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SOLID DISPERSIONS: AN OVERVIEW OF IMPROVING SOLUBILITY

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ABSTRACT
Solid dispersion technique is a highly efficient method for enhancing the rate at which weakly water-soluble medicines dissolve, hence increasing their bioavailability. Water-soluble carriers are employed in the formulation of solid dispersions to augment the pace at which poorly water-soluble drugs dissolve. The technique of dispersing one or more active medicinal substances in a carrier at the solid state is referred to as solid dispersion. The solubility behaviour of a medicine is a particularly difficult element to address in formulation creation, especially when compared to traditional forms like tablets or capsules. Solid dispersion, on the other hand, offers several advantages over these conventional dosage forms and can be created using numerous methods. This review paper specifically examines the benefits, drawbacks, categorization, preparation methods, mechanisms, and characterization of solid dispersions.

KEYWORDS: Solid dispersion, aqueous solubility, carrier, bioavailability.

1. INTRODUCTION

Drugs with low water solubility generally exhibit poor bioavailability due to limited absorption. Solid dispersion refers to the dispersion of one or more hydrophobic active substances in a hydrophilic inert carrier, achieved through methods such as fusion, solvent, or melting solvent. The user's text is.[1] The Noyes Whitney equation can be utilized to quantify the rate of dissolution, offering multiple parameters to enhance the bioavailability of a medication with low solubility.[2]

Nevertheless, the process of reducing medications to micron size frequently causes the particles to clump together, leading to decreased capacity to mix with liquids. Drugs that experience poor absorption in the gastrointestinal tract due to their slow dissolution rate typically exhibit enhanced solubility and bioavailability when their particle size is reduced. [3] The utilization of solid dispersion formulation is a highly promising and feasible strategy to enhance solubility. A solid dispersion system refers to the dispersion of one or more active substances in an inert carrier or matrix. This dispersion is created through processes such as fusion, solvent evaporation, or melting-solvent. The matrix is hydrophilic, while the medication is hydrophobic. Different types of solid dispersion include simple eutectic mixtures, solid solution, glass solution, glass suspension, and amorphous precipitation in a crystalline carrier compound or complex form.[4] The most straightforward and convenient method of delivering medication is via the oral route. When the ability of a medicine to dissolve in water is lower than 100mg/ml, it is said to have poor solubility, resulting in a low intrinsic dissolution rate.[5]

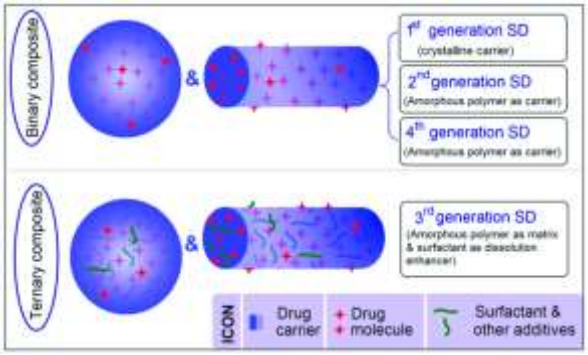

Figure 1: A diagram illustrating the progression of solid dispersions (sds) from the initial first generation to the subsequent third and fourth generations.[6]

1.1 Advantages

- Solid dispersion leads to the formation of smaller particles, resulting in an improved surface area and increased dissolving rate. Therefore, the bioavailability is enhanced. [7]

- To convert the drug's crystalline structure into an amorphous form.
- It exhibits a high rate of dissolution.
- The solubility of the drug is influenced by parameters such as particle size, porosity, and wettability. [8]

1.2 Disadvantages

- The data demonstrates the alterations in crystallinity and reduction in dissolution rate as the material ages.
- Temperature and moisture have a greater detrimental impact on solid dispersions compared to physical mixes.
- These substances are thermodynamically unstable and do not release the drug at an accelerated rate.
- Limited manufacturing on a large scale is hindered by costly preparation methods.
- Challenges arise when integrating it into the formulation of dosage forms.
- Polymers employed in solid dispersion have the capacity to absorb moisture, potentially leading to phase separation and crystal formation.

