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DEVELOPMENT AND CHARACTERIZATION OF AMORPHOUS SOLID DISPERSION OF DARIDOREXANT FROM IMPROVED SOLUBILITY AND BIOAVAILABILITY

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ABSTRACT

This is because about 40 percent of the drugs and 70-90 percent of drug pipeline candidates have poor aqueous solubility, which interferes with oral bioavailability and therapeutic efficacy. Amorphous solid dispersion (ASD) technology has become a commercially viable approach, where the drugs are dispersed in the amorphous state in hydrophilic polymeric carriers to form high-energy states which lead to rapid dissolution and supersaturation. The present review is a systematic review of the basics of ASD such as the principles of thermodynamics, the idea of the spring-parachute effect in which amorphous drugs dissolve quickly (spring) and crystallization is prevented by polymers (parachute). Many polymeric carriers that are important (HPMC, HPMCAS, PVP, Soluplus, and others) are studied, with the criteria of selection being drug-polymer miscibility, molecular interactions, and glass transition temperature. Major preparation method spray drying and hot melt extrusion are compared in terms of scalability, thermal needs and commercial feasibility. Extensive characterization methods (DSC, XRPD, FTIR, dissolution testing) assure physical condition and performance. Mitigation strategies are used to solve critical stability issues such as the crystallization mechanisms and effects of moisture. A wide range of marketed products (Sporanox®, Zelboraf®, Kalydeco®) show clinical efficacy with a 2-10 fold bioavailability enhancement. Emerging trends are the mesoporous silica systems, 3D printing, and artificial intelligence application. ASD technology is still in its progress although there have been difficulties in predictive technology and scale-up; this technology is still in use as a pharmaceutical strategy to overcome solubility constraints in drug development.

KEYWORDS: Amorphous solid dispersion, bioavailability enhancement, poorly water-soluble drugs, hot melt extrusion, spray drying, supersaturation, polymeric carriers.

1. INTRODUCTION

1.1 Solubility Challenges in Modern Drug Development

The pharmaceutical industry is faced with rising incidences of ill-soluble drug candidates in water by the modern discovery programs. Biopharmaceutics Classification System (BCS) classifies drugs into four classes, which depend on the solubility and permeability. Class II (low solubility, high permeability) and Class IV (low solubility, low permeability) drugs are a significant problem with regard to formulation. About 40 percent of the products sold into the market and 70-90 percent of development compounds have poor aqueous solubility (yield less than 100 0g/mL). This trend is supported by modern drug discovery methods, which focus molecular interactions with biological targets rather than physicochemical characteristics, for example, the use of high-throughput screening and computational design.[1] The current candidates have an increased molecular weight, lipophilicity (log P >5) and structural complexity compared to the earlier generations of drugs. Even though it has the advantage of binding its target, these attributes interfere with aqueous solubility. The lack of solubility has far reaching impacts beyond the formulation challenges.[2] Low aqueous solubility reduces dissolution rate in gastrointestinal fluids the rate-limiting step in the absorption of BCS Class II drugs to achieve incomplete and variable oral bioavailability and requires increased doses. Unpredictable pharmacokinetics and the variability of absorption lead to difficulty in optimizing the dose and may impair safety.[3] The effect of pronounced food in the intake of the drug complicates the dosage instructions and results. Drug response varies between individuals, therefore making it difficult to have a common therapeutic regime. Development wise, low solubility puts risk on clinical failure, lengthens timelines and raises costs. Preclinical research can limit the therapeutic potential through under-exposure, whereas clinical trials can fail in spite of good in vitro performance. The industry has invested heavily in the provision of formulation technologies to surpass solubility barriers.[4]

1.2 Solubility Enhancement Strategies: An Overview

There are many different pharmaceutical methods of solving solubility problems.

Micronization or nanosizing of particles reduces their size, which raises the amount of surface area available to dissolve in a solution according to the NoyesWhitney equation, but has practical nanoscale limitations, and does not raise the dissolution of very poorly soluble compounds.[5] Saltation enhances aqueous solubility of the ionizable drugs with the right pKa significantly and is restricted to ionizable compounds, as well as can cause manufacturing/stability issues. The solubility benefits may be lost in the gastro intestinal acidic variable pH. Cyclodextrin complexation entraps drugs inside cyclodextrin hydrophobic cavities to form water-soluble inclusion complexes that may be used in both parenteral and liquid oral preparations, but has limited solubilization and may cause high-concentration safety issues.[6] Lipid-based nanoparticles (SEDDS, solid lipid nanoparticles) dissolve lipophilic drugs in oil phases, which undergoes lymphatic absorption. Although it is suitable with highly lipophilic molecules, such systems need dedicated manufacturing and have been found to suffer stability issues due to lipid oxidation and phase separation. Cocrystal formation entails crystalline drug-coformer complex through non-covalent interactions. Though crystalline stability is retained, solubility improvement can be low and must be accompanied by careful choice of conformer.[7]

1.3 Amorphous Solid Dispersions: A Promising Approach

One of the most triumphant, commercially feasible technologies to enhance the bioavailability of poorly water soluble drugs is called amorphous solid dispersion (ASD) technology. ASDs entail drug dispersion at the molecular scale of drugs in amorphous (non-crystalline) in hydrophilic polymeric carrier matrices. In contrast to ordered crystalline materials, amorphous forms are in high-energy, disordered states which give them much greater apparent solubility and dissolution rates.[8] The underlying principle of the ASD advantage is that amorphous drug dissolves readily to produce supersaturation (the spring), and polymer prevents crystallization to sustain supersaturation (the parachute), which produces longer absorption windows. In 1961, Solid dispersions were proposed by Sekiguchi and Obi who showed that poorly soluble drugs were better absorbed in water soluble carriers.[9] First generation designs were unstable physically, complicated to manufacture, and had scaling problems. Over twenty years of polymer science, processing technologies, and amorphous understanding system development made ASDs cease being a perfunctory topic of scholarly interest to become a common technology in the pharmaceutical industry. Several therapeutic products are commercially marketed using the ASD: Sporanox (itraconazole), Intelence, Zelboraf, Kalydeco, and they have proven their clinical viability and regulatory approval. Technology is still advancing through innovations in the choice of polymer and processing techniques and stability measures.[10]

The present review gives detailed insights into ASD technology as a bioavailability enhancement method, which systematically discusses the basics of amorphous state, thermodynamic and kinetic aspects, solubility enhancement, and polymeric carrier. The preparation techniques such as solvent based, and fusion techniques are given with their comparison. Elaborate strategies of characterization of physical condition, molecular interactions, morphology, and performance are considered. Key stability issues and maintenance policies are taken care of. Technology translation is successful in clinical applications and commercial products. The challenges, emerging trends, and the future perspectives give an insight of further development of ASD technology in solving pharmaceutical development solubility crises.

