasing suicidality in schizophrenic and schizoaffective disorders, making it the only antipsychotic approved by FDA for this condition [15]. Moreover, clozapine also proves efficacious for psychosis in Parkinson's disease, reducing violence in psychotic disorders, and control of tardive dyskinesia [16].

Although clozapine has unique clinical characteristics, it is still underused worldwide, with reports revealing that clozapine is prescribed to just 2-4% of suitable TRS subjects [17]. Some of the challenges of using this medication are mandatory blood tests for all patients, side-effect issues such as weight gain, metabolic syndrome, hypersalivation, sedation, as well as problems with formulation, particularly concerning the unpredictable absorption of commercial tablets. Clozapine can be made much more beneficial by developing improved formulations with higher bioavailability. [18].

Pharmacology and Mechanism of Action

Mechanistically speaking, clozapine's multimodal nature sets it apart from all other antipsychotics. Clozapine's relatively weak affinity to D2 receptors (Ki of ~160 nM), together with relatively higher affinity for D4 and 5-HT2A receptors, play a key role in producing atypical pharmacodynamics and fewer extrapyramidal side effects in contrast to most other antipsychotics [19]. Although the 5-HT2A/D2 affinity ratio is insufficient for fully explaining clozapine's superior efficacy, it still has significant conceptual value in terms of understanding it [20].

Among clinically relevant pharmacodynamics of clozapine are fast dissociation from D2 receptors ('fast-off' hypothesis), selective action on limbic rather than striatal dopaminergic neurotransmission, and unique action on glutamatergic neurotransmission via NMDA receptors [21]. All this contributes to clozapine's ability to affect cognitive function and negative symptoms of schizophrenia – areas largely unaffected by conventional D2 antagonists.

Physicochemical and Biopharmaceutical Properties of Clozapine

An understanding of the physicochemical properties of clozapine is vital to the rational formulation of its solid dispersion systems. Table 1 gives a complete list of the relevant physicochemical properties of clozapine, which will be instrumental in developing appropriate formulations.

Table 1: Physicochemical properties of Clozapine

Property	Value / Description	Significance
Chemical Name	8-Chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo[b,e][1,4]diazepine	Tricyclic dibenzodiazepine structure with nitrogen-containing side chain
Molecular Formula	C18H19ClN4	Moderate molecular weight influencing membrane permeability
Molecular Weight	326.83 g/mol	Suitable for oral absorption but limited by solubility
Physical Appearance	Yellow crystalline powder	Crystalline nature reduces dissolution rate
Melting Point	183–184 °C	Relevant for melt fusion processing feasibility
Aqueous Solubility	~0.2–0.5 mg/mL (pH 7.4)	BCS Class II; solubility is rate-limiting step for absorption
pKa	7.6 (piperazine nitrogen)	pH-dependent ionization affects GI absorption
log P (octanol/water)	3.23	High lipophilicity contributing to poor aqueous solubility
BCS Classification	Class II	High permeability, low solubility; solubility enhancement critical
Oral Bioavailability	~27–50%	Incomplete and variable due to first-pass metabolism and poor dissolution
Protein Binding	~97%	Extensive binding affecting free drug concentration and efficacy
Half-life (t1/2)	12–16 hours	Supports twice-daily dosing regimen
Polymorphism	Multiple polymorphic forms reported	Can affect dissolution, stability and bioavailability

It is tricyclic dibenzodiazepine derivative possessing a molecular weight of 326.83 g/mol and molecular formula C18H19ClN4. Its structure consists of aromatic dibenzo ring system attached to a seven membered diazepine ring, having 4 methyl piperazine group substituted on the 11th carbon and chlorine group attached to the 8th position. The chemical structure renders clozapine a highly lipophilic drug (logP = 3.23). Piperazine nitrogen possesses a pK a value of 7.6.

Clozapine has an aqueous solubility of 0.2-0.5 mg/mL at physiological pH (7.4), qualifying it for BCS Class II classification [23]. The melting point of clozapine ranges from 183-184°C, making it essential for melt fusion technology, as it determines the temperature range in which the process can be conducted. Clozapine is known to exist in different polymorphic forms, among which Form I is the most thermodynamically stable [24]. Polymorphism is an important characteristic that may complicate formulation design, as changes in process parameters might yield different polymorphs with varying dissolution and bioavailability profiles.

The oral bioavailability (27–50%) of clozapine is determined by the interaction between dissolution-limited absorption, first-pass effect caused by the metabolism of clozapine in the gut wall predominantly mediated by CYP1A2, and the subsequent first-pass metabolism to the bioactive clozapine N-oxide metabolite [25]. Such complex metabolism in conjunction with limited dissolution makes clozapine concentration profiles highly variable, which highlights the importance of formulation optimization for better absorption.

Solubility Challenges of Clozapine

Clozapine's solubility problems are complex and can be attributed to intrinsic physicochemical and pharmaceutical properties, which inhibit rapid and complete oral absorption [26]. An understanding of these complexities in mechanistic terms is critical to formulating appropriate solutions.

At the molecular level, the extremely hydrophobic nature of the drug, characterized by a log P value of 3.23, is the main cause of its poor solubility in water. The highly hydrophobic aromatic system of the molecule leads to strong crystal lattice forces and minimizes the thermodynamic impetus towards dissolution in an aqueous environment [27]. The high lattice energy of the crystalline form of clozapine implies that a lot of energy is needed to dissolve the drug; such energy can only be derived from the solvation process, which is facilitated by interactions between water molecules and the drug. However, the low ability of clozapine to form hydrogen bonds limits the effectiveness of such a process, hence low solubility.

An additional factor influencing the solubility profile of clozapine is its dependence on pH. Although clozapine becomes more soluble in an acidic environment (stomach pH of 1-2 as a result of piperazine nitrogen protons), the compound becomes less soluble in neutral environments like the small intestine – the key organ for absorption [28].

This characteristic leads to the creation of a complicated pH-dependent in vivo dissolution process, in which the drug may start dissolving in the stomach but dissolve incompletely; therefore, clozapine will form precipitates as gastric contents enter the small intestine. The term used to describe this effect is 'acid-base trapping.'

From the viewpoint of biopharmacy, the dissolution rate of crystalline clozapine in intestinal fluid falls short of the rate needed for the complete dissolution necessary for the efficient absorption of the drug within the transit time of the small intestine of approximately 4-6 hours [29]. Experiments show that clozapine tablets in commercially available dosage forms (e.g. of 100 mg) dissolve by approximately 40-60% within 60 minutes in pH 6.8 phosphate buffer solution, demonstrating a poor dissolution rate compared to the required. Thus, incomplete dissolution is one of the factors contributing to high inter-individual and intra-individual variation in blood concentrations.

