REVIEW PAPER

Novel Solid Dispersion Technologies in Drug Delivery: Recent Progress and Applications

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ABSTRACT

The main problems faced in pharmaceutical development are the poor water solubility of the drugs, as around 70-90% of new chemical entities are poorly soluble in water. Solid dispersion (SD) technology has been identified as a promising approach to overcome the bioavailability issues of such drugs owing to its ability to increase the apparent solubility and dissolution rate. This review offers a detailed overview of novel solid dispersion technologies such as hot melt extrusion (HME), spray drying, supercritical fluid technology, electrospinning and recent advancements like KinetiSol® technology and microwave-induced solid dispersion. The principles behind these technologies, the different carriers used (polymers, surfactants and new carriers like mesoporous silica or cyclodextrins), and the preparation methods are discussed. Further, this review highlights recent advances in solid dispersion technology using nanotechnology, formulation design with the help of artificial intelligence, and the continuous manufacturing methods. Applications to oral drug delivery, controlled release systems and special formulation for pediatric and oncology are discussed. Other topics include characterization techniques, regulatory aspects and future directions in terms of industrial scale-up and personalized medicine.

Keywords: Solid dispersion, Amorphous solid dispersion, Solubility enhancement, Bioavailability, Hot melt extrusion, Spray drying, Poorly soluble drugs, Polymeric carriers, Drug delivery systems, Nanotechnology.

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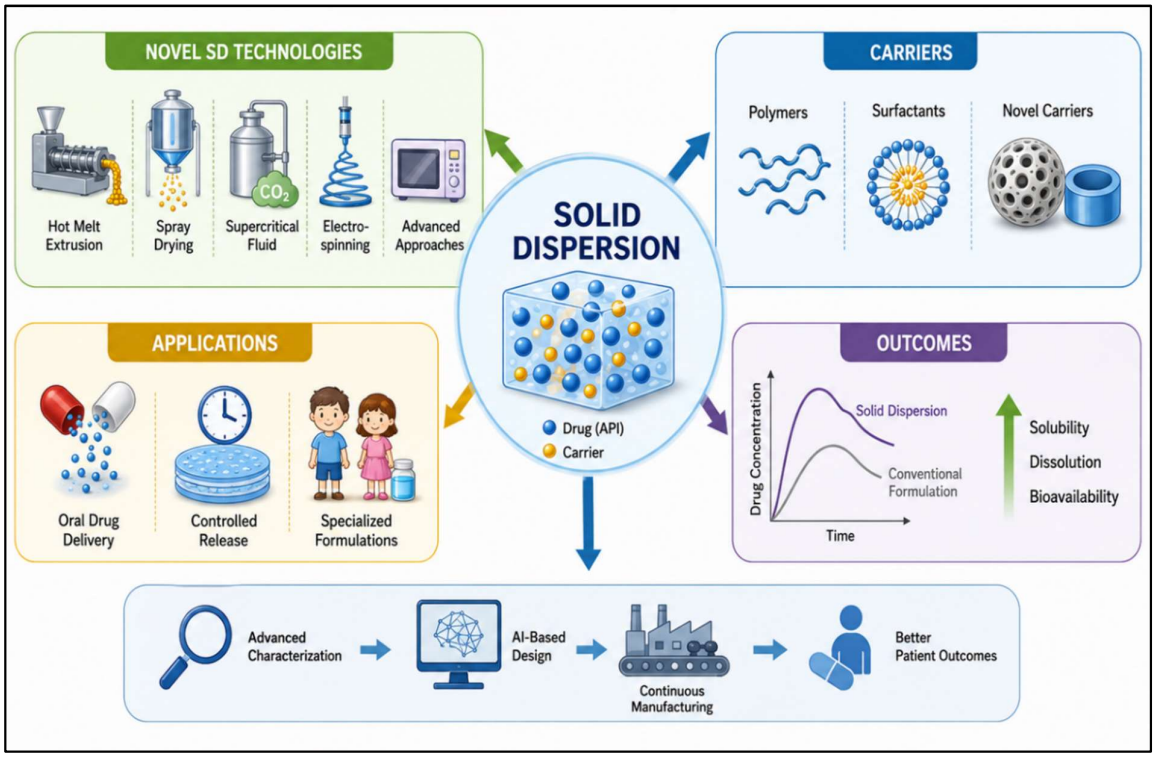