2. FUNDAMENTALS OF AMORPHOUS SOLID DISPERSIONS

2.1 Amorphous State versus Crystalline State

To realize the benefits and limitations of ASD technology it is important to understand its underlying differences between amorphous and crystalline states. In crystalline substances, the molecules are packed in a very regular, repetitive, lattice structure in the 3 dimensional space and the molecular order is long-range. This crystalline structure is an ordered form in thermodynamic equilibrium, or a low-energy state, with distinct melting temperatures and with particular crystal forms. The periodic arrangement of atoms in crystalline substances makes the material to show sharp transitions in thermal analysis and have characteristic diffraction patterns in X-ray analysis.[11] Amorphous materials, on the other hand, do not have long-range molecular order, and are found in an amorphous, "glass-like" form just like supercooled liquids of exceptionally high viscosity. Molecules in amorphous systems do not form a periodic structure with the arrangement being random unlike crystals. This non-equilibrium is a condition of higher-energy thermodynamic instability. Instead of showing a sharp melting point, amorphous materials show a glass transition temperature (Tg) that, below which the substance is in the form of a rigid glass, and above which, it acts like a viscous liquid or rubbery solid. Thermodynamically, the crystalline form of any particular compound is always more stable than the amorphous form at any particular temperature and pressure. The free energy (G) of the amorphous form is greater than that of the crystalline form which provides a thermodynamic driving force of crystallization.[12] The relationship can be expressed as: ΔG

= G(amorphous) - G(crystalline) > 0 This positive free energy difference explains why amorphous systems tend to crystallize over time, representing the primary stability challenge in ASD formulations. However, this high- energy state is precisely what confers the solubility advantage. The excess free energy of the amorphous form translates into higher apparent solubility and faster dissolution rates compared to the crystalline form. The solubility advantage of amorphous forms can be quantified using thermodynamic relationships.[13] The ratio of amorphous solubility (Sa) to crystalline solubility (Sc) can be approximated by.

$Sa/Sc = \exp(\Delta Hf/RT \times (1 - T/Tm))$

where ΔHf is the heat of fusion, R is the gas constant, T is the temperature, and Tm is the melting point. This relationship demonstrates that compounds with higher melting points and heats of fusion exhibit greater solubility advantages in their amorphous forms. Typical solubility enhancements range from 10 to 1600-fold, depending on the compound's physicochemical properties.[14]

2.2 Mechanisms of Solubility Enhancement in Amorphous Solid Dispersions

The solubility and bioavailability enhancement achieved through ASD technology operates through several interconnected mechanisms that work synergistically to improve drug dissolution and absorption.

Increased Dissolution Rate: The Noyes-Whitney equation states that the rate of dissolution is proportional to (saturation solubility- Cs) divided by bulk concentration (C). Amorphous forms are much more soluble in appearance than crystalline counterparts, so the concentration gradient of dissolution is further enhanced tremendously. Moreover, the amorphous drug in an ASD is molecularly dispersed in the polymer structure, which literally decreases the drug to its tiniest possible size at the molecular scale. This maximizes the amount of surface that is capable of dissolution.[15]

Supersaturation and the Spring-Parachute Effect: Creation and sustenance of supersaturated concentrations of drugs is one of the most crucial mechanisms underlying ASD performance. Upon contact of an ASD with dissolution media, the amorphous drug dissolves readily forming drug concentrations that surpass the equilibrium crystalline solubility. This is a thermodynamically unstable state of supersaturation that gives a great pushing power to drug absorption across biological membranes based on the law of diffusion as defined by Fick. This is described nicely by the spring-parachute model. The amorphous drug is like a spring, which dissolves fast to create supersaturation. The polymer acts as a parachute, preventing nucleation and crystal growth to keep the supersaturated state over a long duration. This time of increased supersaturation is critical in increasing bioavailability since the drug has got enough time to be absorbed before it precipitates. The ways through which polymers prevent crystallization are: raising the viscosity of the solution to slow down the movement of the drug molecules, the presence of a drug-polymer interaction that stabilizes the dissolved drug molecules and adsorption of the crystal nuclei, preventing the growth of the nuclei. The capability of various polymers to sustain supersaturation is highly variant and constitutes a formulation factor of high importance.[16]

Improved Wettability: A large number of poorly water-soluble drugs are also hydrophobic and have poor wetting properties. The wettability of the drug-containing particles of ASDs is enhanced by the hydrophilic polymers, which promote the penetration of dissolution media into the matrix and release of the drug. This is specially needed in drugs that have extremely low solubility in aqueous solutions where the rate-limiting step can be wetting.[17]

Reduced Particle Aggregation: Hydrophobic drugs can also readily form aggregations and agglomerate in aqueous mediums in their crystalline form because they contain low surface energy. ASDs contain a polymer, which is known to sterically stabilize the aggregation of the particles and keep the drug in the molecularly dispersed form.[18]

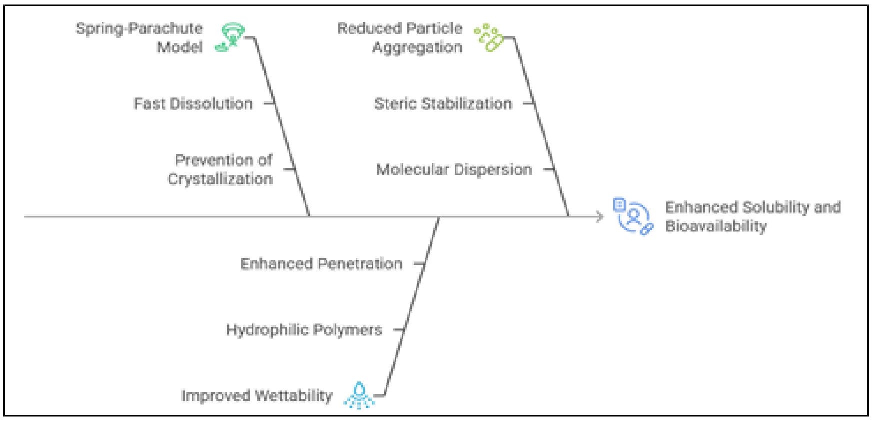

Figure 1: Mechanisms of Solubility Enhancement in Amorphous Solid Dispersions.