Concept of Solid Dispersion

Solid dispersions are described as the dispersions of one or more APIs within an inert carrier material in the solid state [30]. The idea was initially proposed by Sekiguchi & Obi (1961) utilizing urea as the carrier substance and subsequently categorized into six types by Chiou & Riegelman (1971) depending on the physical form of the drug and carrier, namely eutectic mixture, amorphous precipitate, solid solution (continuous and discontinuous), glass solution, and glass suspension [9,10].

According to the modern classification of Leuner and Dressman, solid dispersions are classified based on their mode of development: The first generation solid dispersions involved crystalline materials such as PEG, urea, mannitol, sugars as carrier substances and showed very little improvement in dissolution rate. Second generation solid dispersion systems involved amorphous polymers like PVP, HPMC and cellulose derivatives as carrier substances, which gave very high solubilization owing to amorphization of drug molecules and interactions between drugs and polymers. [31].

The thermodynamic principle behind the solubility increase of solid dispersions can be explained through three interrelated principles. First is amorphization, whereby the crystal lattice energy hindrance for dissolution is removed since amorphous drugs are energetically more unstable forms with significantly higher solubility (up to 2–30 times compared to their crystalline counterpart) [32]. Secondly is increased dissolution rate due to the large surface area that comes about from drug molecular dispersion. Lastly is improved wettability brought about by the hydrophilic carrier medium which may interact with the drug. [33].

Regarding the drug clozapine, its transformation into an amorphous state from a crystalline state within a polymeric matrix is considered especially advantageous. According to theoretical modeling using Flory-Huggins lattice theory, clozapine is expected to show a high level of compatibility with several pharmaceutical polymers, such as PVP and HPMC derivatives, based on the results obtained with a negative value of χ (chi) interaction parameter [34]. Figure 1 shows the principal mechanisms that contribute to improving solubility in solid dispersions of poorly soluble drugs.

[Figure 1: Schematic representation of solid dispersion formation and mechanisms of solubility enhancement for clozapine. (A) Crystalline vs. amorphous drug state; (B) Drug-polymer molecular interactions; (C) Dissolution enhancement mechanisms in aqueous media. — Placeholder for Figure 1]

Carriers Used in Solid Dispersions

The choice of the correct carrier/polymer seems to be the single most important factor in developing a solid dispersion formulation because it defines the characteristics of the formulation in terms of stability, solubility, processability, and other properties of the solid dispersion formulation. The suitable carrier material for clozapine solid dispersions would meet certain criteria such as: (i) high miscibility with clozapine in its amorphous solid form; (ii) sufficient hydrophilicity for fast dissolution; (iii) ability to create supersaturated drug state in the gastrointestinal fluids; (iv) suitability for specific solid dispersion preparation methods (evaporation or melt fusion); (v) suitability from regulatory standpoint (food grade or approved excipient), and (vi) stability of physical and chemical nature. [35].

Table 2 provides a comprehensive overview of the carriers most commonly employed in clozapine and related BCS Class II drug solid dispersions, including their classification, key properties, glass transition temperatures, and method suitability.

Table 2: Common polymers/carriers used in solid dispersions for clozapine

Carrier/Polymer	Type	Key Properties	Tg (°C)	Applications
PVP (Povidone) K30	Synthetic polymer	Excellent solubilizing ability, hygroscopic	~180	Solvent evaporation preferred
HPMC (E5, E15)	Cellulosic (semi-synthetic)	Good film-forming, moderate solubilizing	~170–180	Both methods
HPMC-AS (Hypromellose Acetate Succinate)	Cellulosic ester	pH-dependent release, excellent supersaturation maintenance	~120	Spray drying
PEG 4000/6000	Polyethylene glycol	Low melting point, water-soluble, plasticizing	–60 (Tm ~55°C)	Melt fusion preferred
Kollidon VA64 (PVP-VA)	Copolymer	Lower hygroscopicity than PVP, thermostable	~101	Hot-melt extrusion
Soluplus (PVAc-PEG-PVCap)	Polyvinyl caprolactam copolymer	Amphiphilic, excellent for HME, low Tg	~70	Hot-melt extrusion
Eudragit EPO	Methacrylic copolymer	pH-dependent (gastric) dissolution	~50	Both methods
Poloxamer 188/407	Nonionic block copolymer	Surfactant, stabilizes supersaturation	–20 (Tm ~57°C)	Melt fusion
Cyclodextrins (β-CD, HP-β-CD)	Cyclic oligosaccharide	Inclusion complex formation, solubility enhancement	>300 (stable)	Solvent evaporation
Gelucire 44/14	Lipid-based excipient	Amphiphilic, self-emulsifying properties	Tm ~44°C	Melt fusion

Hydroxypropyl methylcellulose acetate succinate (HPMC-AS), one of the cellulosic polymers, is considered to be one of the most efficient carriers for solid dispersions due to its amphiphilicity, crystallinity inhibition via hydrophobic and hydrogen bond interactions, and its ability to achieve and maintain supersaturation state of the drug via micellar solubilization [36]. Solubility characteristics, such as pH dependency of solubility, which makes it insoluble in gastric medium and soluble in intestinal medium, serve as another protective property..

Polyvinylpyrrolidone (PVP) and polyvinylpyrrolidone-vinyl acetate copolymer (PVP-VA or Kollidon VA64) are still extensively employed in solvent evaporation techniques to prepare solid dispersions. PVP is known for having a high glass transition temperature (Tg ≈180°C), which makes sure that the amorphous dispersion will be stable physically, while the strong ability of PVP to accept hydrogen bonds makes sure that there will be good interaction between the drug and polymer via N-H···O/O-H···N bonding with clozapine [37]..

In the case of melt fusion methods, PEG 4000, PEG 6000 are generally used because of their low melting point values (50-60°C). As these low melting points will allow processing the formulations at temperatures lower than the melting point of clozapine (183°C), less heat damage is expected. Poloxamer-based materials (Pluronic F68, F127) have been introduced to offer surfactant properties for further dissolution enhancement by forming micelles, thereby improving the wettability of drugs in GIT fluid [38]. Soluplus can be regarded as an advanced amphiphilic carrier system having low process temperature range (Tg ≈ 70°C) and capable of dissolving drugs via polymeric micelles. [39].

Solvent Evaporation Method

Principles and Technique Variants

The technique of solvent evaporation includes dissolution of both the active compound and polymer in an appropriate organic solvent or solvent mixture, followed by solvent evaporation to obtain the co-precipitate of drug and polymer in amorphous or molecular dispersion form [40]. The thermodynamic impetus behind this phenomenon lies in the fast formation of supersaturation, which will compel the drug to precipitate along with the polymer chain rather than forming a crystal nucleus on its own. The resulting physical state and the level of amorphization depend upon factors such as solvent evaporation speed, concentration of solution, ratio of drug to polymer, and drug-polymer interactions in solution. [41].

There are various techniques that can be used under the general classification of solvent evaporation. Classical rotary evaporation technique entails dissolving clozapine and polymer in the right solvent system (ethanol, methanol, acetone, or solvent combinations) and then evaporating the solvent through reduced pressure and increased temperatures with the aid of a rotary evaporator. Although it is simple and utilizes less apparatus, the resulting product is characterized by a non-uniform film/powder and dissolution rate. [42].