Figure 1: Novel Solid Dispersion Technologies for Enhanced Drug Delivery

1. INTRODUCTION

The inability to achieve drug candidates with good aqueous solubility is one of the greatest challenges in today's drug development [1]. Based on the solubility and permeability properties of the drug, the U.S. Biopharmaceutics Classification System (BCS) classifies the drugs into four classes [2]. Many of the new drug entities belong to BCS Class II (low solubility, high permeability) and BCS Class IV (low solubility, low permeability) [3] that need intervention to improve dissolution and bioavailability.

There are a number of problems associated with poor aqueous solubility that occur in the drug development process and during clinical use: lack of gastrointestinal tract absorption, high intra- and inter-subject variations in plasma concentration, potential dependency on food consumption, and inability to reach therapeutic concentrations [4]. Therefore, the ability to design effective strategies to enhance solubility has become more critical. There are several approaches available, such as: chemical modification (salt formation, prodrugs, crystal engineering), pharmaceutical technologies (micronization, nanonization) and formulation based strategies [5].

Solid dispersion (SD) technology is one of these methods, and it has attracted a lot of interest due to its high efficiency and versatility in enhancing the apparent solubility and bioavailability of poorly water soluble drugs [6]. It was first coined by Sekiguchi and Obi in 1961 under the name of solid dispersion that is the dispersion of an active pharmaceutical ingredient (API) in a pharmacologically inert carrier matrix [7]. This technology has undergone a tremendous development in the last two decades, in terms of the evolution of sophisticated manufacturing techniques and novel carrier systems.

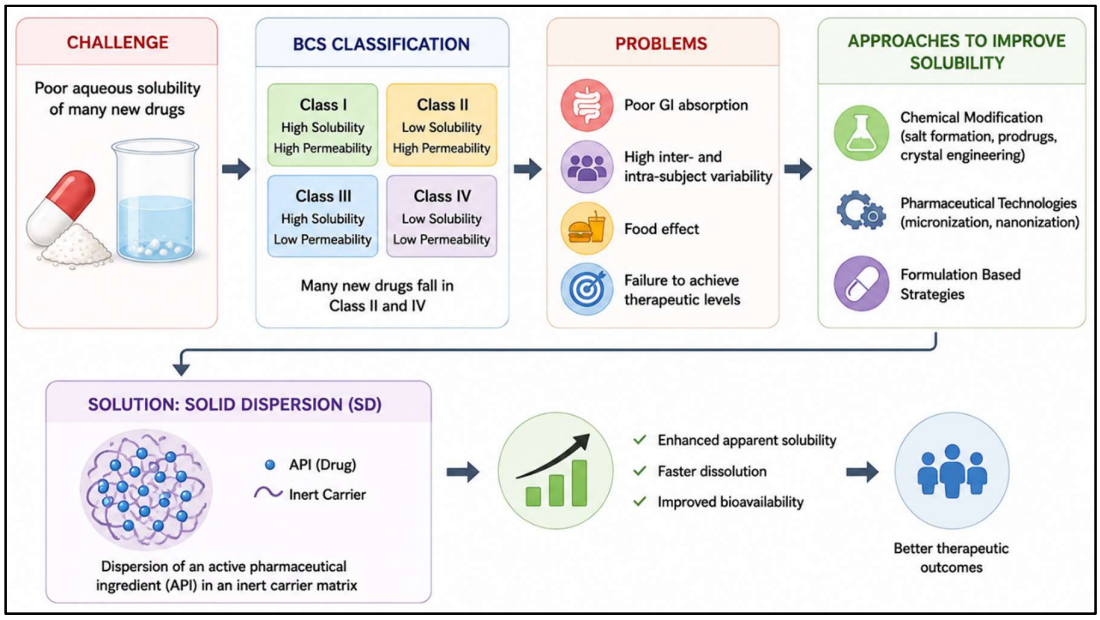

Figure 2: Solid Dispersion Technology for Improving Drug Bioavailability

2. CONCEPT OF SOLID DISPERSION

2.1 Definition and Historical Background

A solid dispersion is a dispersion of one or more active pharmaceutical ingredient(s) in an inert carrier or matrix in the solid state, which is formed by different preparation methods [8]. These systems are traditionally defined by Sekiguchi and Obi as intimate mixtures of a drug and a carrier; however, today more complex systems such as amorphous dispersions, semi-crystalline composites and nanostructured formulations are included in the concept of intimate mixture.