2.3 Thermodynamic and Kinetic Stability Considerations

This thermodynamic instability of the amorphous systems is their main strength as well as their main weakness. It is imperative to have knowledge of the factors that govern physical stability in order to have successful ASD development.

Glass Transition Temperature (Tg): The most significant parameter of the amorphous systems is the glass transition temperature. At temperatures below Tg, the amorphous material is in the form of a rigid glass over which the mobility of the molecules is very restricted. The glassy state is very viscous and kinetically blocks the crystallization of molecules in their disordered structure in the presence of thermodynamic driving forces. Beyond Tg, molecular mobility increases exponentially, highly increasing the danger of crystallization. To achieve acceptable physical stability, the ASDs are to be stored at temperatures that are considerably lower than their Tg, and generally, ASDs are kept at temperatures that are 50 C or below, or preferably more so. Tg of drug-polymer ASDs Tg of the mixture can be calculated with the help of the Gordon-Taylor equation or the Fox equation that depend on weight fractions and the Tg of the components.[19]

Molecular Mobility: The amorphous state is crystallized by providing enough mobility of the molecules to form a nucleus and grow the crystal. Molecular mobility depends on factors including temperature as compared to Tg, water content (water is a plasticizer that lowers Tg), polymer properties and drug-polymer interactions. Hydrogen bonding or ionic interactions can result in strong drug-polymer interactions that can cause a high decrease in molecular mobility and increase stability.[20]

Drug Loading: The stability is greatly determined by the percentage of drug in the ASD. Increased drug loadings in general raise the risk of crystallization because of increased likelihood of drug-drug molecular contacts which can act as sites of nucleation. Commercial ASDs that have performed best have drug loadings between 10-40% w/w however this can be different based on the type of drug-polymer mixture.[21]

Crystallization Kinetics: Crystallization can be slowed down kinetically even in thermodynamically favorable conditions. Kelvin equation proves that smaller nuclei are not very stable compared to bigger crystals and an energy barrier to nucleation is provided. Even in cases of thermodynamic instability, polymers have the ability to raise this nucleation barrier and retard the crystal growth kinetics, which offers kinetic stability.[22]

3. POLYMERIC CARRIERS IN ASD FORMULATIONS

3.1 Selection Criteria for Polymeric Carriers

The selection of an appropriate polymeric carrier is one of the most critical decisions in ASD development, as the polymer largely determines the formulation's physical stability, dissolution performance, and processability. Several key criteria guide polymer selection

Drug-Polymer Miscibility: The soluble state of the drug and the polymer to be mixed in the solid state is completely mixed on the molecular level to ensure that the final product is amorphous and phase separation does not occur. Theoretical methods that are applicable in the prediction of miscibility include the Flory-Huggins theory that is related to the interaction parameter.[23] Small positive or negative χ value means favorable mixing. Experimentally, miscibility can be determined by thermal analysis, e.g. by DSC in which a single Tg of the mixture indicates the mixture is miscible, whereas two Tg together indicate the mixture is phase-separated or immiscible.[24]

Molecular Interactions: Mighty firm interactions between the drug and polymer, such as hydrogen bonding, ionic interplay or van der Waals forces are very favored. These interfaces stabilize the amorphous structure by decreasing the mobility of the molecules and impeding crystallization energy barriers.[25] These interactions can be determined and characterized by spectroscopic methods, including FTIR and solid-state NMR. Functional groups in the polymers that can react with the functional groups of the drug (hydroxyl, carboxyl, amine group) are desirable.[26]

Glass Transition Temperature: The Tg of the polymer must also be great enough to make the ASD remain in the glassy state at room temperature. Tg values of polymers when Tg exceeds 100 o C are usually desired in the context of storage stability at room temperature. Gordon-Taylor equation is able to estimate the Tg of the drug-polymer mixture using the respective Tg values and weight fractions.[27]

Hygroscopicity: The polymer can absorb water, and this may have a considerable impact on ASD stability as a plasticizer by lowering Tg and raising the molecular movement. Preferably polymers that absorb less water are used, but to the extent that some hygroscopicity is desirable to dissolve quickly in aqueous solutions. The compromise between the increase in dissolution and stability has to be maximized.[28]

Solubility and Dissolution Properties: The polymer must be dissolvable or swellable very fast in aqueous solutions to release the drugs. PH sensitive polymers can be used to release triggered in particular areas of the gastrointestinal tract. Indicatively, acid-labile drugs can be protected by the use of enteric polymers that dissolve at the intestinal pH and release their drug to the small intestine where absorption occurs.[29]

Safety and Regulatory Status: The polymer has to be orally administrable and of acceptable pharmacologic properties as well as regulated and approved. Polymers of GRAS (Generally Recognized as Safe) status, or those registered in a pharmacopoeial monograph, can be easily approved by the regulators and decrease development time.[30]

Processing Compatibility: The polymer should be able to lend itself to the manufacturing process selected. In the case of hot melt extrusion, the thermal stability and rheology of the polymer should be suitable. In the case of spray drying, the polymer must dissolve in pharmaceutically acceptable solvents and give stable solutions at suitable concentrations.[31]

3.2 Commonly Used Polymeric Carriers Cellulosic Polymers

The most common type of polymers employed in the ASD formulations are cellulosic derivatives, which are present in a number of commercial products. Hydroxypropyl methylcellulose (HPMC) is very versatile and has good film forming properties, good solubility in water and organic solvents and relatively low hygroscopicity. The grades of HPMC are determined by the molecular weight and degree of substitution and influence viscosity, solubility, and performance.[32] Effective use in the products Sporanox ® (itraconazole) and Certican ® (everolimus). Hydroxypropyl methylcellulose acetate succinate (HPMCAS) is a pH-soluble cellulosic polymer that is insoluble in gastric acid, but dissolves in intestinal acid. Amphiphilic nature is given by acetyl and succinoyl substituents which could increase the maintenance of supersaturation. Grades of acetyl succinoyl (AS-LF, AS-MF and AS-HF) with ratios of acetyl and succinoyl groups give distinct pH solubility profiles. One of the most common successful ASD products, which use HPMCAS, are Zelboraf (vemurafenib), Intelence (etravirine), and Incivek (telaprevir). Hydroxypropyl cellulose (HPC) is a water soluble polymer with high film forming properties and low T g than HPMC. Although it is miscible with many drugs well, some formulations with this product may have stability issues due to its relatively low Tg and hygroscopic nature.[33]