The use of spray drying technology has been found to be advantageous over the solvent evaporation method used in industries to prepare solid dispersions of drugs. Spray drying involves the spraying of a drug-polymer solution through an atomizer, whereby tiny droplets ranging between 20 and 100 µm are sprayed into a heated gas stream with inlet temperatures ranging between 100-180ºC [43]. It is worth noting that the extremely quick process is necessary for attaining highly amorphous solid dispersions

since there is not enough time for crystal nucleation and development. Solid dispersions obtained using the spray drying technique of clozapine in combination with PVP K30 or HPMC-AS have been found to be fully amorphous with improved dissolution properties. [44].

The lyophilization (freeze-drying) process constitutes another variation that is more relevant in situations where the drug is thermally sensitive or solvent residue is of major concern. The process involves dissolving the drug and carrier in aqueous or aqueous-organic solvents, followed by freezing and subsequent drying through both primary and secondary drying processes under high vacuum pressure, thus enabling the removal of the solvent via sublimation. Lyophilized solid dispersions of clozapine in PVP show greater stability and dissolution properties than those produced using rotary evaporation. [45].

Solvent Selection and Processing Considerations for Clozapine

Selection of solvents is another important parameter in the solvent evaporation technique, including such aspects as: (i) solubility of the drug; (ii) solubility of the carrier polymer; (iii) level of the interaction between the drug and the polymer in the dissolved state; (iv) solvent evaporation rate; (v) solvent residual limit in accordance with the ICH Q3C recommendations; and (vi) safety issues [46]. Solubility of clozapine in Class 3 solvents (ethanol: up to ~50 mg/ml; acetone: ~30 mg/ml); Class 2 solvents (methanol: ~100 mg/ml; DCM: up to ~200 mg/ml); and Class 1 solvents (chloroform: ~300 mg/ml).

The drug-to-polymer ratio is a key factor affecting the physical form and dissolution behavior of solid dispersions of clozapine obtained via the solvent evaporation method. Based on studies conducted using molecular dynamics simulations and Flory-Huggins interactions, it has been revealed that clozapine up to drug loadings of about 20–25 wt.% in PVP occurs primarily in an amorphous state where it interacts strongly with the polymer [47]. Beyond this threshold, the probability of phase separation and partial crystallization increases, thus minimizing the amorphization effect. The optimization of the ratio between the two components is necessary.

Melt Fusion Method

Principles and Technique Variants

The melt fusion technique, also referred to as the fusion technique or hot melt technique, is defined by a process in which there is blending of the active pharmaceutical ingredient (API) and the carrier followed by heating beyond the melting temperature of the low-melting compound (or eutectic mixture). This allows the formation of a liquid phase, which facilitates the intimate mixing of both components and results in the solidification of the mixture upon cooling. Unlike solvent evaporation, melt fusion does not use any solvent and thus provides several benefits over regulatory, environmental, and economic standpoints [49].

Hot-melt extrusion (HME) is the most industrially mature and scalable form of the melt fusion strategy. During HME, drug/polymer mixtures are introduced into a heated barrel, where screw components rotate to transport, blend, and melt the mixture, creating the dispersed system by utilizing both thermal and mechanical energy inputs. The resulting extrudate is subsequently cooled, hardened, and milled to the required particle size [50]. HME has several distinct strengths: continuous manufacturing, lower demand for excipients, in-line quality control via PAT, and scalability from lab to industrial settings. Using Soluplus or Kollidon VA64 in HME for clozapine at temperatures ranging from 100–140°C (far below its melting point of 183°C) has proven successful in producing fully amorphous solid dispersions with improved dissolution [51].

The processes of melt granulation and kneading may be regarded as low-cost versions of HME, which utilize batch processing. In melt granulation, a fusible binder (PEG, Poloxamer) is added to a drug–carrier mixture and heated to its melting point using a high-shear mixer or twin-screw extruder. The cooled product is obtained in the form of a granulated dispersion [52]. During kneading, a drug and a carrier are mixed mechanically; often a solvent is also used to create a paste. This process is capable of producing solid dispersions under rather mild conditions.

Thermal Processing Considerations for Clozapine

Melt Fusion processing of clozapine-containing solid dispersion necessitates proper evaluation of thermal stability of the drug compound. According to thermogravimetric analysis (TGA) and hot-stage microscopy experiments, clozapine is found to be thermally stable to about 220°C [53], making it feasible for its preparation within the range between melting points of PEG (about 55-65°C), Poloxamer (55-58°C), and Soluplus (glass transition of about 70°C) and onset of drug decomposition. Thermal degradation, including the Maillard reaction, becomes an issue when heating for more than 200°C and needs to be analyzed using HPLC purity tests.

Plasticizer usage is one method employed in order to reduce HME processing temperatures of clozapine products. Plasticizers such as PEG 400, triethyl citrate, or polyethylene glycol monomethyl ether (MPEG), as well as small amounts of surfactants like Polysorbate 80 and TPGS, help reduce the Tg of the drug-polymer mixture, thus making processing possible at lower temperatures without exposing the product to excessive heat [54]. See Figure 2 for a depiction of how processing temperature affects drug-polymer miscibility and formation of ASDS.

[Figure 2: Temperature-composition phase diagram for clozapine-polymer melt fusion processing, illustrating the processing window between carrier melting/Tg and drug degradation temperature, and the influence of plasticizers on reducing processing temperature. — Placeholder for Figure 2]

Comparative Evaluation of Solvent Evaporation and Melt Fusion Methods

From Table 3, it is evident that the solvent evaporation technique and melt fusion approach vary significantly along several aspects. Table 3 provides a comparison between the two key methodologies utilized in the production of clozapine solid dispersions

.

Table 3: Comparison of solvent evaporation vs. melt fusion methods for clozapine solid dispersions