The earliest solid dispersions were prepared by fusion technique with crystalline carriers, e.g., urea and citric acid, in the past [10]. These systems had, however, a number of drawbacks such as lack of stability, phase separation and inadequate bioavailability enhancement. The development of polymeric carriers, especially the hydrophilic polymers such as polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) was a revolutionizer in the field [11]. The solid dispersion technology has been further extended with the development of amorphous solid dispersions (ASDs) and the advent of new manufacturing technologies like hot melt extrusion, spray drying and supercritical fluid extraction [12].

2.2 Mechanisms for Solubility and Bioavailability Enhancement

The ability of solid dispersions to increase drug solubility and bioavailability has been attributed to several different mechanisms [13].

a) **Particle Size Reduction:** The enhancement of the specific surface area available for dissolution, when a drug substance is converted to fine particles or amorphous state, greatly increases the

dissolution rate as described by the Noyes-Whitney equation [14].

b) **Conversion to Amorphous State:** The energy required for dissolution can be lowered by eliminating the energy barriers in the dissolution process due to conversion from crystalline to amorphous state [15].

c) **Increased Wettability:** The dispersion's hydrophilic polymers and surfactants increase the water penetration into the drug particles and improve wettability characteristics, which leads to better dissolution rate [16].

d) **Enhanced Porosity and Surface Area:** Many solid dispersions have been shown to have higher surface area than pure crystalline drug, allowing for more surface area for interaction with solvents [17].

e) **Prevention of Crystal Nucleation:** The polymeric carriers present in the solid dispersion, prevent the drug crystal nucleation and growth, which keeps the drug in higher energy amorphous state [18].

3. CLASSIFICATION OF SOLID DISPERSIONS

3.1 Classification Based on Molecular Arrangement

Sekiguchi and Obi's initial classification system classified solid dispersions into four types depending on their crystalline or amorphous nature [7]. The modern solid dispersions may be divided into.

a) **Eutectic Mixtures:** Physical mixtures of drug and carrier in 1:1 molar ratio which have a eutectic melting point lower than either of the components [19].

b) **Solid Solutions:** True solutions at the molecular level are where the drug is dispersed molecularly in the carrier matrix (Solid Solutions) [20].

c) **Amorphous Solid Dispersions (ASDs):** The drug is present in a non-crystalline or amorphous state in a polymer carrier matrix, the most popular one used today in the field of modern pharmaceutical development [21].

d) **Glass Solutions/Suspensions:** Crystalline drug particles suspended in an amorphous glassy carrier matrix [22].

3.2 Classification Based on Carrier Type

Carrier Type	Examples	Characteristics
Hydrophilic Polymers	PVP, PEG, HPMC, Soluplus®	Enhance wettability, prevent crystallization, most widely used
Hydrophobic Polymers	Ethyl cellulose, EUDRAGIT®	Enable sustained/pH-dependent release control
Surfactants	Poloxamers, Tween®, Gelucire®	Micelle formation, improved solubilization

4. NOVEL SOLID DISPERSION TECHNOLOGIES

4.1 Hot Melt Extrusion (HME)

One of the most commonly used technologies to prepare solid dispersion at laboratory and industrial scale is the hot melt extrusion [23]. The technique consists of feeding into a heated extruder a mixture of API and carrier(s), which are melted, mixed intensely and extruded through a die to form solid dispersions in the form of strands or pellets [24].

a) **Benefits:** Solvent-free process without the presence of solvent residues, scale-up is cost effective, continuous manufacturing process, better stability than solvent process, and thermostable formulations [25]. Recent developments include the twin-screw extrusion process, which offers a better mixing efficiency, and the modular barrel configuration, which provides flexibility in process control [26].

b) **Recent applications and case studies:** HME has been successfully used to improve the bioavailability of challenging molecules such as itraconazole, posaconazole and ritonavir [27]. Several marketed products have been developed using HME technology, which shows its industrial viability. Recently, the use of HME to prepare amorphous formulations of thermally sensitive and high melting point compounds has been investigated [28].