Polyvinylpyrrolidone and Derivatives

Polyvinylpyrrolidone (PVP) is a very hydrophilic polymer that is water-soluble with great solubilizing ability and high hydrogen-bonding strength. PVP is also found in many grades of molecular weight (PVP K12, K17, K25, K30, K90) and finds numerous applications in the pharmaceutical industry. The pyrrolidone rings consume the hydrogen bonds with the drug molecules which have hydrogen bond donors which create strong hydrogen bonds with the carbonyl groups of the pyrrolidone rings and thus the molecules are well stabilized against crystallization.[34] PVP, however, is very hygroscopic and this may lower Tg and jeopardize physical stability at humid temperatures. Products that are using PVP successfully include Sporanox oral solution. Copovidone (PVP-VA) is a copolymer of vinylpyrrolidone and vinyl acetate, which has lower hygroscopicity than PVP homopolymers and is also well solubilizing. The Tg is increased by the addition of vinyl acetate component and decreases water uptake, which are some of the limitations of PVP. In Kaletra (lopinavir/ritonavir) tablets PVP-VA is implemented.[35]

Polymethacrylates

The Eudragit® products are a family of polymethacrylate-based polymers with a variety of properties applicable to a wide range of applications in ASD. Eudragit E PO is a cationic copolymer of dimethylaminoethyl methacrylate, butyl methacrylate and methyl methacrylate which is soluble in acidic environment, and which can be used as drug that needs gastric release or enhancement of solubility.[36] Eudragit L100 and L100-55 are anionic copolymer made of methacrylic acid and methyl methacrylate and have a pH dependent solubility profile with a pH greater than 6.0 and pH greater than 5.5 respectively. These intestinal specific release is made possible through these enteric polymers. Eudragit S100 is highly dissolved in even greater PH (> 7.0) and release will occur at the colon.[37]

Soluplus® and Newer Generation Polymers

Soluplus (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) is a more recent generation amphiphilic polymer that is formulated with solid dispersion in mind. The distinctive structure has integrated hydrophilic and lipophilic parts, which give it good solubilizing properties and maintenance of supersaturation. Soluplus can be hot melted and sprayed dried, its hygroscopicity is moderate, and physical stability is good. It has already found application in some of the marketed product, and is still finding its way to the forefront in ASD formulations.[38,39]

Table 1: Commonly Used Polymers in Amorphous Solid Dispersion Formulations.[40,43]

Polymer	**Type**	**Key Properties**	**Advantages**	**Limitation s**	**Example Products**
HPMC (Hydroxypropyl methylcellulose)	Cellulosic	Water- soluble, Tg: 120-180°C, Low hygroscopic ity	Versatile, good film- former, broad compatibility	Limited crystallizati on inhibition for some drugs	Sporanox ®, Certican®
HPMCAS (Hydroxypropyl methylcellulose acetate succinate)	Cellulosic (enteric)	pH- dependent solubility (pH > 5.5- 6.5), Amphiphili c	Excellent supersaturat ion maintenanc e, enteric protection	Requires organic solvents for processing	Zelboraf® , Intelence ®, Incivek®
HPC (Hydroxypropyl cellulose)	Cellulosic	Water- soluble, Tg: 100-130°C	Good film- former, processable	Lower Tg, hygroscopi c	Various formulati ons
PVP (Polyvinylpyrrolid one)	Synthetic homopolymer	Highly water- soluble, Strong H-bonding,	Excellent solubilizing capacity, strong drug interactions	Highly hygroscopi c, stability concerns in humidity	Sporanox ® solution
		Tg: 110- 180°C (MW dependent)			
PVP-VA (Copovidone)	Synthetic copolymer	Water- soluble, Tg: ~106°C, Reduced hygroscopic ity vs PVP	Better moisture resistance than PVP, good miscibility	Still somewhat hygroscopi c	Kaletra®
Eudragit® E PO	Polymethacry late (cationic)	Soluble in gastric pH, Tg: 48°C	Immediate release, taste masking	Low Tg requires plasticizer for HME	Various immediat erelease formulati ons
Eudragit® L100/L100-55	Polymethacry late (anionic)	pH- dependent (pH> 6.0/5.5), Tg: 130- 140°C	Enteric protection, targeted intestinal release	Requires organic solvents	Enteric ASD formulati ons
Soluplus®	Amphiphilic graft copolymer	Amphiphili c, Tg: 70°C, Moderate hygroscopic ity	Excellent supersaturat ion maintenanc e, HME compatible	Relatively new, limited long-term data	Viekira Pak®

3.3 Role of Surfactants and Other Excipients

While the primary carrier polymer is the dominant component in ASDs, additional excipients often play critical supporting roles in enhancing performance and stability.

Surfactants: Hydrophobic drugs can be made to wet and dissolve better with the help of anionic surfactants like sodium lauryl sulfate (SLS) or docusate sodium. Supersaturated states may be improved by the use of nonionic surfactants such as polysorbates (Tween series) or vitamin E TPGS (D- alpha -tocopheryl polyethylene glycol 1000 succinate). Vitamin E TPGS is especially fascinating since it has surfactant capability and possible absorption efficacy when used as an inhibitor of P-glycoprotein. Surfactants are however to be used sparingly because their high concentrations may lead to destabilization of the amorphous form or may lead to processing challenges.[44]

pH Modifiers: Localized acidic micro-environments can be formed by organic acids, like citric acid, tartaric acid or fumaric acid and help dissolve weakly basic drugs. On the other hand, simple substances can be incorporated to increase dissolution of acidic drugs. A combination of these pH modifiers with enteric polymers may be especially helpful in controlling release profiles.[45]

Plasticizers: Hot melt extrusion: Polyethylene glycol (PEG), triethyl citrate, or triacetin can be used as plasticizers to decrease the processing temperatures and enhance the flow characteristics to the polymer. Nevertheless, plasticizers decrease Tg and have to be chosen with caution not to lose their physical stability. Low molecular weight PEGs (PEG 400, PEG 3350) are the most commonly used however their effect on long term stability is to be evaluated.[46]

Antioxidants and Stabilizers: Antioxidants (butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), or ascorbic acid) can be added to drugs prone to oxidative degradation. They are of special interest in the hot melt extrusion in which high temperatures cause oxidation.[47]

PREPARATION METHODS OF AMORPHOUS SOLID DISPERSIONS

Manufacturing method selection is crucial for ASD development, as different methods suit specific drug-polymer combinations with distinct scalability, drug loading capacity, and stability advantages.