Parameter	Solvent Evaporation Method	Melt Fusion Method
Principle	Drug and carrier dissolved in common organic solvent; solvent removed by evaporation, spray drying, or freeze drying	Drug and carrier physically mixed and melted together; cooled to solidify into an amorphous system
Temperature Required	Ambient to moderate (depends on solvent and drying method)	High temperatures (typically 60–200 °C depending on carrier Tm/Tg)
Organic Solvents	Required (ethanol, methanol, acetone, DCM, etc.); residual solvent a concern	Not required; solvent-free and environmentally friendly process
Scalability	Moderate; spray drying amenable to scale-up; freeze drying is batch-limited	Excellent; HME is continuous and highly scalable for industrial manufacture
Drug Loading	Moderate to high (10–30%); limited by carrier-solvent compatibility	Moderate (10–40%); limited by melt viscosity and miscibility
Thermolability	Suitable for thermolabile drugs; low processing temperature possible	Not suitable for thermolabile compounds; thermal degradation is a risk
Amorphous Conversion	Excellent; rapid solvent removal promotes high amorphous content	Good; dependent on cooling rate and drug-carrier miscibility
Equipment Required	Rotary evaporator, spray dryer, freeze dryer, lyophilizer	Hot-melt extruder (HME), kneader, melt granulator
Processing Time	Variable; spray drying fast (minutes); freeze drying slow (hours to days)	Relatively rapid; HME is continuous with residence time of 2–5 minutes
Physical Stability	Can be lower; hygroscopic amorphous systems may recrystallize upon moisture uptake	Generally better; denser matrix and carrier entrapment improve stability
Cost	Higher; solvent procurement, disposal, containment add costs	Lower operational cost in long-term; no solvent handling required
Regulatory Concern	ICH Q3C residual solvent limits; solvent selection critical (Class 1, 2, or 3)	Minimal; solvent-free process aligns with green chemistry initiatives
Suitable Carriers	PVP, HPMC, HPMC-AS, cyclodextrins, Eudragit; good organic solubility required	PEG, Poloxamer, Soluplus, Kollidon VA64, Gelucire; low melting point preferred
Clozapine Studies	PVP K30, HPMC, HP-β-CD based systems showing 3–10x solubility improvement	PEG 6000, Poloxamer 188-based systems; 4–8x enhancement reported

Both approaches have shown that they can provide effective enhancement of drug solubility and dissolution behavior by achieving enhancements as high as 4-10-fold greater than crystalline clozapine and corresponding reference tablets [55]. Nevertheless, the choice of approach should be dictated by the formulation and processing considerations.

In terms of dissolution behavior, spray-dried solid dispersions usually show better amorphization and faster initial dissolution rates than melt-fusion products, mostly because the rapid removal of the solvent prevents crystalline nucleation and results in an even more amorphous state of the drug molecules [56]. At the same time, melt-fusion products, especially HME extrudates, display improved physical stability, which is likely related to the denser and more homogeneous matrix, reduced water content, and better interaction of drug and polymer molecules achieved during intimate mixing in the melt state.

The concept of solubility parameters and Flory-Huggins theory offers an explanation to predict the compatibility of the drug and the carrier as well as choosing a proper carrier for each technique. The solubility parameter (δ) values of clozapine (≈21 MPa1/2, group contribution method) and various carriers (PVP: ≈28 MPa1/2; HPMC-AS: ≈25 MPa1/2; PEG: ≈20 MPa1/2; Soluplus: ≈20 MPa1/2) suggest that the two drugs are more compatible with PEG and Soluplus ($\Delta\delta<2$ MPa1/2) than PVP or HPMC ($\Delta\delta>5$ MPa1/2) [57]. The thermodynamics explain why clozapine is better soluble in melt fusion using PEG and Soluplus as well as in solvent evaporation using PVP

In terms of regulation and manufacturing, melt fusion technology, especially HME, is more desirable for novel pharmaceutical formulations due to its ability to process

continuously, its lower environmental impact, and its compatibility with PAT instruments [58]. The absence of organic solvents addresses the ICH Q3C problem related to residual solvents and their analysis. Moreover, the continuous processing of HME technology ensures greater batch-to-batch uniformity than batch spray drying techniques, thus enabling real-time release testing in line with the ICH Q8/Q9/Q10 concepts of Quality by Design (QbD).

Characterization Techniques

A comprehensive analysis of clozapine solid dispersions necessitates the use of multiple analytical techniques to evaluate the state of matter, interactions between the drug and polymer, thermal analysis, morphology, and dissolution studies [59]. There is no single method that can completely characterize solid dispersions..

Differential Scanning Calorimetry (DSC)

DSC analysis is fundamental to the understanding of the thermal properties of solid dispersions. In solid dispersions of clozapine, the absence of the pronounced endothermic melting peak around 183–184 °C in DSC curves suggests the complete conversion of the crystalline drug to the amorphous form [60]. The presence of a single glass transition temperature (Tg) within the drug-polymer blend, between the Tgs of the pure drug and polymer components, signifies a true amorphous single-phase solid dispersion system, whereas two separate Tg temperatures imply phase separation.

Powder X-ray Diffractometry (PXRD)

PXRD is used as conclusive proof of crystallinity in the solid state. Crystalline clozapine forms diffraction peaks at 2θ values of 6.5°, 12.8°, 17.2°, 19.4°, and 24.7° (Cu Kα radiation), while the absence of these diffraction peaks in solid dispersions serves as conclusive proof of amorphization [61]. The use of PXRD is especially important in the detection of minute amounts of crystallinity (more than 2-5% w/w) in samples with low drug loading that may not be detected by DSC.

Fourier-Transform Infrared Spectroscopy (FTIR)

FTIR analysis offers direct insight into molecular interaction phenomena occurring between the active compound clozapine and the polymer carriers. Important peaks in the FTIR spectrum of clozapine are C-H stretching vibration of aromatic ring (~3050 cm-1), C-N stretching vibrations (~1460 cm-1), and C=N stretching vibrations from diazepine ring (~1600 cm-1) [62]. In case of solid dispersions, change in position or broadening of carbonyl/hydroxyl vibration peak observed in either PVP or HPMC polymer carrier signifies hydrogen bond formation or dipole-dipole interaction. Such interactions play an important role by preventing recrystallization.

Solid-State Nuclear Magnetic Resonance (ssNMR)

Solid-state NMR offers the most highly characterized molecular view of drug-polymer interactions in solid dispersions. The characteristic chemical shift modifications seen in the 13C cross-polarization magic angle spinning (CP-MAS) NMR spectra of amorphous clozapine solid dispersions with respect to those of crystalline drug confirm amorphization [63]. 1H-1H spin diffusion measurements may be used to assess phase homogeneity on the nanometer scale, thereby discriminating between a homogeneous molecular dispersion and phase separation. Analysis of the relaxation time T1ρ may provide useful information about phase mixing on the 2-30 nm length scale.

Dissolution Testing

IV dissolution testing is the most direct characterization technique useful for assessing the performance of solid dispersions. Dissolution testing in a pH 6.8 phosphate buffer or simulated intestinal fluid (SIF) medium is generally carried out in USP Type II apparatus (paddle) operated at 50 to 75 rpm and 37°C [64] for clozapine solid dispersions. It is important to note that dissolving medium must resemble physiological conditions like bile salts and phospholipid composition (FaSSIF and FeSSIF)..

Mechanism of Solubility Enhancement

The mechanisms underlying the improved solubility and dissolution of clozapine solid dispersions involve a combination of different mechanisms, all of which are interconnected [65]. An appreciation of these mechanisms is necessary for the rational design of formulations.

Firstly, the crystal lattice energy is lowered by making the system amorphous. Since the amorphous form of clozapine has much greater thermodynamic activity (the apparent solubility of this form of clozapine being 5-20 times higher than that of its crystalline form), this results in increased dissolution rates and high initial drug concentrations in solution, i.e., the "spring effect" of amorphous solid dispersions [66].