1.3 Applications of Solid Dispersion

- It boosts the solubility of medications with low solubility, leading to a rise in the rate at which they dissolve.
- This, in turn, improves the absorption and bioavailability of the drug.
- To enhance the solubility of unstable pharmaceuticals and protect them from decomposition processes such as hydrolysis and oxidation.
- To prevent undesired incompatibilities.
- The objective is to achieve a uniform dispersion of a tiny quantity of medication in a solid form.
- The process of administering solid dosage forms containing liquid or gaseous chemicals, with a maximum concentration of 10%.[9]

2. CLASSIFICATION

Six distinct forms of solid dispersions can be identified based on their molecular arrangement. (Displayed in Table-1) Furthermore, the categorization of solid dispersions in different studies relies on the method used for their synthesis. Nevertheless, due to the potential variation in subtypes resulting from various production procedures, it might be contended that solid dispersions have to be identified based on their specific molecular arrangement. Furthermore, it is the molecular arrangement, rather than the preparation method, that determines the attributes of solid dispersions. Hence, it is crucial to choose terminology that signifies the molecular configuration in solid dispersions. Understanding the molecular arrangement will enhance comprehension of the characteristics and behaviour of solid dispersions. Moreover, it would streamline the process of enhancing their features to meet the specific requirements of a particular application.[10]

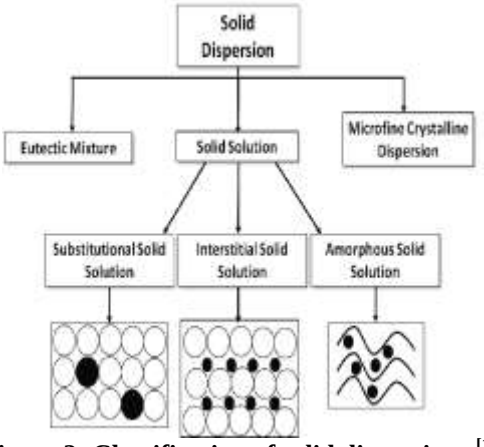

Figure 2: Classification of solid dispersions.[11]

Table 1: Classification of solid dispersions in six subtypes.

Class	Solid Dispersion Type	Matrix	Drug	Remarks	No. Phases
1	Eutectics	C	C	The first type of solid dispersion prepared	2
2	Amorphous precipitations in crystalline matrix	C	A	Rarely encountered	2
3	Solid solutions				
	Continuous solid solutions	C	M	Miscible at all compositions, never prepared	1
	Discontinuous solid solutions	C	M	Partially miscible, 2 phases even through drug is molecularly dispersed	2
	Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 15% from matrix (solvent) diameter, in that case the drug and matrix are substitutional. Can be continuous or discontinuous, when discontinuous: 2phases even through drug is molecularly dispersed	1 or 2
	Interstitial solid solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous	2
4	Glass suspensions	A	C	Particle size of dispersed phase dependent on colling/ evaporation	2

				rate. Obtained after crystallization of drug in amorphous matrix	
5	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/ evaporation rate many solid dispersions are of this type	2
6	Glass solution	A	M	Requires miscibility/ solid solubility, complex formation or upon fast cooling/ evaporation during preparation, many (recent) examples especially with PVP	1

A: Matrix in the amorphous state, **C:** Matrix in the crystalline state, **M:** drug molecularly dispersed throughout the matrix.

The chemical stability of the medicine is influenced by the physical state of the matrix. The degree of crystallinity in the matrix affects the movement and reorientation of the drug molecules, which are essential for degradation events to occur. Understanding and predicting the impact of drug load and method of preparation on dissolving behaviour and stability of solid dispersions is possible when the relationship between these properties and the mode of incorporation is recognized.[12]

3. MECHANISM

Solid dispersions enhance the pace at which weakly water-soluble medicines dissolve through one of the following methods.

- Decrease in particle size
- Enhancement in wetting and dispersing properties
- Transformation of drug's crystalline structure into an amorphous state
- Diminishment of drug particle aggregation and agglomeration.[13]

The Noyes-Whitney equation is a useful tool for quantifying the rate at which a substance dissolves. It offers a range of factors that can be utilized to enhance the bioavailability of medications with low solubility.

$$DC/DT = AD(Cs-C)/h \quad (3.1)$$

The surface area available for dissolution is denoted as A, whereas the diffusion coefficient of the substance is represented as D. Cs - The compound's solubility in the dissolution medium. C represents the drug's concentration in the medium at a specific time t. h refers to the thickness of the dissolution boundary layer that is located next to the surface of the dissolving chemical.