3.4 Solvent-Based Methods Solvent Evaporation

Drug and polymer are dissolved in common organic solvent(s), and then evaporation to solid dispersion is obtained through fume hood evaporation, rotary evaporation or freeze-drying. Very fast solvent removal inhibits crystallization, entraping drug in an amorphous state. Implementation benefits: ease, heat-sensitive drug applicability. Limitations: challenging total solvent extraction, solvent residue issues, lack of scalability beyond laboratory scales, necessitates secondary milling which will cause crystallization.[48]

Spray Drying

The commonest, highly commercially successful ASD preparation method is spray drying. Drug-polymer solution is atomized in heated drying chamber with rapid solvent evaporation producing fine amorphous droplets between 10-200 00:m. The droplets are in contact with high surface area heated drying gas (nitrogen/air) which allows milliseconds to seconds evaporation of the droplets, kinetically trapping drug in amorphous form. The important parameters are: inlet/ outlet temperature, feed rate, atomization pressure, gas flow rate. Merits: highly scalable (laboratory to commercial), fast drying generates uniform 1-30 µm particles that can be capsulized/ tableted with little secondary processing, the short residence time is appropriate with thermally sensitive compounds, and well-developed technology is accepted by the regulators. It has certain weaknesses such as the need of organic solvents, which is why a recovery system and explosion-proof equipment are necessary, hygroscopic particles, which need to be kept dry, and phase separation, which should be optimized.[49]

Co-precipitation

Drug-polymer solution added to non-solvent (often water) causes simultaneous precipitation. Relatively simple but challenges in particle size control, drug-polymer mixing, residual solvent removal, and scale-up limit commercial application.[50]

3.5 Fusion/Melting Methods Hot Melt Extrusion (HME)

HME is continuous manufacturing that is solvent-free and highly scalable. Drug and polymer are introduced into extruders, through conveyors, mixed, melted/softened and forced through dies to form continuous extrudate which is then cooled and milled. Twin-screw extruders are dominant, as they are better in mixing. Heated barrels with many temperature zones having two intermeshing, co-rotating screws. Residence time, mixing degree and shear forces are determined by screw configuration (conveying elements, kneading blocks, mixing zones). Feed gets mixed physically through volumetric/gravimetric feeders. Material melts/glass transition and mixes intensively using hot barrel. High temperature, shear and residence time of 1-5 minutes result in homogeneous molten mass that has the drug dispersed at a molecular level. The parameters that are important in HME include barrel temperature profile, screw speed (50-300 rpm), feed rate, screw configuration. Cryogenic mills (also known as cooled extrudate mills, hammer mill, controlled micronization) that was used to make powder which can be used as a tablet/cap where required. The merits of HME include zero solvent-free elimination of residual solvent/environmental issues/explosion-safe plants, continuous operation is amenable to PAT implementation allowing real-time control, high mixing results in high homogeneous dispersions, highly scalable, high regulatory acceptance. Used in Kaletra®, Norvir®, Onmel®. HME constraints include high temperatures are restricted to thermally stable substances (drugs with high melting points (>200°C) or extensive degradation are hard to achieve), must have suitable rheological behaviors, large drug doses are not easy when using low-melting drugs, shear is to be carefully controlled.[51]

Fusion Method

Classical fusion heats drug-polymer mixture above melting points, allowing melting/mixing, followed by cooling and milling. Poor control over mixing homogeneity and cooling rate often results in non-uniform dispersions or partial crystallization. Extended temperature exposure increases degradation risk. HME has largely superseded this for commercial manufacturing.[52]

3.6 Emerging Technologies KinetiSol® Technology

Innovative fusion method using high-speed kinetic mixing generating frictional heat rather than external heating. Drug-polymer mixture subjected to extremely high shear forces with frictional heat rapidly creating molten mass. Ultra-short processing (10-30 seconds) followed by rapid cooling. Ultra-short processing significantly reduces thermal exposure versus HME, enabling processing of thermally labile compounds. Successfully applied in Onmel®.[53,54]

Electrospinning

Novel approach producing ultrafine fibers containing drug dispersed in polymer. Drug-polymer solution subjected to high voltage electric field creates charged droplets drawn to grounded collector with solvent evaporating producing 50-500 nm diameter fibers. Resulting nanofibers have extremely high surface areas enabling ultrafast dissolution. Challenges: low production rates, scaling difficulties, solvent handling, converting fibers to conventional dosage forms. Remains primarily research tool.[55]

Table 2: Comparison of Major ASD Preparation Methods [56,59]

Method	Process Temp	Solvent	Scalability	Advantages	Limitations	Examples
Spray Drying	Low- Medium (50- 120°C)	Required	Excellent	Heat- sensitive suitable, uniform particles, direct powder, established technology	Solvent recovery, hygroscopic particles, explosion- proof equipment	Intelence®, Zelboraf®, Incivek®
HME	High (80- 200°C)	Not required	Excellent	Solvent- free, continuous, excellent mixing, PAT integration	Thermally stable drugs only, high energy, secondary milling	Kaletra®, Norvir®, Onmel®
KinetiSol®	High but brief (120- 200°C)	Not required	Good	Ultra-short exposure, solvent- free, high loading	Specialized equipment, limited experience	Onmel®
Solvent Evaporation	Low (ambient- 60°C)	Required	Poor	Simple, heat- sensitive suitable	Scale-up difficult, residual solvents, milling required	R&D only
Co- precipitation	Low (ambient)	Required	Poor-Fair	Simple, ambient	Particle control difficult, incomplete mixing	Limited use

3.7 Method Selection Criteria

Stability of drugs is the most important: heat-sensitive demands spray drying, thermally stable allows HME/KinetiSol. Melting point of drug is more than 200 o C which is an obstacle to traditional HME. Selection is based on polymer properties (thermal stability, Tg, solvent solubility). Choice is influenced by desired drug loading; HME can only accept a limited number of loadings and spray drying higher loadings. Scale/volume of production: spray drying and HME are both proven to scale, solvent evaporation is laboratory scale. Environmental/ regulatory issues prefer solvent-free techniques. It is possible to assess both spray drying and HME in the course of development.[60]

4. CHARACTERIZATION TECHNIQUES

Comprehensive characterization confirms physical state, molecular interactions, stability, and performance using complementary analytical techniques.