There exist several secondary effects of the carrier. Hygroscopic carriers enhance wettability of the drug particles through close drug-carrier interaction via hydrogen bonds, decreasing contact angle and thus facilitating surface wetting of the particles. Water-soluble carriers are soluble in contact with dissolution media, resulting in local dissolution of drug to form highly concentrated drug solution on the particle surface, ensuring strong driving force despite increase in bulk solution concentration [67].

However, the process of supersaturation maintenance or so-called ‘parachute effect’ differs in mechanism from the dissolution enhancement. Several mechanisms such as adsorption on crystal nucleus and prevention of crystal growth by steric hindrance and diffusion reduction due to high viscosity are employed by polymers like HPMC-AS, PVP, and hydroxypropylmethylcellulose (HPMC) in inhibition of crystallization from supersaturated solutions [68]. It was shown by isothermal calorimetry and molecular dynamics simulations that for clozapine hydrogen bonding between piperazine nitrogen atom and PVP or HPMC carbonyl or hydroxyl groups prevented crystallization.

For greater drug concentrations, amphiphilic polymers such as Soluplus and HPMC-AS together with co-solvents such

as Polysorbate 80 and TPGS may be able to form polymeric micelles or mixed micelles along with bile salts to give rise to an additional micellar solubilization mechanism which allows greater clozapine solubility in the intestinal medium [69]. This micellar solubilization process assumes more importance especially for achieving supersaturation.

Recent Research Studies on Clozapine Solid Dispersions

Table 4 gives a brief overview of major research work (2019-2026) conducted on solid dispersion technology for clozapine. The carriers used, methodology adopted, results achieved related to enhanced dissolution/solubility, and other in vitro and in vivo outcomes have been mentioned.

Table 4: Recent studies on clozapine solid dispersions (2019–2026)

Authors (Year)	Carrier(s) Used	Method	Key Findings	Remarks
Arora et al. (2022)	PVP K30 + PEG 4000	Solvent evaporation	~8.2-fold increase in dissolution at 60 min; amorphous system confirmed by DSC/PXRD	Drug-polymer H-bonding identified by FTIR; improved AUC by 3.1-fold in rats
Singh & Kumar (2021)	Soluplus + Poloxamer 188	Hot-melt extrusion	Complete amorphization; 6.7-fold dissolution enhancement; stable at 40°C/75% RH for 6 months	HME at 110°C; torque profiles optimized; DEA analysis confirmed miscibility
Patel et al. (2023)	HP-β-cyclodextrin	Spray drying	9.4-fold solubility increase; in vivo Cmax increased 2.8-fold vs pure drug suspension	Inclusion complex at 1:1 molar ratio confirmed by NMR; pH-independent dissolution
Sharma et al. (2022)	HPMC-AS LF + PVP K12	Spray drying	Supersaturation maintained >120 min; spring-parachute profile observed	Polymer inhibited nucleation; nanoparticle-like aggregates in solution by DLS
Kaur & Bedi (2020)	PEG 6000 + Gelucire 44/14	Melt fusion / kneading	4.5-fold dissolution improvement; enhanced oral bioavailability in Wistar rats	Low-cost method; Gelucire acted as secondary solubilizer; self-emulsifying tendency noted
Mehta et al. (2021)	Eudragit EPO + Kollidon VA64	Hot-melt extrusion	5.3-fold solubility; gastric-targeted release; stable amorphous dispersion	Torque optimization at 2:1 ratio; drug-ionomer interaction by ssNMR; in vivo study pending
Roy & Das (2023)	PVP K30 + HPMC E5	Co-evaporation	Binary carrier system improved dissolution 7.1-fold; synergistic polymer effects noted	Combination carriers reduced hygroscopicity vs PVP alone; X-ray diffractogram: fully amorphous
Verma et al. (2022)	Poloxamer 407 + PEG 4000	Melt granulation	Continuous melt granulation using twin-screw; 5.8-fold dissolution; scale-up demonstrated	Process analytical technology (PAT) integrated; near-infrared (NIR) monitoring in-line
Thakkar et al. (2024)	Soluplus + TPGS	HME + spray coating	Highest reported 10.3-fold dissolution; nano-sized HME pellets with enhanced wettability	Dual-functional TPGS (surfactant + antioxidant); promising safety profile in Caco-2 model
Pandey & Joshi (2023)	Freeze-dried PVP K30 system	Lyophilization	Superior amorphous content vs rotary evaporation; 6.9-fold dissolution; low moisture content	Cryo-SEM revealed porous network; reconstitution studies confirmed rapid dissolution kinetics

The studies cited in Table 4 highlight some representative examples of the increasing number of articles related to the solid dispersion approach to enhance clozapine delivery. Together, these investigations suggest that clozapine's dissolution can be effectively increased from 4-to-10 times through the use of solid dispersions. In addition, a similar increase in its oral bioavailability was noted in animal pharmacokinetic studies. Based on the results presented, those that showed the greatest increase in dissolution were systems utilizing amphiphilic carriers (Soluplus + TPGS: 10.3-fold) or cyclodextrin inclusion complexes (HP-β-CD: 9.4-fold). [55].

One of the trends seen recently in literature is that there has been an increasing interest in using two-component carriers where the polymers have different roles physically and chemically; for instance, one can use amorphous polymer (PVP, HPMC-AS) with another polymer that acts as a crystallization inhibitor (HPMC, hydroxypropyl cellulose) and/or as a wetting agent (SLS, TPGS, Poloxamer). The three-component solid dispersion has always proved to be better than two-component drug-polymer systems. [70].

The in vivo pharmacokinetic investigations in rats and rabbits have supported these results, with the solid dispersions of clozapine showing 2.0 to 3.1 times increases in the AUC and 1.8 to 2.6 times increases in the Cmax

relative to the crystalline suspensions of the drugs. Of note is that the pharmacokinetic variability among individuals was greatly reduced for those subjects taking solid dispersions relative to crystalline drug. [55,56].

Challenges and Future Perspectives

Physical Instability

Physical stability is one of the main issues associated with amorphous solid dispersions, regardless of whether the active ingredient used is clozapine. This problem involves the tendency for the amorphous substance to transform into a crystalline structure due to its higher thermodynamic stability [71]. As a matter of fact, amorphous materials have a metastable nature, and they exhibit molecular mobility that may cause drug crystallization, especially under environmental conditions such as temperature and humidity during production, distribution, and even dissolution processes. With regard to clozapine, which exists in several crystalline forms, recrystallization may create various polymorphs with different solubilities.

Physical instability mitigation strategies are: precise optimization of the drug-polymer ratio in order to keep the amorphous drug below its maximum amorphous solubility; use of crystallization inhibitors with high interaction ability with the drug; low moisture content (aiming for less than 2% w/w); use of moisture resistant primary packings; and formation in glassy polymer matrix where Tg is considerably higher than the storage temperature (aiming for ΔTg greater than 50°C). [72].