4. POLYMERS

4.1 Vinyl Pyrrolidone Derivatives

The process of polymerization of N-vinylpyrrolidone results in the formation of a chemical called polyvinylpyrrolidone, which is soluble in water. This material was patented in 1939. The classification of these derivatives of N-vinylpyrrolidone is determined on their crosslinking properties. As a result, polyvinylpyrrolidone (PVP) is now extensively used as an additive in the pharmaceutical sector. [14] Subsequent findings have demonstrated that N-vinylpyrrolidone experiences crosslinking at temperatures over 100°C in the presence of alkali hydroxide via a phenomenon referred to as popcorn polymerization. The resultant cross-linked product, referred to as Crosspoint, demonstrates different physicochemical characteristics in comparison to PVP.[15]

4.2 Poly Vinyl Pyrrolidone (PVP)

PVP stands out as one of the most commonly utilized polymeric carriers for creating solid dispersions. A search of the Scopus database revealed approximately 939 records of solid dispersions based on PVP from 1978 to the present. Commercially available, PVP comes in various grades, each characterized by an average (mean) molecular weight within the range of 10,000 to 120,000.[16,17] The assigned K values for different PVP polymer grades are reflective of the average molecular weight, degree of polymerization, and intrinsic viscosity, determined through viscosity measurements and calculated using Fickenscher's formula. As a hydrophilic polymer, PVP possesses an amorphous physical state and is soluble in water, ethanol, isopropyl alcohol, and chloroform.[18,19]

4.3 Copovidone

Copovidone is a copolymer composed of vinyl-pyrrolidone and vinyl-acetate in a ratio of 6:4. It is commercially known by the brand names Kollidon VA64 (BASF, Germany) and Plasdone S-630 (Ashland, USA). It is classified as an amorphous polymer that dissolves in water and is commonly used as a binder and agent for creating films in the pharmaceutical sector.[20] Copovidone demonstrates superior processability when compared to PVP. Dispersions containing Copovidone generate nanoparticles when dissolved, resulting in enhanced solubility and permeability. [21] Furthermore, it exhibits a greater capacity to absorb moisture in comparison to Soluplus.

4.4 Polyethylene Glycol (PEG)

Polyethylene glycol (PEG) is a polymer made up of ethylene oxide units. Its molecular weight can vary between 200 and 300,000 g/mol. The physical properties of PEG depend on its molecular weight. Polyethylene glycol (PEG) with a molecular weight less than 600 is in the form of thick liquids at room temperature. However, PEG with molecular weights up to 8000 and 20,000 solidify into waxy and dry solid forms, respectively.[22,23,24] This polymer demonstrates a semi-crystalline characteristic, comprising both crystalline and amorphous constituents, and possesses a relatively low melting point within the temperature range of 55 to 68°C. It has high solubility in water and several volatile organic solvents such methanol, ethanol, and chloroform.[25] Solid dispersions are considered to be interstitial solid solutions within the framework of PEG.

4.5 Cellulose Derivatives

Cellulose derivatives are often used polymers to stabilize amorphous solid dispersions. Their appeal arises from their substantial molecular weight, ability to resist absorption in the gastrointestinal tract, potent interaction with medicinal molecules, and increased glass transition temperature (Tg). Cellulose is a polysaccharide made up of linear chains of β-D-anhydro glucopyranose units that are connected together in a 1-4 fashion. The lengths of these chains might vary. Methylcellulose (MC), ethylcellulose (EC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), and hydroxypropyl methylcellulose (HPMC) are frequently used derivatives of cellulose that belong to the class of ethers. The categorization of cellulose derivatives is determined by criteria such as solubility in water, chemical substituents, and response to pH.[26]