4.2 Spray Drying Technology

Spray drying is a technique that consists of atomization of the solution, suspension or emulsion of the drug and carrier(s) into a heated chamber where the solvent evaporates rapidly to give fine particles [29]. This technology is very versatile and is especially applicable in the case of heat sensitive APIs.

a) **Mechanism and Advantages:** The very fast drying process (millsecond scale) does not allow the crystallization of the products, and produces amorphous products with enhanced dissolution. Spray drying offers independent adjustment of the drug/carrier ratio, multiple carriers and excipients can be incorporated and can be manufactured at scale [30]. Some recent innovations have involved multi-fluid nozzle systems for better particle size distribution control [31].

b) **Recent developments:** Modem spray drying equipment includes online particle size measurement and real-time process monitoring [32]. Applications have been extended to the formulation of nanoparticles and new carriers like polymer blends and self-emulsifying systems [33].

4.3 Supercritical Fluid Technology

Supercritical fluid technology, mainly using supercritical carbon dioxide ($scCO_2$), has proven to be an eco-friendly method for manufacturing solid dispersions [34]. The unique properties of supercritical fluids are a combination of the solvency power of liquids and the diffusivity of gases.

a) **Process Principles and Advantages:** Several methods based on SCF have been developed such as rapid expansion of supercritical solutions (RESS), supercritical fluid extraction of emulsions (SFEE) and particle from gas saturated solutions (PGSS) [35]. Benefits comprise the use of green solvents, control of the process parameters, and production of the particles with the desired morphology. The processes have recently been optimized resulting in high yields and economic viability [36].

b) **Clinical Relevance:**Worth to note, is the fact that compounds such as cyclosporine A, risperidone and docetaxel have been successfully formulated as SCF based solid dispersions that have shown to improve their bioavailability [37]. The technology is especially useful for the synthesis of thermally unstable compounds, which are not susceptible to thermal degradation [38].

4.4 Electrospinning for Nanofiber-Based Dispersions

The innovative method of forming a nanofiber-based solid dispersion in which the drug is loaded in the very fine polymeric fibers (50–500 nm diameter) is called electrospinning. Nanofibers have an exceptionally high surface area to volume ratio that can provide an unprecedented degree of dissolution enhancement.

a) **Technology Overview and Advantages:** Electrospinning technology uses a viscous polymer solution that contains the drug, and a high electrical potential is applied to the polymer solution to create a charged jet which is collected by a collector as ultrafine fibres [40]. The advantages consist of the high specific surface area, fast dissolution rate of the drug and the possibility to incorporate hydrophobic drugs with improved amorphous stability [41]. New developments have been coaxial electrospinning for core-shell structures and multi-spindle systems that have led to higher production rates [42].

b) **Bioavailability Enhancements:** In the case of poorly soluble drugs like ibuprofen, celecoxib, and curcumin, the dissolution rate of the drug was improved by 2-5 fold in studies with electrospun nanofibers in comparison with the dissolution rate of the crystalline drug and conventional solid dispersion. Scale-up technologies and pathway clarification have driven an increased pharmaceutical interest [44].

4.5 KinetiSol® Immersion Technology

The proprietary high energy fusion technology developed by Viterion, called KinetiSol®, delivers simultaneous application of heat, kinetic energy and shear force as a way to create solid dispersions [45]. This new process has unique benefits over traditional melt processes.

The KinetiSol® process is based on a specifically designed rotor-stator system which is able to achieve an exceptional shear and frictional heat, thus achieving rapid mixing and homogenization of the components [46]. This technology is especially useful for polymers with high glass transition temperatures and heat-sensitive drug components, as the processing time is extremely short (usually 5-15 minutes) in comparison to conventional extrusion [47]. Clinical studies have shown that over time, KinetiSol®-prepared dispersions have better long-term stability and bioavailability than dispersions prepared by HME [48].

4.6 Freeze Drying / Lyophilization

Freeze drying is still a valuable method for the preparation of solid dispersions, especially from solutions or suspensions [49]. This is done by freezing the solution containing a drug-carrier, and then sublimating the frozen solvent under vacuum.