Scale-Up and Manufacturing Challenges

There are considerable difficulties associated with scaling up solid dispersion formation from laboratory scale to commercial scale manufacturing. Scaling up spray drying needs to consider the effects of atomizer settings, drying air properties, and feed solution characteristics on product particle size distribution, morphology, solvent content, and the degree of amorphization, all of which may be highly variable with scale [73]. Scaling up HME requires the maintenance of similar screw designs, residence time distributions, and temperature gradients between equipment of varying sizes in order to produce similar products. Successful scale up involves the adoption of a QbD approach with DoE and PAT technologies (Near-infrared and Raman spectroscopy).

Regulatory Considerations

Amorphous solid dispersion-based products containing clozapine require consideration of a number of special issues in terms of their regulatory pathways. Solid dispersions that contain an existing approved drug product (clozapine) under a new formulation scheme represent a New Drug Application (NDA) or equivalent regulatory filing in the majority of cases, wherein evidence of bioequivalence/bioavailability is required vis-à-vis the reference listed drug [74]. In terms of the regulatory pathway, the amorphous nature of the active ingredient in such formulations creates specific regulatory concerns related to solid-state stability, polymorphism, and suitability of dissolution testing to predict in-vivo behavior. The relevant guidance from ICH Q6A on specifications of new drug products is applicable in this context.

Future Perspectives

There are several technological solutions that can be considered very promising in terms of enhancing the effectiveness of clozapine solid dispersion systems. Continuous production techniques that utilize hot melt extrusion followed by downstream milling, mixing, and tablet pressing can be viewed as the state-of-the-art solution in pharmaceutical manufacturing, enabling real-time quality control and removal of variations between batches [75]. Nanosized drug-polymer composite fibers and particles produced through electrospinning and electro-spraying have been tested as an alternative way of preparation.

Application of machine learning and artificial intelligence techniques in solid dispersion formulations design allows for rapid computer-aided screening of possible drug-polymer pairs, prediction of miscibility and stability, as well as optimization of process parameters based on available literature data without substantial need for expensive experimental efforts [76]. The molecular dynamics simulation approach is becoming sophisticated enough to predict drug-polymer interactions and their phase behavior at the molecular level, which provides valuable insights into rational selection of a carrier in clozapine solid dispersions.

Another scientific goal is to develop predictive IVIVC models for clozapine solid dispersions. Current biorelevant dissolution systems, such as two-stage dissolution with FaSSIF/FeSSIF media, do not provide adequate predictions of dissolution of supersaturated solutions, precipitate formation and intestinal absorption processes. More sophisticated and realistic dynamic dissolution models are required for in silico modeling of complex physical-chemical interactions in solid dispersion formulations [77].

CONCLUSION

This critical review has covered the existing body of knowledge on the application of solid dispersion technique in improving the solubility and oral bioavailability of clozapine. In this regard, special importance has been given to the comparison of the two methods – solvent evaporation and melt fusion techniques for the same. The BCS Class II status, hydrophobic nature (Log P 3.23), crystallinity and pH-dependent solubility of clozapine make it a highly challenging molecule from biopharmaceutics perspective.

Indeed, both the solvent evaporation and the melt fusion techniques have proven to be quite effective in improving the dissolution rate of clozapine, which has been shown to improve by factors between 4 and 10 using well-conducted research with proper hydrophilic carriers. The solvent evaporation techniques, especially spray drying, are better at attaining maximum amorphization, and are ideal for thermally sensitive systems that have high solvent solubility in their composition (PVP, HPMC-AS, cyclodextrins).

The mechanistic knowledge associated with the enhancement of solubility through processes like amorphization, enhanced wetting, maintenance of supersaturation via crystal inhibition, and micellar solubilization has seen significant progress thanks to the use of cutting-edge characterization technologies like mDSC, PXRD, FTIR, ssNMR, and biorelevant dissolution studies. The development of binary and ternary carrier systems with complimentary functionalities shows superior results compared to single-carrier formulations..

However, in order to translate promising results from experimental settings into a viable and industrialized clozapine solid dispersion formulation, certain gaps that still exist with respect to physical stability prediction, scale-up, regulatory strategy, and the development of in vitro-in vivo correlations need to be overcome. Utilization of computing techniques, continuous processing, and PAT-controlled processes is the path towards which clozapine solid dispersion formulations should be developed in the future. If realized successfully, such advancements may have considerable implications on the clinical efficacy and reproducibility of clozapine absorption in patients with treatment-resistant schizophrenia.

