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SOLID DISPERSION: AN APPROACH TO ENHANCE ORAL BIOAVAILABILITY OF POORLY WATER SOLUBLE DRUGS

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ABSTRACT: Improving oral bioavailability of drugs those used as solid dosage forms remains a challenge for the formulation scientists due to solubility problems associated with it. The dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form of relatively insoluble drugs. Solid dispersion techniques have attracted the considerable interest in improving the dissolution rate of highly lipophilic drugs, thereby improving their bioavailability by micronization, improving wettability and use of a surface active agent. The term solid dispersion refers to a cluster of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. This article reviews the historical background of solid dispersion technology, limitations, classification, and various preparation techniques with its advantages and disadvantages. This review also discusses the recent advances in the field of solid dispersion technology. The experience with solid dispersions over the last 10-15 years indicates that this is a very fruitful approach in improving the release rate and oral bioavailability of poorly water-soluble drugs. Hence, this approach is expected to form a basis for the development of many poorly water-soluble and water-insoluble drugs in their solid-dispersion formulations in the future.

Keywords: Solubility; Dissolution, Bioavailability, Solid dispersion, Solubility enhancement

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INTRODUCTION: The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of administration. From a patient's perspective, swallowing a dosage form is a comfortable and familiar means of taking medication.

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As a result, patient compliance and hence, drug treatment is typically more effective with orally administered medications as compared with other routes of administration. The poor aqueous solubility and dissolution rate of API is one of the biggest challenges in pharmaceutical development and is becoming more common among new drug candidates over the past two decades due to the use of high throughput and combinatorial screening tools during the drug discovery and selection phase. According to the Biopharmaceutics Classification System (BCS), a drug compound is poorly soluble if the highest dose strength is not soluble in 250 ml

aqueous media over the pH range at 37 °C between 1 and 7. Such compounds are classified as BCS class II drugs. If drugs are both poorly soluble and poorly permeable through the membranes of the gastrointestinal (GI) tract, then they are classified as class IV. Formulation scientists were pushed to come up with strategies to develop such problematic compounds into orally bioavailable and therapeutic effective drugs [5].

Solubility and the amorphous state various approaches to overcome the poor aqueous solubility of drug candidates have been investigated in drug research and development such as salt formation, prodrug formation, particle size reduction, complexation, micelles, microemulsions, nanoemulsions, nanosuspensions, solid–lipid nanoparticle and solid dispersion which is considered one of the most successful strategies to improve the dissolution profile of poorly soluble drugs. The term solid dispersions have been defined as a dispersion of one or more API in an inert carrier or matrix at the solid state prepared by solvent, melting or solvent–melting method [6, 7].

The API in solid dispersions can be dispersed as separate molecules, amorphous particles, or crystalline particles while the carrier can be in the crystalline or amorphous state. Numerous studies on solid dispersions have been published and have shown many advantageous properties of solid dispersions in improving solubility and dissolution rate of poorly water-soluble drugs. Solid dispersion systems can increase dissolution rate and bioavailability of water-insoluble drugs as when these are exposed to aqueous media, the carrier dissolves, and the drug is released as very fine colloidal particles.

This greatly reduces particle size and increases surface area, which results in improved dissolution rates per oral absorption. Furthermore, no energy is required to break up the crystal lattice of a drug during the dissolution process. Drug solubility and wettability may be increased by surrounding hydrophilic carriers. This approach has been used for a variety of poorly soluble drugs such as nimesulide, ketoprofen, tenoxicam, nifedipine, nimodipine, ursodeoxycholic acid, carbamazepine, celecoxib, and albendazole. Various hydrophilic carriers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl cellulose (HPC), hydroxypropylmethylcellulose (HPMC), gums, sugar, mannitol, urea, hydroxy-propyl methyl cellulose phthalate, gelucires, eudragits, and chitosan have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs.

Solid Dispersions: The term solid dispersion refers to a group of solid products consisting of at least two different components, a hydrophilic matrix, and a hydrophobic drug. The drug can be dispersed molecularly, in amorphous particles (clusters) or crystalline particles. Pharmaceutical polymers are used to create this matrix, and their selection is based on many factors, including physicochemical (*e.g.*, drug-polymer miscibility and stability) and pharmacokinetic (*e.g.*, rate of absorption) constraints. Fig. 1 categorizes various possible categories of solid dispersions [3].