Optimization of pre-formulation to ensure the ice-nucleation behaviour is predicted by differential scanning calorimetry, the use of controlled-rate freezing to ensure uniformity in products, and the use of novel cryoprotectants are areas of recent advances in freeze-drying technology [50]. A special interest are lyophilized solid dispersions for parenteral and oral fast dissolving formulations [51]. It has successfully been used to make amorphous dispersions of drugs such as itraconazole and aprepitant [52].

4.7 Emerging Technologies

Microwave Induced Solid Dispersion (MISD): This is a novel technology which uses microwave irradiation to induce heat and molecular mobility, which allows for fast mixing of the drug and carrier at lower temperatures than traditional heating methods [53]. Early experiments show that thermolabile compounds can be processed without loss of amorphous stability [54].

a) **3D Printing-Based Formulations:** Drug loading and geometry of personalized solid dispersions have been realized by using 3D Printing-Based Formulations (3DPF), a technology based on the use of fused deposition modeling (FDM) or selective laser sintering (SLS) [55]. This allows new formulations to be made on-demand and quick prototypes to be produced [56].

b) **Continuous Manufacturing Systems:** The pharmaceutical industry is moving to continuous manufacturing of solid dispersions [57]. Integrated continuous lines that involve spray drying and/or HME followed by downstream processing and characterisation with real-time quality assurance provide better process control, waste minimisation and superior quality assurance [58].

Technology	Main Idea	Major Benefit
Hot Melt Extrusion (HME)	Drug and polymer are melted and mixed together.	Solvent-free and easy for large-scale production
Spray Drying	Drug solution is sprayed and dried rapidly.	Produces amorphous particles with faster dissolution
Supercritical Fluid Technology	Uses supercritical CO_2 to prepare particles.	Eco-friendly and suitable for heat-sensitive drugs
Electrospinning	Forms drug-loaded nanofibers using electricity.	Very fast drug dissolution due to high surface area
KinetiSol® Technology	Uses high shear and heat for rapid mixing.	Better stability and short processing time
Freeze Drying	Frozen solution is dried under vacuum.	Useful for thermolabile and fast-dissolving drugs
Microwave-Induced SD	Microwave energy mixes drug and carrier rapidly.	Faster processing at lower temperature
3D Printing-Based SD	Uses 3D printing for personalized formulations.	Customized drug delivery systems
Continuous Manufacturing	Continuous production of solid dispersions.	Better quality control and reduced waste

5. CARRIERS USED IN SOLID DISPERSION TECHNOLOGY

5.1 Polymeric Carriers

Polymeric carriers remain the most widely employed materials in contemporary solid dispersion formulations [59]. Hydrophilic polymers enhance drug dissolution through wetting effects and prevention of crystallization [60].

Polymer	Key Properties	Applications
PVP (Polyvinylpyrrolidone)	Hydrophilic, amorphous, excellent solubility	Rapid-release formulations, oral dispersions
PEG (Polyethylene Glycol)	Plasticizer effect, thermal stability, biocompatible	HME systems, modified-release formulations
HPMC (Hydroxypropyl Methylcellulose)	pH-independent, viscosity control, film-former	Sustained-release, orodispersible tablets
Soluplus® (Polyvinyl Caprolactam-PVP-TPGS)	High loading capacity, self-emulsifying, enhanced solubilization	HME, lipophilic drug formulations
EUDRAGIT® E/L/S	pH-dependent release, enteric protection, targeted delivery	Colonic delivery, acid-labile drug protection
Kollicoat® IR	Rapid release polyvinyl acetate copolymer	Immediate-release tablets, dispersions
Copovidone (Kollidon VA64)	Vinyl acetate-PVP copolymer, good plasticity	HME processing, film coatings

5.2 Surfactant-Based Carriers

Solid dispersions containing surfactants either as carrier or as co-carrier with polymers have been developed [73]. These are typically used in the form of poloxamers (Pluronic®), polysorbates (Tweens) or Gelucire grades. The wettability and solubilization of hydrophobic drugs is improved by these materials due to their micelle formation and emulsification effect [74]. There have been recent studies on polymersurfactant combinations with the aim of synergistic solubilization and stability [75].