4.6 Hydroxy Propyl Methyl Cellulose (HPMC)

HPMC is classified as a cellulose-based polymer. Cellulose, which is widely present in the structural elements of plants, has been a fundamental source material for diverse uses for more than 150 years.[27,28,29] HPMC, or hydroxypropyl methylcellulose, is a water-soluble polymer that can also dissolve in other organic solvents such as methanol, ethanol, propanol, and dichloromethane. It is a non-ionic and hydrophilic compound. Due to its ability to dissolve in volatile organic solvents, it is well-suited for creating solid dispersions using techniques like solvent evaporation and large-scale processes such as spray drying. HPMC is present in an unordered state and has a considerably elevated glass transition temperature (Tg) of 180°C. [30] Therefore, when it comes to HPMC-based dispersions, fusion techniques such as Hot Melt Extrusion are not the ideal approaches, especially for APIs with low melting points. Nevertheless, fusion techniques have been widely employed in ternary dispersions, with HPMC playing the role of a crystal nucleation inhibitor and anti-plasticizer. [31]

4.7 Hydroxy Propyl Methyl Cellulose Acetate Succinate (HPMCAS)

HPMCAS is a compound made by combining cellulose succinate, which is a type of ester, with cellulose. It is an amorphous amphiphilic derivative of cellulose. The product is offered in three different grades: L, M, and H, which are determined by the levels of acetyl and succinoyl content.[32] The succinate group in HPMCAS has a pKa of 5.0, causing it to be mostly uncharged below pH 4.0 and charged above pH 6.0. This ionization behavior is a contributing factor to the solubility of the polymer, which is dependent on the pH. HPMCAS is an amphiphilic compound that demonstrates thermal stability and solubility in organic solvents.[33,34] Spray drying is the ideal approach for making solid dispersions based on HPMCAS due to its advantageous features.[35] The inhibition of recrystallization of Nimodipine, Carbamazepine, and Phenytoin, leading to increased solubility and dissolution rates, is attributed to drug-polymer interactions in the solution phase. Furthermore, the addition of lipophilic substituents to a hydrophilic cellulose structure expands the range of solubility for HPMCAS. HPMCAS has the ability to dissolve in APIs with different log P values. This solubility of the drug-polymer combination is believed to contribute to the physical stability of solid dispersions based on HPMCAS.

4.8 Soluplus

Soluplus is a triblock graft copolymer consisting of polyethylene glycol (13% PEG 6000), polyvinyl caprolactam (57%), and polyvinyl acetate (30%). This polymer exhibits amphiphilic properties, where the hydrophilicity is attributed to the presence of PEG, while the lipophilic nature is found within the vinyl caprolactam and vinyl acetate domains within the polymer matrix. The molecular weight of Soluplus generally falls within the range of 90,000 to 140,000 g/mol. It is classified as an amorphous polymer and has a comparatively low glass transition temperature (Tg) of 70°C. [36,37] The expansive characteristic of Soluplus can be harnessed for the creation of delayed-release solid dispersions. Furthermore, as a result of its amphiphilic properties, Soluplus has the ability to create micelles that possess a hydrophobic core. These micelles possess the potential to dissolve different solutes, hence enhancing the extent and speed of dissolution. Often, Soluplus forms micelles that are nanoscale in size, potentially with an average particle size smaller than 100 nm.

5. Techniques For Formulating Solid Dispersions

5.1 Melting method

The melting procedure is alternatively referred to as the fusing method. This approach is suitable for compounds with a low melting point and that are not affected by high temperatures. This method involves the fusion of a medication and a water-soluble carrier at a temperature slightly higher than their eutectic point. The liquefied liquid is swiftly chilled in an ice bath with vigorous stirring until it solidifies into a mass, which is then crushed, pulverized, and sieved.

Ex. The procedure involved the preparation of a solid dispersion of albendazole and urea.[38]

5.2 Freeze drying method

Heat and mass are transferred to and from the product being prepared during the freeze-drying process. The solvent evaporation method can be substituted with this technique. In order to create a lyophilized molecular dispersion, the drug and carrier are co-dissolved in a shared solvent, frozen, then sublimed. This process is known as lyophilization. During the solid dispersion creation process, the medication undergoes low heat stress when using this approach. As soon as the solution is vitrified, phase separation risk can be reduced using this technique.[39]

5.3 Solvent evaporation method

This approach involves dissolving the medication and carrier in a volatile solvent that is acceptable for both substances. The mixture is then evaporated until only a solvent-free film remains. The film is subsequently dehydrated until it reaches a stable weight. The procedure can be accomplished in two sequential stages.

1. Formulating a solution that includes both the matrix material and the medication.
2. The extraction of solvent(s) leading to the creation of a solid dispersion.