The solid-dispersion components consist mainly of active pharmaceutical ingredients (API), the polymer, plasticizers, stabilizers, and other agents. Chiou and Riegelman defined the term solid dispersion as "A dispersion involving the formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixtures" In solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid and excess drug precipitates as fine colloidal particles or oily globules of submicron size.[12] The development of solid dispersions as a practically viable method to enhance the bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization, cosolvency, and particle size reduction.

The Classification of Solid Dispersions: Depending on the physical state of the carrier which is crystalline or amorphous, the solid dispersions are divided into crystalline solid dispersions and amorphous solid dispersions respectively. The solid dispersions can also be classified into four generations based on their composition.

First Generation Solid Dispersions: The first description of solid dispersions was from Sekiguchi and Obi in 1961. They noted that the formulations

of eutectic mixtures improve the rate of drug release and, consequently, the bioavailability of poorly water-soluble drugs. In the same decade, several solid dispersions were described using poorly water-soluble drugs, such as sulfathiazole and chloramphenicola using urea as high water-soluble carrier [7]. These solid dispersions produced faster release and higher bioavailability than conventional formulations of the same drugs. The small particle size and the better wettability of the drug were the main reasons for the observed improvements in bioavailability.

Later, Levy and Kaning developed solid dispersion systems, containing mannitol as a carrier, by preparing solid solutions through molecular dispersions instead of using eutectic mixtures. The observed Improvements were attributed to a faster carrier dissolution, releasing microcrystals or particles of the drug. These solid dispersions, which could be designed as first generation solid dispersions.

Second Generation Solid Dispersions: In history, it was observed that solid dispersions, where the drug was maintained in the crystalline state, might not be as effective as the amorphous, because the former were more thermodynamically stable. Therefore, the second generation of solid dispersions appeared, containing amorphous carriers instead of crystalline. Indeed, the most common solid dispersions do not use crystalline carriers but amorphous. In the latter, the drugs are molecularly dispersed in an irregular form within an amorphous carrier, which is usually polymers. Polymeric carriers have been the most successful for solid dispersions because they can originate amorphous solid dispersions.

They are divided into fully synthetic polymers and natural product-based polymers. Fully synthetic polymers include povidone (PVP), polyethylene glycols (PEG) and polymath acrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxyl propyl methyl cellulose (HPMC), ethyl cellulose or hydroxyl propyl cellulose or starch derivates, like cyclodextrins.[22] Amorphous solid dispersions can be classified according to the molecular interaction of drug and carriers in solid solutions, solid suspensions or a mixture of both. In amorphous solid solutions, drug and carrier are miscible and soluble, originating a homogeneous molecular interaction between them. In these systems, the drug and carrier interaction energy is extremely high, resulting in a true solution. The use of polymers in the preparation of a true solid solution creates an amorphous product in which the crystalline drug is dissolved.

This type of amorphous solid dispersion is homogeneous on a molecular level. Therefore, only one phase is present. Amorphous solid suspensions occur when the drug has limited carrier solubility or an extremely high melting point. Drugs with a high melting point are candidates for producing an amorphous solid suspension. Molecularly, the obtained dispersion does not have a homogeneous structure but is composed of two phases. Small drug particles, when dispersed in polymeric carriers, can provide an amorphous final product [9].

When a drug is both dissolved and suspended in the carrier, a heterogeneous structure is obtained with mixed properties of amorphous solid solutions and amorphous solid suspension. In second generation solid dispersions, the drug is in its supersaturated state because of forced solubilization in the carrier. These systems can reduce the drug particle size to nearly a molecular level, to solubilize or co-dissolve the drug by the water-soluble carrier, to provide better wettability and dispersibility of the drug by the carrier material, and to produce amorphous forms of the drug and carriers. In these solid dispersions, the carrier dissolution (or mixtures of carriers) dictates the drug release profile [13, 14].

Third Generation Solid Dispersions: Recently, it has been shown that the dissolution profile can be improved if the carrier has a surface activity or self-emulsifying properties, therefore the third generation solid dispersions appeared. These contain a surfactant carrier or a mixture of amorphous polymers and surfactants as carriers. These third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization. Other surfactants and emulsifiers such as sodium lauryl sulfate (SLS), tween 80, d-alpha tocopheryl polyethylene glycol 1000

succinate (TPGS 1000), polyoxyethylene hydrogenated castor oil and sucrose laurate are used as additives in solid dispersions. De Waard *et al*., incorporated SLS in the sugar glass based solid dispersions and prepared tablets [18]. A physical mixture of SLS and sugar glass based solid dispersions were also compressed to make standard tablets. The dissolution of tablets prepared from solid dispersions in which SLS was incorporated was strongly improved compared to standard tablets.