4.1 Physical State Characterization Differential Scanning Calorimetry (DSC)

The thermal analysis most popular with ASDs. Heat flow as a function of temperature indicates glass changes, crystallization, melting. Crystalline materials are characterized by sharp endothermic melting points; none, amorphous conversion. Glass transition (T g) was monitored as change in heat capacity at the baseline. Single Tg drug/polymer implies miscibility. The two different Tg values indicate the existence of phases. Gordon-Taylor equation is used to predict theoretical Tg; miscibility has been confirmed by experimentation. Exotherms during the crystallization are signs of instability. In modulated DSC, overlapping thermal events are separated. Procedure: ambient heat until all the melting has taken place, at temperatures ranging between 5-20 degrees Celsius/min, inert atmosphere, 2-10 mg sample, hermetically sealed aluminum pans.[61]

X-Ray Powder Diffraction (XRPD)

Unambiguous crystallinity detection. Bragg law Crystalline material gives sharp peaks of diffraction at certain angles of 2 θ. Amorphous materials create broad and diffuse halos. Complete lack of crystalline peaks is an affirmation of amorphous conversion. Sensitivity -5% crystallinity. Compare XRPD patterns of pure crystal drug, polymer, physical mixtures, and ASD. The crystallization behavior is observed using variable temperature XRPD. Standard parameters: 5-50° 2θ scan range, 0.02-0.05° step size.[62]

Thermogravimetric Analysis (TGA)

Measures sample mass versus temperature, revealing moisture, residual solvents, thermal degradation, composition. Initial mass loss <150°C indicates moisture/residual solvent critical for stability as moisture plasticizes reducing Tg. Stepwise thermal degradation confirms ASD composition. Coupled TGA-FTIR/TGA-MS identifies evolved gases, definitively identifying residual solvents. Standard: ambient to 500-600°C, 10-20°C/min, nitrogen/air, 5-20 mg sample.[63]

4.2 Molecular Interaction Studies

Fourier Transform Infrared Spectroscopy (FTIR)

None more crucial in identifying/characterizing drugpolymer molecular interactions. Detects the infrared absorption in the form of molecular vibrations. The alterations in the molecular environment or hydrogen bonding are shown by the changes in peak position/intensity/width. As a result of hydrogen bonding, there is a characteristic change in spectrals. Broadening causes a shift to lower wavenumber (red shift) of the donor groups (O-H, N-H). Frequency shifts are observed in acceptor groups (C=O). Compare spectra of pure drug, physical mixtures, polymer, and ASDs.

Raman Spectroscopy

Complementary to FTIR, based on inelastic light scattering. Sensitive to symmetric vibrations and non-polar groups. Advantages: minimal preparation, analyzes through transparent containers, strong aromatic signals. Detects crystallinity sensitively crystalline produces sharper bands versus broadened amorphous bands. Raman chemical imaging enables spatial composition mapping.

Solid-State NMR (ssNMR)

Most definitive for molecular-level interactions and miscibility, requires specialized equipment/expertise. Employs magic angle spinning, cross-polarization, high-power decoupling. ^{13}C CP-MAS NMR detects drug-polymer interactions via chemical shifts. ^{1}H T_1 measurements and 2D correlation definitively establish molecular mixing. Similar relaxation times indicate nanometer-scale mixing; large differences indicate phase separation. Time-consuming, expensive; reserved for detailed studies.[64]

4.3 Morphological Characterization Scanning Electron Microscopy (SEM)

High-resolution imaging of particle morphology, surface characteristics, microstructure. Nanometer-scale resolution reveals particle size, shape, texture, homogeneity. Spray-dried ASDs: spherical/near-spherical with smooth surfaces. HME ASDs: irregular post-milling morphology. Reveals surface crystallization, phase separation. Sample preparation: carbon tape mounting, conductive sputter-coating, high vacuum, 5-20 kV.[65]

Atomic Force Microscopy (AFM)

Three-dimensional surface topography at nanometer resolution. Reveals surface crystallization, nano-scale phase separation. Less common than SEM but valuable for surface phenomena understanding.[66]

4.4 Performance Assessment Dissolution Testing

The majority of critical performance assessment. Traditional USP apparatus (Apparatus 1/2) using biorelevant media (pH 1.2, 4.5, 6.8 buffers; FaSSIF, FeSSIF). Compare crystalline drug, physical mixtures and ASDs with demonstration of solubility advantage. ASDs exhibit increased dissolution rates, increased dissolution levels. The condition of non-sink dissolution resembles in vivo supersaturation, displaying the capability of formulation to create/sustain the supersaturated status.

In Vitro Supersaturation Studies

Specialized assays dissolve ASD in minimal amounts forming high supersaturation, and track the concentration as time progresses. Real-time monitoring is possible using UV-Vis probes, HPLC probes or fiber-optic. The main parameters: maximum attained supersaturation (supersaturation ratio: concentration/crystalline solubility) and time of maintenance.

5. STABILITY CHALLENGES AND MITIGATION STRATEGIES

Physical and chemical stability represent the most significant ASD development challenges.

5.1 Physical Stability: Crystallization and Phase Separation

The process of crystallization consists of nucleation (formation of first nuclei) and crystal growth (addition of molecules to nuclei). They both need to have enough molecules mobility to diffuse/rearrange. Kelvin equation characterizes heightened small nuclei free energy as compared to bulk crystals, forming energy barrier (critical nucleus size). Temperature critical: much lower than Tg Mobility is highly restricted and crystallization is kinetically poisoned. Mobility grows and crystallization likely as Tg is approached. At temperatures above Tg (rubbery state), crystallization is rapid due to high mobility. Water is a strong plasticizer. Absorbency decreases Tg due to the augmentation of free volume and mobility. Even relatively high moisture increments can cause Tg to decrease to a temperature even lower than storage temperature, further speeding up the rate of crystallization by a significant factor.[68]

Affecting Factors

Tg with respect to storage temperature paramount: Tg-storage>50 ^{o}C indicates excellent stability; Tg-storage approaching high risk. Increased drug loading increases the risk of crystallization through the increased probability of drug-drug molecular contacts. The stability of drug-polymer dissolubility and attributes of certain interactions (hydrogen bonding) increase stability at the cost of mobility and the formation of nucleation hindrance. Protectiveness against moisture essential through low permeability packaging (aluminum foil, high barrier films). Mobility directly depends on the conditions in the storage (temperature, humidity). Processing history affects stability through different degrees of mixing of the molecular, residual stress, initial stability. Crystallization thermodynamically is more favourable at a smaller size.[69]

5.2 Chemical Stability

Concerns degradation reactions (hydrolysis, oxidation, drug-polymer reactions) altering potency or forming degradation products.