Optimal dissolving qualities are achieved by mixing at the molecular level. The primary benefit of this approach is that it can prevent the thermal degradation of medications or carriers due to the comparatively low temperatures needed for the evaporation of organic solvents.[40]

5.4 Melt extrusion method

This method utilizes a co-rotating twin screw extruder to achieve thorough mixing of the active ingredient and carrier, which are manufactured through hot-stage extrusion. The extruder is composed of a barrel, hopper, kneading screw, heating jacket, and die. The carrier and drug are combined in a physical mixture, which is then placed into the hopper. It is then fed via a screw and extruded out the die.[41]

The medication concentration in the dispersion consistently remains at 40% (w/w). The primary benefit of this approach is the ability to produce a wide range of shapes and designs for the heated drug-matrix mixture, which can be used in ocular inserts, implants, and oral dosage forms. Additionally, this technology allows for continuous production. The drawback lies in the fact that thermolabile compounds may undergo degradation as a result of the heat generated by the extruder.[42]

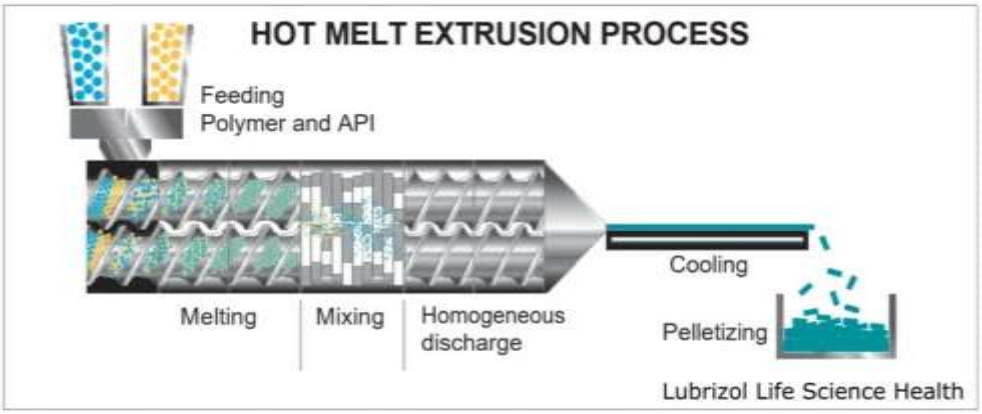

Figure 4: Hot melt extrusion method process.[43]

5.5 Melt Agglomeration Process

This technique is employed to generate solid dispersions, wherein the binder acts as a carrier. SD(s) can be prepared in two different methods:

1. The melting technique involves heating the binder, medication, and excipient to a temperature higher than the melting point of the binder.
2. Administering a solution of medication in melted binder onto the heated substance (spray-on method) using a high-speed mixer.[44]

A rotary processor is a viable substitute for melt agglomeration due to its superior temperature control and ability to integrate higher amounts of binder into the agglomerates.[45]

5.6 Super critical fluid (SCF) technology

Supercritical fluid techniques mostly utilize carbon dioxide (CO2) as a solvent for drugs and matrices, or as an anti-solvent. Supercritical CO2 is employed as a solvent to dissolve both the matrix and medication. The resulting solution is then sprayed through a nozzle into an expansion vessel with lower pressure, causing the formation of particles. The mixture undergoes adiabatic expansion, leading to a swift decrease in temperature. This method does not necessitate the utilization of organic solvents, and due to the ecologically beneficial nature of CO2, it is commonly referred to as a "solvent-free" procedure. The method is referred to as Rapid Expansion of Supercritical Solution (RESS). Nevertheless, the utilization of this method is highly restricted due to the minimal solubility of the majority of medicinal compounds in CO2, which is below 0.01wt-% and diminishes as polarity rises. Hence, attempting to expand this method to a kilogram-scale would be unfeasible.