Fourth Generation: The fourth generation solid dispersion is a controlled release solid dispersion (CRSD) containing poorly water-soluble drugs with a short biological half-life. CRSD of poorly water-soluble drugs often requires two targets: solubility enhancement and extended release in a controlled manner. In CRSD, the molecular dispersion of poorly water-soluble drugs in carriers will improve the drug solubility while water-insoluble polymers or swellable polymers can be used to retard the drug release in the dissolution medium [1]. The CRSD can deliver an adequate amount of drug for an extended period and thus offer many advantages such as improved patient compliance due to reduced dosing frequency, decreased side effects, more constant or prolonged therapeutic effect for poorly water-soluble drugs.

The conventional polymers used for retarding the release of poorly water-soluble drugs in CRSD include ethyl cellulose (EC), HPMC, Eudragit- RS, RL, poly (ethylene oxide) (PEO) and carboxy-vinylpolymer (Carbopol). These polymers, which are insoluble or dissolve very slowly in water, can sustain the release of poorly water-soluble drugs [9]. The CRSD uses these sustainable polymers or combines these polymers in solid dispersion systems or can use other materials having the solubilizing capacity and sustaining action. The CRSD has two main mechanisms by which the drug can be released: diffusion and erosion.

Cui *et al.,* prepared sustained-release nitrendipine microspheres having solid dispersion structure. HPMCP-55 and aerosil were used as the solid dispersing agents to improve the dissolution of nitrendipine while Eudragit- RS PO and EC were selected as the retarding agent to control the drug release rate. The bioavailability results in dogs showed the superior prolonged absorption profile and bioavailability improvement of solid dispersion microspheres compared to the reference tablets (Baypress™) and the conventional tablets.

Ohara *et al.,* investigated the dissolution mechanism of indomethacin from extended release solid dispersion system with EC and HPMC (1:1). It was concluded that the hydrophobic interaction between indomethacin and EC occurred under lower pH region and strongly delayed the dissolution of indomethacin. Tran et al. prepared polyethylene oxide (PEO)-based CRSD is containing aceclofenac, Gelucire 44/14, poloxamer 407, and pH modifier (Na_2CO_3) for controlled release of the poorly water-soluble drug. The CRSD improved the dissolution profile of

Mechanism of Drug Release from Solid Dispersions: There are two main mechanisms of drug release from immediate release solid dispersions: drug-controlled release and carrier controlled release. When solid dispersions are dispersed in water, the carriers often dissolve or absorb water rapidly due to their hydrophilic property and form concentrated carrier layer or gel layer in some cases.[12, 17] If the drug dissolves in this layer, and the viscosity of this layer is high enough to prevent the diffusion of the drug through it, the rate-limiting step will be the diffusion of the carrier into the bulk phase, and this mechanism is carrier-controlled release.

If the drug is insoluble or sparingly soluble in the concentrated layer, it can be released intact to contact with water, and the dissolution profile will depend on the properties of drug particles (polymorphic state, particle size, drug solubility). These two mechanisms often occur simultaneously because the drug may be partly soluble or entrapped in the concentrated carrier layer. However, these mechanisms help explain the different release behaviors of solid dispersions [13].

Advantages of Solid Dispersions over Other Strategies to Improve the Bioavailability of Poorly Water-Soluble Drugs: Improving drug bioavailability by changing their water solubility has been possible by chemical or formulation approaches. Chemical approaches to improving bioavailability without changing the active target

can be achieved by salt formation or by incorporating polar or ionizable groups in the main drug structure, resulting in the formation of a pro-drug. Solid dispersions appear to be a better approach to improve drug solubility than these techniques because they are easier to produce and more applicable [20]. For instance, salt formation can only be used for weakly acidic or basic drugs and not for neutral.