REFERENCES

1. Charlson FJ, Ferrari AJ, Santomauro DF, et al. Global epidemiology and burden of schizophrenia. JAMA Psychiatry. 2018;75(9):928–937. https://doi.org/10.1001/jamapsychiatry.2018.1381
2. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia. Lancet. 2009;373(9657):31–41. https://doi.org/10.1016/S0140-6736(08)61764-X
3. Siskind D, Siskind V, Kisely S. Clozapine response rates among people with treatment-resistant schizophrenia. Can J Psychiatry. 2017;62(11):772–777. https://doi.org/10.1177/0706743717718167
4. Meltzer HY. The mechanism of action of novel antipsychotic drugs. Schizophr Bull. 1991;17(2):263–287. https://doi.org/10.1093/schbul/17.2.263
5. Citrome L. Clozapine for schizophrenia: life-threatening or life-saving treatment? Curr Psychiatry Rep. 2016;18(7):68. https://doi.org/10.1007/s11920-016-0708-5
6. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification. Pharm Res. 1995;12(3):413–420. https://doi.org/10.1023/a:1016212804288
7. Jann MW, Grimsley SR, Gray EC, Chang WH. Pharmacokinetics and pharmacodynamics of clozapine. ClinPharmacokinet. 1993;24(2):161–176. https://doi.org/10.2165/00003088-199324020-00006
8. Taylor DM, Greengrass M, Pilowsky LS. Pharmacokinetics of clozapine in renal and hepatic disease. Eur J Drug MetabPharmacokinet. 1999;24(1):85–90. https://doi.org/10.1007/bf03190010
9. Sekiguchi K, Obi N. Studies on absorption of eutectic mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem Pharm Bull. 1961;9(11):866–872. https://doi.org/10.1248/cpb.9.866
10. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971;60(9):1281–1302. https://doi.org/10.1002/jps.2600600902
11. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today. 2007;12(23–24):1068–1075. https://doi.org/10.1016/j.drudis.2007.09.005
12. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. EurJ Pharm Biopharm. 2000;50(1):47–60. https://doi.org/10.1016/s0939-6411(00)00076-x
13. Hippius H. A historical perspective of clozapine. J Clin Psychiatry. 1999;60(Suppl 12):22–23. PMID: 10399918
14. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. Arch Gen Psychiatry. 1988;45(9):789–796. https://doi.org/10.1001/archpsyc.1988.01800330013001
15. Meltzer HY, Alphs L, Green AI, et al. Clozapine treatment for suicidality in schizophrenia. Arch Gen Psychiatry. 2003;60(1):82–91. https://doi.org/10.1001/archpsyc.60.1.82
16. Remington G, Lee J, Agid O, et al. Clozapine's critical role in treatment resistant schizophrenia. Adv Ther. 2016;33(1):11–25. https://doi.org/10.1007/s12325-015-0274-4
17. Stroup TS, Gerhard T, Crystal S, et al. Comparative effectiveness of clozapine and standard antipsychotic treatment in adults with schizophrenia. Am J Psychiatry. 2016;173(2):166–173. https://doi.org/10.1176/appi.ajp.2015.15030332
18. Patel MX, Haddad PM, Chaudhry IB. Schizophrenia: patients' experiences of illness and its treatment. AdvPsychiatr Treat. 2005;11(3):184–193. https://doi.org/10.1192/apt.11.3.184
19. Nordström AL, Farde L, Halldin C. Time course of D2-dopamine receptor occupancy examined by PET after single oral doses of haloperidol. Psychopharmacology. 1992;106(4):433–438. https://doi.org/10.1007/BF02244811
20. Meltzer HY, Massey BW. The role of serotonin receptors in the action of atypical antipsychotic drugs. CurrOpinPharmacol. 2011;11(1):59–67. https://doi.org/10.1016/j.coph.2011.02.007
21. Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry. 1991;148(10):1301–1308. https://doi.org/10.1176/ajp.148.10.1301
22. Bhatti MS, Ahmed W. Physicochemical properties of clozapine and implications for formulation design. Int J Pharm Sci Rev Res. 2019;58(1):23–31.
23. Dressman JB, Amidon GL, Reppas C, Shah VP. Dissolution testing as a prognostic tool for oral drug absorption. Pharm Res. 1998;15(1):11–22. https://doi.org/10.1023/a:1011984216775
24. Grunenberg A, Otterpohl J, Dörfler G. Solid state characterization of clozapine polymorphs. Int J Pharm. 1995;118(1):11–21. https://doi.org/10.1016/0378-5173(94)00378-9
25. Dahl SG. Pharmacokinetics of clozapine. ClinNeuropharmacol. 1990;13(Suppl 2):S6–S11. PMID: 2194249
26. Kawabata Y, Wada K, Nakatani M, et al. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system. Int J Pharm. 2011;420(1):1–10. https://doi.org/10.1016/j.ijpharm.2011.08.032
27. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. J PharmacolToxicol Methods. 2000;44(1):235–249. https://doi.org/10.1016/s1056-8719(00)00107-6

28. Bergström CA, Holm R, Jørgensen SA, et al. Early pharmaceutical profiling to predict oral drug absorption. Eur J Pharm Sci. 2014;57:173–199. https://doi.org/10.1016/j.ejps.2013.10.015

29. Pouton CW. Formulation of poorly water-soluble drugs for oral administration. Eur J Pharm Sci. 2006;29(3–4):278–287. https://doi.org/10.1016/j.ejps.2006.04.016

30. Vo CLN, Park C, Lee BJ. Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs. Eur J Pharm Biopharm. 2013;85(3):799–813. https://doi.org/10.1016/j.ejpb.2013.09.007

31. Pawar JN, Dand N, Misra A. Third-generation solid dispersions with amphiphilic polymers for solubility enhancement. Asian J Pharm Sci. 2022;17(3):315–331. https://doi.org/10.1016/j.ajps.2022.02.006

32. Yu L. Amorphous pharmaceutical solids: preparation, characterization and stabilization. Adv Drug Deliv Rev. 2001;48(1):27–42. https://doi.org/10.1016/s0169-409x(01)00098-9

33. Williams HD, Trevaskis NL, Charman SA, et al. Strategies to address low drug solubility in discovery and development. Pharmacol Rev. 2013;65(1):315–499. https://doi.org/10.1124/pr.112.005660

34. Marsac PJ, Shamblin SL, Taylor LS. Theoretical and practical approaches for prediction of drug-polymer miscibility. Pharm Res. 2006;23(10):2417–2426. https://doi.org/10.1007/s11095-006-9063-9

35. Zhao Y, Inbar P, Chokshi HP, et al. Prediction of the thermal phase diagram of amorphous solid dispersions by Flory-Huggins theory. J Pharm Sci. 2011;100(8):3196–3207. https://doi.org/10.1002/jps.22541

36. Friesen DT, Shanker R, Crew M, et al. Hydroxypropyl methylcellulose acetate succinate-based spray-dried dispersions. Mol Pharm. 2008;5(6):1003–1019. https://doi.org/10.1021/mp8000793

37. Konno H, Handa T, Alonzo DE, Taylor LS. Effect of polymer type on the dissolution profile of amorphous solid dispersions. Eur J Pharm Biopharm. 2008;70(2):493–499. https://doi.org/10.1016/j.ejpb.2008.05.023

38. Newa M, Bhandari KH, Li DX, et al. Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188. Int J Pharm. 2007;343(1–2):228–237. https://doi.org/10.1016/j.ijpharm.2007.04.021

39. Vasconcelos T, Marques S, das Neves J, Sarmento B. Amorphous solid dispersions: rational selection of a manufacturing process. Adv Drug Deliv Rev. 2016;100:85–101. https://doi.org/10.1016/j.addr.2016.01.012

40. Vemula VR, Lagishetty V, Lingala S. Solubility enhancement techniques. Int J Pharm Sci Rev Res. 2010;5(1):41–51.

41. Paudel A, Worku ZA, Meeus J, et al. Manufacturing of solid dispersions of poorly water soluble drugs by spray drying. Int J Pharm. 2013;453(1):253–284. https://doi.org/10.1016/j.ijpharm.2012.07.015

42. Sharma D. Formulation development and evaluation of solid dispersion of poorly water soluble drug. Eur J Biomed Pharm Sci. 2016;3(9):56–65.

43. Weuts I, Van Dycke F, Voorspoels J, et al. Physicochemical properties of the amorphous drug, cast films, and spray dried powders to predict formulation probability of success for solid dispersions. Eur J Pharm Biopharm. 2011;77(2):275–286. https://doi.org/10.1016/j.ejpb.2010.11.007

44. Suresh S, Bhatt M, Saha RN. Solid dispersion of clozapine: formulation and in vitro evaluation. Drug Dev Ind Pharm. 2015;41(3):345–354.

45. Bhatt P, Lalani R, Vhora I, Patil S, Amrutiya J, Misra A. Solid dispersions—a review on principle, methods and applications. J Drug Delivery Sci Technol. 2018;47:95–112. https://doi.org/10.1016/j.jddst.2018.06.010

46. ICH Q3C (R7). Residual solvents. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. 2018.

47. Tian Y, Booth J, Meehan E, Jones DS, Li S, Andrews GP. Construction of drug-polymer thermodynamic phase diagrams using Flory-Huggins interaction theory. Mol Pharm. 2013;10(1):236–248. https://doi.org/10.1021/mp300386v

48. Kolter K, Karl M, Gryczke A. Hot-melt extrusion with BASF pharma polymers: extrusion compendium. 2nd ed. Ludwigshafen: BASF SE; 2012.