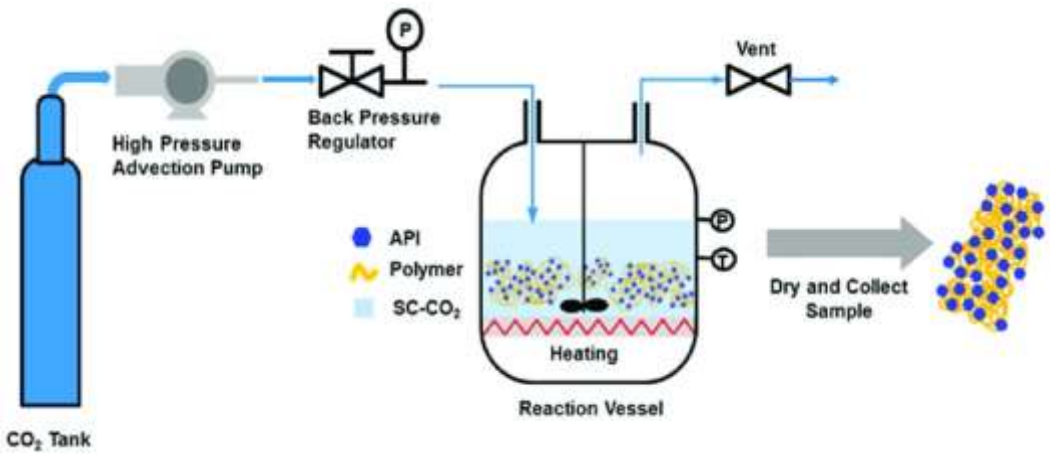

Figure 5: Super critical fluid technology.[46]

5.7 Spray-drying

Spray-drying is one of the most commonly used solvent evaporation procedures in the production of solid dispersions. It consists of dissolving or suspending the drug and carrier, then spraying it into a stream of heated air flow to remove the solvent. Due to the large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation. [47] prepared an alternative solid dispersion by spraying a povidone and diazepam solution into liquid nitrogen, forming a suspension that was then lyophilized.

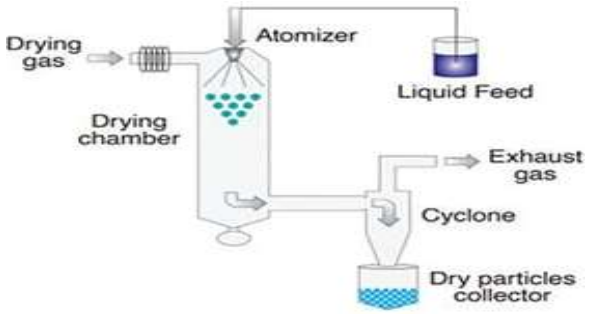

Figure 6: illustration if the spray drying process.[48]

5.8 Dropping solution method

The dropping method enables the crystallization of various substances and yields spherical particles from molten solid dispersions. During laboratory-scale preparation, a molten combination of a drug and carrier is transferred using a pipette and subsequently deposited onto a plate, where it undergoes solidification and forms spherical particles. The viscosity of the melt and the dimensions of the pipette can exert an influence on the size and morphology of the particles. Due to the strong correlation between viscosity and temperature, it is crucial to carefully regulate the temperature to ensure that the molten substance solidifies into a spherical form upon being placed on the plate. Utilizing carriers that undergo solidification at ambient temperature can facilitate the process of dropping. The droplet technique not only streamlines the production process, but also yields a higher dissolving rate. It avoids the use of organic solvents, therefore eliminating any issues related to solvent evaporation. The approach also circumvents the challenges of pulverization, sieving, and compressibility that are typically experienced with alternative melt methods. The dropping approach has limitations, such as the requirement for thermostable medicines and the additional problem posed by the physical instability of solid dispersions.[49]

5.9 Direct capsule filling

Filling hard gelatin capsules directly with the liquid melt of solid dispersions prevents alterations in the drug's crystallinity caused by grinding. Upon cooling to ambient temperature, the molten dispersion solidifies, creating a solid barrier within the capsule. This effectively minimizes the risk of cross contamination and exposure to operators in a dust-free setting. Additionally, the use of this technique resulted in improved fill weight and content uniformity compared to the traditional powder-fill method. Nevertheless, PEG proved unsuitable as a carrier for the direct capsule-filling technique due to its quick dissolution compared to the drug. This led to the formation of drug-rich layers on the surface of the dissolving plugs, hindering further drug dissolution.[50]