Furthermore, it is common that salt formation does not achieve better bioavailability because of it's *in-vivo* conversion into acidic or basic forms. Moreover, these type of approaches has the major disadvantage that the sponsoring company is obliged to perform clinical trials on these forms since the product represents an NCE. Formulation approaches include solubilization and particle size reduction techniques, and solid dispersions, among others [23, 12]. Solid dispersions are more acceptable to patients than solubilization products since they give rise to solid oral dosage forms instead of a liquid as solubilization products usually do.

Milling or micronization for particle size reduction is commonly performed as approaches to improve solubility, based on the increase in surface area. Solid dispersions are more efficient than these particle size reduction techniques since the latter has a particle size reduction limit around 2–5 mm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine and, consequently, to improve the bioavailability. Moreover, solid powders with such a low particle size have poor mechanical properties, such as low flow and high adhesion, and are extremely difficult to handle [1].

The Advantageous Properties of Solid Dispersions: Management of the drug release profile using solid dispersions is achieved by manipulation of the carrier and solid dispersion particles properties. Parameters, such as carrier molecular weight and composition, drug crystallinity and particle porosity and wettability, when successfully controlled, can produce improvements in bioavailability.

Particles with Reduced Particle Size: Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution, the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water-soluble drug and highly soluble carriers. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability [3].

Particles with Improved Wettability: A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts, when used, can significantly increase the wettability properties of drugs. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects [8]. Recently, the inclusion of surfactants in the third generation solid dispersions reinforced the importance of this property.

Particles with Higher Porosity: Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties, for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile [17].

Drugs in the Amorphous State: Poorly water-soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state because no energy is required to break up the crystal lattice during the dissolution process [19, 23].

In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher

amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them [22].

Methods of preparations of solid dispersion are as follows:

A) Solvent Evaporation Method: After complete dissolution of drug and carrier in an organic solvent, the solvent is evaporated. The solid mass is ground, sieved, and dried. Okonogi *et al*., were prepared solid dispersions of ofloxacin with polyethylene glycol by a solvent evaporation method. Modified solvent evaporation method Drug is dissolved in an organic solvent at its saturation solubility with continuous stirring for some time. The polymer is suspended in a sufficient amount of water (up to a wet mass of polymer). The drug solution is poured at once into polymer suspension. The entire solvent is evaporated. The mass obtained is dried [3].

B) Melting Fusion Method: This method involves the preparation of a physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized, and sieved. The modification in the method can be done by pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate.

Also, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process [2]. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures. Advantage of the melting method is that it is economic and solventless process, however, this method is not suitable for the drug or carrier which is unstable at fusion temperature or evaporates at a higher temperature.

Some of the means to overcome these problems could be by heating the physical mixture in a sealed container or melting it under vacuum or in the presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier. *E.g.,* Albendazole and urea solid dispersions were prepared by this method [5].

C) Solvent Melting Method: Accurately weighed drug is dissolved in an organic solvent. The solution is incorporated into the melt of mannitol and cooled suddenly, and mass is kept in a desiccator for complete drying. The solidified mass is crushed, pulverized, and passed through a sieve. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose (less than 50 mg).

D) Kneading Method: A mixture of accurately weighed drug and carrier is wetted with solvent and kneaded thoroughly for some time in a glass mortar. The paste formed is dried and sieved. Chaulang et al. was prepared furosemide and crospovidone solid dispersions by this method.

E) Co-Grinding Method: Accurately weighed drug powder and the carrier are mixed for some time using a blender at a specified speed. The mixture is then charged into the chamber of a vibration ball mill. A certain number of steel balls are added. The powder mixture is ground. Then the sample is collected and kept at room temperature in a screw-capped glass vial until use. Nokhodchi prepared chlordiazepoxide and mannitol solid dispersion by this method [12].

F) Co-Precipitation Method (Co-Evaporates): Accurately weighed carrier is dissolved in water and drug is dissolved in an organic solvent. After complete dissolution, the aqueous solution of carrier is then poured into the organic solution of the drug. The solvents are then evaporated. The dispersion is pulverized with pestle and mortar, sieved and dried.

G) Spray Drying Method: The Accurately weighed amount of drug with lipid carrier is dissolved in methanol to obtain a clear solution. This solution is then spray dried using a laboratory scale dryer. The sample is stored over silica gel in a vacuum desiccators [19].

H) Gel Entrapment Technique: Carrier which has a tendency to swell is dissolved in a suitable organic solvent to form a clear and transparent gel. The drug is then dissolved in the gel by sonication

for a few minutes. The organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by glass mortar and sieved.