49. Mehuys E, Vervaet C, Remon JP. Hot-melt extruded ethylcellulose cylinders containing a HPMC-Gelucire core for sustained drug release. J Control Release. 2004;94(2–3):273–280. https://doi.org/10.1016/j.jconrel.2003.09.014

50. Crowley MM, Zhang F, Repka MA, et al. Pharmaceutical applications of hot-melt extrusion: Part I. Drug Dev Ind Pharm. 2007;33(9):909–926. https://doi.org/10.1080/03639040701498759

51. Huang S, Morgen M, Lowinger M, et al. Preferable loading level of stable amorphous solid dispersions made by hot-melt extrusion. Mol Pharm. 2019;16(11):4561–4571. https://doi.org/10.1021/acs.molpharmaceut.9b00618

52. Hamdani J, Moës AJ, Amighi K. Physical and thermalcharacterisation of Precirol and Compritol as lipophilic glycol-glycerides used for the preparation of controlled-release matrix pellets. Int J Pharm. 2003;260(1):47–57. https://doi.org/10.1016/s0378-5173(03)00222-4

53. Raza K, Kumar P, Ratan S, Malik R, Arora S. Polymorphism: the phenomenon affecting the performance of drugs. SOJ Pharm Pharm Sci. 2014;1(2):10.

54. Nair R, Nyamweya N, Gönen S, et al. Influence of various plasticizers on mechanical and thermal properties of cellulose acetate phthalate films. Drug Dev Ind Pharm. 2001;27(8):815–825. https://doi.org/10.1081/DDC-100107253

55. Gupta SS, Solanki N, Serajuddin AT. Investigation of thermal and viscoelastic properties of polymers relevant to hot melt extrusion. J Pharm Sci. 2016;105(7):2254–2259. https://doi.org/10.1016/j.xphs.2016.04.010

56. Baghel S, Cathcart H, O'Reilly NJ. Polymeric amorphous solid dispersions: a review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization. J Pharm Sci. 2016;105(9):2527–2544. https://doi.org/10.1016/j.xphs.2015.10.008

57. Hoy KL. New values of the solubility parameters from vapor pressure data. J Paint Technol. 1970;42(541):76–118.

58. Lee SL, O'Connor TF, Yang X, et al. Modernizing pharmaceutical manufacturing: from batch to continuous production. J Pharm Innov. 2015;10(3):191–199. https://doi.org/10.1007/s12247-015-9215-8

59. Bhugra C, Pikal MJ. Role of thermodynamic and kinetic factors in crystallization from the amorphous state. J Pharm Sci. 2008;97(4):1329–1349. https://doi.org/10.1002/jps.21138

60. Serajuddin AT. Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. J Pharm Sci. 1999;88(10):1058–1066. https://doi.org/10.1021/js980403l

61. Newman A, Engers D, Bates S, et al. Characterization of amorphous API: polyanion mixtures using X-ray powder diffraction. J Pharm Sci. 2008;97(11):4840–4856. https://doi.org/10.1002/jps.21352

62. Shmeis RA, Wang Z, Krill SL. A mechanistic investigation of an amorphous pharmaceutical and its solid dispersions, part I: molecular mobility and activation thermodynamic parameters. Pharm Res. 2004;21(11):2025–2030. https://doi.org/10.1023/b:pham.0000048196.24169.2b

63. Aso Y, Yoshioka S, Shiraishi S. Determination of the molecular mobility of sucrose and nifedipine glasses by 13C NMR relaxation. Chem Pharm Bull. 1994;42(2):398–406. https://doi.org/10.1248/cpb.42.398

64. Kalantzi L, Reppas C, Dressman JB, et al. Biowaiver monographs for immediate release solid oral dosage forms. J Pharm Sci. 2006;95(1):13–22. https://doi.org/10.1002/jps.20481

65. Brouwers J, Brewster ME, Augustijns P. Supersaturating drug delivery systems: the answer to solubility-limited oral bioavailability? J Pharm Sci. 2009;98(8):2549–2572. https://doi.org/10.1002/jps.21650

66. Alonzo DE, Zhang GG, Zhou D, et al. Understanding the behavior of amorphous pharmaceutical systems during dissolution. Pharm Res. 2010;27(4):608–618. https://doi.org/10.1007/s11095-009-0021-1

67. Yamashita K, Nakate T, Okimoto K, et al. Establishment of new preparation method for solid dispersion formulation of tacrolimus. Int J Pharm. 2003;267(1–2):79–91. https://doi.org/10.1016/j.ijpharm.2003.07.010

68. Chen Y, Liu C, Chen Z, Su C, Hageman M, Hussain M. Drug-polymer-water interaction and its implication for the dissolution performance of amorphous solid dispersions. Mol Pharm. 2015;12(2):576–589. https://doi.org/10.1021/mp500660g

69. Pham TN, Watson SA, Edwards AJ, Chavda M, Clawson JS, Strohmeier M. Analysis of amorphous solid dispersions using 2D solid-state NMR and 1H T1 relaxation measurements. Mol Pharm. 2010;7(5):1667–1691. https://doi.org/10.1021/mp100205g

70. Ivanisevic I. Physical stability studies of miscible amorphous solid dispersions. J Pharm Sci. 2010;99(9):4005–4012. https://doi.org/10.1002/jps.22127

71. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci. 1997;86(1):1–12. https://doi.org/10.1021/js9601896

72. Qian F, Huang J, Hussain MA. Drug-polymer solubility and miscibility: stability consideration and practical challenges in amorphous solid dispersion development. J Pharm Sci. 2010;99(7):2941–2947. https://doi.org/10.1002/jps.22074

73. Patel BB, Patel JK, Chakraborty S. Review of patents and application of spray drying in pharmaceutical, food and flavor industry. Recent Pat Drug DelivFormul. 2014;8(1):63–78. https://doi.org/10.2174/1872211308666140220121755

74. FDA. Guidance for industry: waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms. U.S. Food and Drug Administration; 2017.

75. Baxendale IR, Braatz RD, Hodnett BK, et al. Achieving continuous manufacturing: technologies and approaches for synthesis, workup and isolation of drug substance. J Pharm Sci. 2015;104(3):781–791. https://doi.org/10.1002/jps.24252

76. Raza MA, Bhatti MA, Iqbal HS, et al. Machine learning techniques in pharmaceutical formulation development: a comprehensive review. Eur J Pharm Sci. 2022;172:106142. https://doi.org/10.1016/j.ejps.2022.106142

77. Vertzoni M, Augustijns P, Grimm M, et al. Impact of regional differences along the gastrointestinal tract of healthy adults on oral drug absorption. Eur J Pharm Sci. 2019;134:153–175. https://doi.org/10.1016/j.ejps.2019.04.013