Heat Exposure: Fusion methods expose materials to temperatures causing thermal degradation. Process optimization minimizes temperature/residence time. Antioxidants protect against oxidative degradation. TGA-MS identifies degradation products.

Drug-Polymer Interactions: While beneficial for physical stability, certain interactions may trigger reactions. Ester-containing polymers may undergo transesterification with hydroxyl/amine drugs. Acidic/basic polymers may catalyze hydrolysis. Comprehensive stability studies essential.

Reactive Impurities: Polymers may contain residual catalysts, peroxides, reactive impurities promoting degradation. Use pharmaceutical-grade polymers with appropriate specifications.

Moisture/Oxygen: Water promotes hydrolysis; oxygen enables oxidation. Appropriate barrier packaging essential. Desiccants in bottles; aluminum foil blisters provide excellent protection.[70]

5.3 Stabilization Strategies

Rational Polymer Selection: Select polymers forming strong specific interactions (hydrogen bonding, ionic) significantly enhancing stability. Flory-Huggins theory/solubility parameters guide screening. Experimental confirmation via thermal analysis/spectroscopy essential.

Optimized Drug Loading: Higher loadings desirable but compromise stability. Stability studies at various loadings identify optimal balance. Most successful commercial ASDs contain 10-40% drug.

Crystallization Inhibitors: Incorporate additional polymers/surfactants specifically inhibiting nucleation/crystal growth. Function via crystal nuclei adsorption, increasing nucleation barriers, altering solution viscosity.

Appropriate Packaging: Low-permeability materials essential for hygroscopic ASDs. Aluminum foil blisters provide excellent moisture barriers. Bottle packaging with foil caps and desiccants can provide adequate protection.

Storage Recommendations: Recommend appropriate conditions (temperature/humidity limits) based on comprehensive stability data. Some ASDs may require refrigeration.

Controlled Release Modifications: For ASDs showing rapid supersaturation followed by precipitation, controlled release strategies (enteric coatings, matrix tablets) modulate release maintaining absorbable supersaturation throughout absorption windows .[71]

6. CLINICAL APPLICATIONS AND MARKETED PRODUCTS

Commercial ASD success demonstrated by numerous marketed products across therapeutic areas validates this bioavailability enhancement approach.

6.1 Marketed ASD Products

Sporanox® (itraconazole), launched 1990s, employed HPMC to enhance poorly soluble antifungal bioavailability, validating the concept.

Antifungal/Antiviral: Onmel® (itraconazole via KinetiSol®), Noxafil® (posaconazole with HPMCAS), Intelence® (etravirine with HPMCAS via spray drying) significantly improved HIV NNRTI bioavailability, Norvir® (ritonavir via HME).

Oncology: Zelboraf® (vemurafenib with HPMCAS) treats BRAF mutation-positive melanoma, enabling oral administration of extremely poorly soluble kinase inhibitor.

Other Areas: Kalydeco® (ivacaftor for cystic fibrosis with HPMCAS), Incivek® (telaprevir for hepatitis C with HPMCAS, discontinued), Fenofibrate ASDs (significantly improved versus micronized), Viekira Pak® (multiple antivirals with Soluplus®).[72,73]

Table 3: Selected Marketed Amorphous Solid Dispersion Products.

Product	**Drug**	**Area**	**Polymer**	**Method**	**Key Benefits**	**Company**
Sporanox®	Itraconazole	Antifungal	HPMC	Spray drying	Improved bioavailability, reduced food effect	Janssen
Onmel®	Itraconazole	Antifungal	HPMCAS	KinetiSol®	Enhanced bioavailability, once-daily	Strides
Noxafil ®	Posaconazole	Antifungal	HPMCAS	Spray drying	Food- independent absorption	Merck
Intelence ®	Etravirine	HIV	HPMCAS	Spray drying	BCS Class IV bioavailability	Janssen
Norvir®	Ritonavir	HIV	Copovidone	HME	Stable solid, improved compliance	AbbVie
Kaletra®	Lopinavir/Ritonavir	HIV	PVP-VA	HME	Combination, no refrigeration	AbbVie
Zelboraf ®	Vemurafenib	Melanoma	HPMCAS	Spray drying	Oral dosing poorly soluble kinase inhibitor	Genentech

Kalydeco®	Ivacaftor	Cystic Fibrosis	HPMCAS	Spray drying	Enhanced absorption	Vertex
Viekira Pak®	Multiple	HCV	Soluplus®	HME	Combination therapy	AbbVie
Fenofibrate	Fenofibrate	Dyslipidemia	Various	HME/ Spray	Improved vs micronized	Multiple

6.2 Clinical Benefits

Improved Bioavailability: 2-10 fold increases versus crystalline formulations, enabling dose reduction, potentially decreasing side effects and improving therapeutic index.

Reduced Food Effects: ASD formulations show reduced food-dependent variability, enabling flexible dosing and improving compliance. Noxafil® tablets show food-independent absorption versus suspension requiring food administration.

Reduced Inter-Patient Variability: More consistent absorption across populations, enabling reliable dose-response relationships and easier titration.

Dose Reduction: Enabled by improved bioavailability reduces pill burden, decreases side effects, improves compliance. Lower doses enable smaller tablets/capsules.

Formulation Flexibility: Converting poorly soluble drug to rapidly dissolving ASD powder enables various dosage forms (tablets, capsules, orally disintegrating tablets, sachets).[74]

6.3 Regulatory Considerations

Widespread regulatory acceptance with numerous FDA, EMA, worldwide approvals. Submissions require comprehensive characterization.

Product Characterization: Demonstrate amorphous nature using multiple techniques (DSC, XRPD, spectroscopy). Characterize drug-polymer interactions and stability role. Thorough stability data under ICH conditions essential.

Process Validation: Demonstrate robust, reproducible production with consistent quality. Critical parameters: inlet/outlet temperatures, feed rate, atomization conditions for spray drying; temperature profiles, screw speed, feed rate for HME. PAT increasingly employed for real-time monitoring.

Bioavailability Studies: Comparative studies demonstrating improved absorption versus conventional formulations support approval.

7. CHALLENGES AND FUTURE PERSPECTIVES

7.1 Current Challenges

Predictive Tools: Polymer selection tools remain inadequate. Flory-Huggins theory/Hansen solubility parameters provide initial guidance but often fail predicting experimental miscibility/long-term stability. Empirical screening remains necessary.