5.3 Novel and Emerging Carriers

a) **Cyclodextrins and Derivatives:** Cyclodextrins are cyclic oligosaccharides which can form inclusion complexes with hydrophobic drugs [76]. Cyclodextrins are also able to offer an extra solubilization mechanism and stability when used as a component of solid dispersions with polymers [77].

b) **Innovative Carriers of Solid Dispersions:** Mesoporous silica materials (MCM-41 and SBA-15) and related materials are novel carriers for solid dispersions [78]. They are useful, in particular, because of their large surface area, adjustable pore size, and their capacity to stabilize amorphous forms of the drug. More recently, silica surfaces have been functionalized with polymers or surfactants in order to improve the loading and release of drugs [79].

c) **Lipid-Based Carriers:** Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are carriers in which solid dispersions are studied and are shown to have some advantages in terms of the lymphatic targeting of these preparations and the

bioavailability of lipophilic drugs [80]. Hybrid systems with improved performance are obtained by combining lipids with polymers [81].

6. CHARACTERIZATION AND EVALUATION METHODS

Product characterization is important to establish the product quality, evaluate in vivo performance and assure batch-to-batch consistency of solid dispersions [82]. Current characterization protocols combine several analyses.

Technique	Information Provided
DSC	Crystallinity, glass transition, thermal behavior, drug-polymer interactions
PXRD/XRD	Crystal structure, polymorphic forms, amorphous content, degree of crystallinity
FTIR	Molecular interactions, hydrogen bonding, drug-polymer compatibility
SEM	Surface morphology, particle size, porosity, crystalline deposits
Dissolution Testing	In vitro bioavailability, solubility enhancement, food effect prediction
LC-MS	Drug content, impurity profile, chemical stability
DLS/Zeta Potential	Particle size distribution, colloidal stability, surface charge

7. APPLICATIONS OF NOVEL SOLID DISPERSION SYSTEMS

7.1 Oral Drug Delivery

The oral route is still the most convenient and compliance method of administration. Solid dispersions have been used for the successful formulation of BCS Class II and BCS Class IV drugs for which the compounds were thought to be candidates for only parenteral use [98]. Some of the most recent marketed product formulations based on solid dispersion technology are posaconazole oral suspension (Noxafil®), ritonavir tablets (Norvir®) and some azole antifungal agents [99].

7.2 Controlled and Modified Release Systems

Controlled release in the form of solid dispersions have been developed by incorporating polymers that control release, such as HPMC, ethyl cellulose, and polyacrylates [100]. The release paradox can actually be exploited by the drug being amorphous, having initial rapid absorption into the polymeric matrix, and then subsequent sustained release as matrix dissolution progresses. Intelligent polymer selection and formulation has led to release profiles which are both pH dependent and time dependent [102].

7.3 Fast Dissolving and Rapidly Dissociating Formulations

Spray dried or electrospun solid dispersions are very flowable and compressible and can be used to produce tablets that disintegrate rapidly or orally disintegrating films [103]. These formulations are especially advantageous for children, the elderly, and those who have some swallowing problems, nausea or vomiting [104]. Incorporation of a flavoring and a sweetening agent in the dispersion to develop taste masked fast-dissolving formulations has been recently developed [105].

7.4 Specialized Formulations

a) **Pediatric Formulations:** Solid dispersions are useful for developing pediatric formulation with lower dose strength, better palatability and easier administration [106]. Better bioavailability allows reductions in dosage (reductive dose), reducing pill burden and improving adherence in children [107].

b) **Oncology and Targeted Delivery:** Solid dispersion technology has been used to successfully formulate a number of poorly soluble cytotoxic and targeted chemotherapies [108]. These include sorafenib, sunitinib and tyrosine kinase inhibitors. Recent methods have involved the use of solid dispersions and nanoparticle technology as well as tumour targeting ligands for increased specificity [109].

c) **Biopharmaceutical and Protein Formulations:** Emerging research relates to solid dispersions used for stabilization of biopharmaceuticals, such as proteins and monoclonal antibodies, using freeze drying and dispersions that contain a cryoprotectant [110]. This method allows the formulation of dry powder with improved stability and storage time [111].