5.10 Co-precipitation method

Co-precipitation is a well-established method for enhancing the solubility of medicines with low water solubility, hence improving their bioavailability. In this technique, a nonsolvent is gradually introduced into the solution containing the medication and carrier, while stirring continuously. During the process of adding a substance that is not a solvent, the medication and carrier are combined to create micro particles through coprecipitation. Finally, the resulting micro particle suspension is filtered and subjected to drying. A clear solution was obtained by combining the necessary amount of polymer and drug, followed by the addition of solvent. The Solution was initially dehydrated using vacuum at ambient temperature and subsequently placed in an incubator at 37°C for a duration of 12 hours. Ultimately, it underwent filtration using sieves.[51]

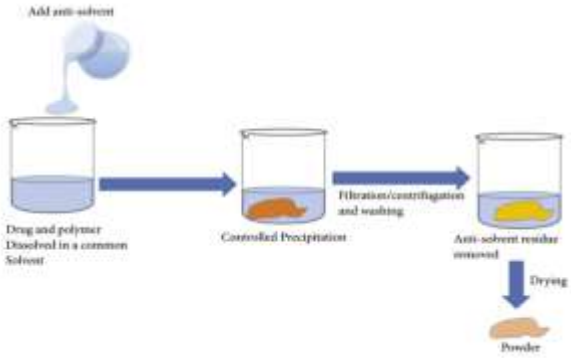

Figure 7: Schematic presentation coprecipitation process.[52]

5.11 Dropping method

This technology, which has been developed to address the challenges associated with the other method, offers a novel approach to creating spherical particles from melted solid dispersions. It aims to facilitate the crystallization of various compounds. A molten drug carrier mixture is dispensed using a pipette and subsequently deposited onto a plate, where it hardens into spherical particles.[53] The dimensions and morphology of the particles can be altered by parameters such as the viscosity of the molten substance and the dimensions of the pipette. The dropping approach circumvents the usage of organic solvents, hence eliminating any issues related to solvent evaporation. This approach also circumvents the challenges of pulverization and compressibility.[54]

6. Evalution of Solid Dispersion

6.1 Estimation of Drug Content

A beaker holding 100ml of phosphate buffer (7.4) is filled with 100mg of solid dispersion. The solid dispersion was repeatedly agitated in a circular motion until it totally released its contents. The solution is subjected to filtration and subsequent analysis using UV spectrophotometry.[55]

6.2 Drug Entrapment Efficiency [EE]

By following formula, the drug entrapment efficiency can be calculated.

EE% = actual drug content /Theoretical drug content ×100 (6.2)

6.3 Particle Size Analysis And Morphological Characteristics

The samples are examined using an electron microscope. A representative sample from each batch has to be extracted and evenly distributed in a phosphate buffer solution with a pH of 7.4.[56]

6.4 Moisture Sorption Characteristics

The solid dispersion is placed in a petri dish and stored in an activated desiccating chamber at a temperature of 10°C for a duration of one week in order to eliminate any remaining residue.[57]

Equilibrium moisture sorption = amount of moisture sorpted at equilibrium /dry weight of material (6.4)

6.5 In-Vitro Drug Release Studies

The dissolution profile of each solid dispersion is assessed using a rotatory paddle, which is immersed in a dissolving media. Subsequently, spectrophotometry is employed to analyze the results.[58]

6.6 Stability Study of The Formulation

The test is conducted on the optimal formulation and is packaged in an amber-colored bottle, securely sealed with cotton and topped with metal.[59]

6.7 Differential Scanning Calorimetry [DSC]

A commonly employed method for quantifying the quantity of crystalline substance is known as "differential scanning calorimetry". The samples undergo heating at a consistent rate, and the DSC detects the energy required for this process. It is capable of identifying the temperatures at which thermal events may occur. Thermal events encompass a range of phenomena including the transition from a glassy state to a rubbery state, recrystallization, melting, or deterioration. Moreover, the energy required for melting and the subsequent formation of crystals may be measured. The thermal energy released during the process of melting can be utilized to determine the quantity of crystalline substance present. [60]

CONCLUSION

The concept of solid dispersion is a straightforward method for enhancing solubility, particularly when compared to other ways. Based on the literature, it can be inferred that the solubility of pharmaceuticals with low water solubility, the stability of unstable drugs, and subsequently the bioavailability may be effectively improved through the use of solid dispersion technology. The enhanced solubility of the medicine is responsible for the rise in its bioavailability. The increased solubility of solid dispersion is attributed to the transformation of the medication into an amorphous state.

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