Scale-Up: Laboratory conditions don't always translate to commercial scale. Spray drying must address droplet size distribution, residence time, drying kinetics differences. HME must account for specific mechanical energy, residence time distribution, heat transfer differences.

Long-Term Stability: Predicting shelf-life from accelerated studies complicated by non-Arrhenius crystallization kinetics. Some ASDs stable in short-term studies show gradual long-term crystallization, necessitating extensive testing.

Cost: ASD manufacturing more expensive than conventional approaches due to specialized equipment, solvent recovery, energy requirements, higher polymer content. Cost-benefit balance requires significant clinical/commercial advantages.

Intellectual Property: Complex landscape with multiple patents covering polymers, processes, drug-polymer combinations challenges development, particularly for generics.

Limited Applicability: Not all poorly soluble drugs amenable to ASDs. Very high melting points, extensive thermal degradation, chemical incompatibility with polymers may preclude ASD approaches. Very high molecular weight drugs/peptides generally unsuitable.[76]

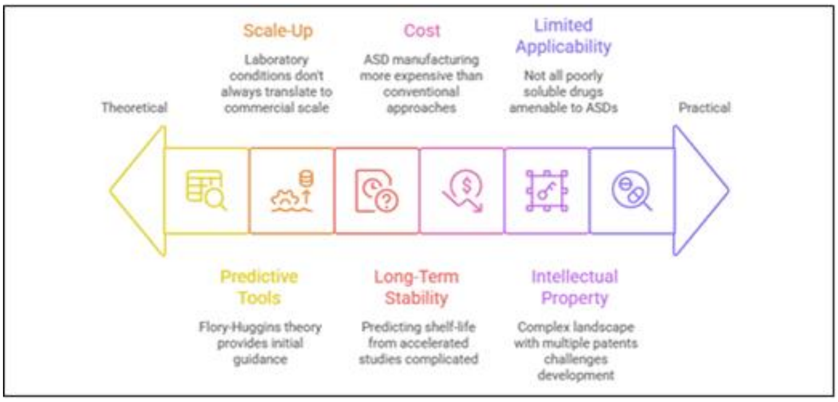

Figure: ASD development challenges range from theoretical to practical.

7.2 FUTURE DIRECTIONS

Increased Adoption: More companies incorporating ASDs for challenging BCS Class II/IV compounds. Maturing technologies make ASDs standard rather than specialized.

Improved Predictive Capabilities: Computational modeling, AI/ML, better physicochemical understanding reduce timelines and increase success rates. Predicting stability/performance from molecular structure would transform development from empirical to rational design.

Hybrid Approaches: Combining ASDs with nanotechnology, lipid-based systems, permeation enhancers addresses standalone limitations, extends applicability. Examples: mesoporous silica with polymer coatings, ASD pellets with release coatings.

Personalized Medicine: 3D printing enabling patient-specific ASDs optimized for individual pharmacokinetics, disease states, genetic polymorphisms. On-demand manufacturing feasible for hospital/pharmacy settings.

Improved Characterization: Advanced ssNMR, nano-thermal analysis, in situ dissolution monitoring provide deeper insights, enabling better formulation design/quality control.

Expansion to Biologics: Future developments may extend principles to biologics, peptides, oligonucleotides stabilization/delivery in solid forms, potentially enabling oral biomacromolecule delivery.[77]

8. CONCLUSION

The amorphous solid dispersion technology is no longer an academic idea, but a mature, commercially proven technology of improving oral bioavailability of poorly water-soluble drugs. Since 40 percent of drugs in the market and as many as 90 percent of preclinical development candidates are poorly soluble in aqueous solution, ASD technology is a solution to a longstanding pharmaceutical problem, namely the conversion of drugs in stable crystalline form to high-energy amorphous form dispersed into hydrophilic polymeric carriers to enable a tremendous enhancement in the rate of dissolution and bioavailability via the generation and maintenance of supersaturation. There is an increased level of scientific knowledge. The thermodynamic basis of amorphous solubility benefits, amorphous solid-state stabilization, and polymer and mechanisms, complex interactions between formulation factors, processing factors, and product performance are better defined, allowing rational design of the formulation. Spray drying and hot melt extrusion are manufacturing technologies that have reached the stage of strong scalability and regulatory acceptance as it is reflected in a number of marketed products in therapeutic indications that show significant clinical advantages such as better bioavailability, diminished food effects, and reliable pharmacokinetics. Thorough characterization methods based on thermal and X-ray examinations, spectroscopy and performance evaluations allow full insight into the physical conditions, the interactions of the molecules, their stability as well as dissolution patterns giving basis to quality management and registration applications. Nevertheless, there are still some obstacles to overcome: physical stability of thermodynamically unstable amorphous states need to be formulated by paying special attention to composition, processing conditions and storage control. The polymer selection and stability forecasting predictive tools need further improvement in terms of reducing empirical screening. Scale-up brings unanticipated challenges that need to be optimized with regard to the processes. In the future, it is expected that the new trends such as mesoporous silica-based systems, co-amorphous formulations, 3D printing, and artificial intelligence usage will be useful to deal with existing limitations and increase the range of applicability. This is strengthened by continuous manufacturing, principles of Quality by Design and process analytical technology. Possible expansion to biologics and peptides would have a enormous scope and influence. Formulation technologies are becoming more essential as new lipophilic candidates of pharmaceutical industry are developed with difficult physicochemical characteristics. With established record, ongoing innovation, and the developing power, ASD technology has been leading the pack with regard to unlocking therapeutic potential of poorly water-soluble drugs, which eventually stands to benefit the patient by improving therapeutic outcomes.

8. OBJECTIVES OF THE STUDY

PRIMARY OBJECTIVE

To develop and characterize an amorphous solid dispersion of Daridorexant for improving its solubility and bioavailability.

SECONDARY OBJECTIVES

- To select suitable hydrophilic polymers for solid dispersion.
- To prepare amorphous solid dispersions using different drug-polymer ratios.
- To evaluate solubility and in-vitro dissolution behavior.
- To study drug-polymer compatibility and solid-state characteristics.
- To compare the performance of ASD with pure drug.

9. DOES OUR STUDY REQUIRE ANY INVESTIGATION INTERVATION TO BECONDUCTED ON PATIENT OR OTHER HUMAN OR ANIMALS?

YES/NO

10. HAS ETHICAL CLEARANCE BEEN OBTAINED FROM YOUR INSTITUTION INCASE OF 10

YES/NO

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