8. FUTURE OPPORTUNITIES AND CHALLENGES

8.1 Nanocomposites

Increases in recent research have led to the inclusion of nanotechnology in the field of solid dispersion, resulting in nanostructured dispersions that exhibit a completely different performance compared with conventional solid dispersions [112]. The enhancement in bioavailability of APIs with nano sized particles, both the nanocrystalline and amorphous, within polymeric matrices is superior. Nano dispersions with particle size in the 50–200 nm range have been obtained using technique such as nanoprecipitation, in combination with polymer incorporation, which resulted in particles with improved permeability and absorption [113].

8.2 Artificial Intelligence and Machine Learning in Formulation Design

Stability profiles, process parameters and optimum formulations have been predicted using machine learning algorithms and artificial intelligence tools [114]. The use of high throughput screening along with AI analysis has helped identify appropriate carrier combinations and manufacturing process quickly and efficiently. A neural network and a decision tree have been successfully applied

to the prediction of drug-polymer miscibility and amorphous stability [115]. This computational approach can shorten the development timelines and the number of experiments, which allows for accelerated translation from discovery to clinical use [116].

8.3 Continuous Manufacturing and Industry 4.0

Solid dispersion production is changing in the pharmaceutical industry with the shift to Continuous Manufacturing [117]. Large pharmaceutical companies have already adopted the integrated continuous processes, which involve synthesis, spray drying, milling, and tablet compression. Advanced process controls, real time process analytical technology (PAT) and data analytics allow for optimization of multiple process parameters simultaneously [118]. The case studies in recent years have shown that continuous HME and spray drying systems provide better batch consistency and shorter manufacturing process time than batch operations [119].

8.4 Personalized Medicine and On-Demand Manufacturing

With the recent interest in personalized medicine, patient-specific solid dispersions are being developed and produced on-demand [120]. The 3D printing technologies allow the manufacturing of formulations, with customized drug loading, release profiles, and dosage forms to maximize the patient's individual pharmacogenetics and comorbidities. Small batch production of personalized medicine can be achieved using microfluidic devices and continuous flow reactors [121]. These now in development technologies are a paradigm shift towards precision pharmacotherapy [122].

8.5 Regulatory Evolution and Quality by Design

FDA and EMA have issued guidance documents that have acknowledged solid dispersion technology and provided guidelines for regulatory approval [123]. Comprehensive understanding of critical quality attributes, critical process parameters and establishment of design space have been incorporated in solid dispersion development using Quality by Design (QbD) principles [124]. Amorphous dispersions are gaining acceptance and expedited pathways for well characterized dispersions have been made. Explicit stability testing procedures for amorphous formulations have been developed, which allow prediction of the long-term behaviour [125].

9. CONCLUSION

Solid dispersion technology has grown beyond its original niche formulation technology into a mainstream pharmaceutical technology to solve the problem of poorly soluble drugs. In the last decade (2016-2026), great efforts have been undertaken in the manufacturing technologies, carrier development and characterization techniques as well as regulatory aspects to make solid dispersions an indispensable tool in the modern drug development. With the advent of advanced technologies like electrospinning, supercritical fluid techniques and KinetiSol® immersion, and the incorporation of nanotechnology, artificial intelligence and continuous manufacturing, solid dispersion systems have broadened in range and effectiveness.

Numerous solid dispersion-based formulations have been successfully introduced into the market and the current acceptance of the amorphous technology by regulators demonstrates the clinical relevance of this technology. Today, the applications range from conventional oral dosage forms to special systems for children, elderly and oncology patients. The latest research where nanotechnology, AI (Artificial Intelligence) aided design and personalized medicine methods are being explored indicate that solid dispersions will become more and more significant in the future development of therapeutic products.

There are several issues that still need to be resolved, however, including long term stability of amorphous systems, batch to batch consistency at commercial scale and regulatory harmonisation. The key to future success will be continued investment in fundamental science, understanding the crystallization process and the stabilization of amorphous forms; development and improvement of advanced tools for characterization and prediction; optimization of manufacturing processes through digital transformation and implementation of Industry 4.0; and harmonization of regulatory frameworks to foster innovation. The combination of solid dispersion technology and the development of new pharmaceutical sciences, such as nanotechnology, personalized medicine and artificial intelligence, is expected to bring revolutionary progress in the delivery system of drugs, leading to better therapeutic results for patients suffering from diseases that were once impossible to treat because of the lack of solubility of the pharmaceuticals.

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