I) Direct Filling: Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross-contamination and operator exposure in a dust-free environment, better fill weight, and content uniformity was obtained than with the powder-fill technique.

However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented the further dissolution of the drug [16].

J) Lyophilization Technique: has been thought of a molecular mixing technique where the drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular Lyophilization dispersion [15].

K) Electrospinning Method: The electrospinning technology was used in the polymer industry combines solid dispersion technology with nanotechnology. In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. As the solvent evaporates, the formed fibers can be collected on a screen to give an on woven fabric, or they can be collected on a spinning mandrel. The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest and the cheapest technique. This technique can be utilized for the preparation of solid dispersions in the future.

L) Supercritical Fluid (SCF) Technology: Supercritical CO_2 anti-solvent induces the precipitation about 100- fold faster than the liquid anti-solvent, not allowing enough time for the drug and the polymer domains to separate. Thus, supercritical CO_2 precipitation can provide a more dispersed solid mixture. Supercritical CO_2 -based precipitation is superior to the liquid based precipitation or the milling process.

Moneghini *et al.*, demonstrated a solid dispersion of carbamazepine in polyethylene glycol (PEG)-4000, produced by CO_2 method, increased the rate and the extent of dissolution of carbamazepine. In this method, a solution of carbamazepine and PEG4000 in acetone was loaded in a pressure vessel, in which supercritical CO_2 was added from the bottom to obtain solvent-free particles. Conventional methods *i.e.* spray drying, solvent evaporation and hot melt method often result in low yield, high residual solvent content or thermal degradation of the active substance.

In supercritical fluid anti-solvent techniques, CO_2 is used as an anti-solvent for the solute but as a solvent concerning the organic solvent. Different acronyms w processes: aerosol solvent extraction system (ASES), precipitation with a compressed fluid anti-solvent (PCA), gas anti-solvent (GAS), solution enhanced dispersion by supercritical fluids (SEDS) and supercritical anti-solvent (SAS) was used by various authors to denote micronization[23].

M) Dropping Solution Method: The dropping method facilitates the crystallization of different chemicals and produces round particles from melted solid dispersions. In laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipette and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature-dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate, it solidifies to a spherical shape.

The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process but also gives a higher dissolution rate. It does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting, and compressibility

difficulties encountered with the other melt methods. Disadvantages of the dropping method are that only thermostable drugs can be used and the physical instability of solid dispersions is a further challenge [17].

Solid Dispersions Disadvantages: Despite extensive expertise with solid dispersions, they are not broadly used in commercial products, mainly because there is the possibility that during processing (mechanical stress) or storage (temperature and humidity stress) the amorphous state may undergo crystallization. The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization [21].

Moreover, most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate. Another drawback of solid dispersions is their poor scale-up for manufacturing [18].

Characterization of Physicochemical Properties:
Differential Scanning Calorimetry (DSC): The basic principle of thermal analytical approaches is the dynamic changes in the solid-state properties of material initiated by the heating or cooling process. DSC, the most commonly used thermal technique for solid dispersion characterization, provides accurate information about melting point, glass transition temperature as well as the energy changes associated with the phase transitions, including crystallization and fusion process.

The lack of a drug melting peak in the DSC thermogram of a solid dispersion indicates that the drug exists in an amorphous form. In DSC, the glass transition endotherm, crystallization exotherm, and fusion endotherm can also be quantified and used to calculate the degree of crystallinity [15].

Powder X-ray Diffraction (PXRD): PXRD is the most widely used method to identify and characterize the crystalline state of drugs in solid dispersions. This method can detect material with long-range order as well as expose sharp diffraction peaks that indicate crystalline compound with characteristic fingerprint region. Thanks to the specificity of the fingerprint, the drug crystallinity can be separately identified from the carrier crystallinity and thus can differentiate the amorphous state and crystalline state of drugs in solid dispersions. However, the crystallinities under 5–10% fraction may not be detected by PXRD [18].

Fourier Transformed Infrared spectroscopy (FTIR): FTIR is a common technique used to investigate the intermolecular interaction and drug–carrier compatibility because it can detect the physical and chemical reaction between drug and carrier. Hydrogen bonding between drugs and carriers, which is very important to explain the physical state and the stability of drugs in solid dispersions can also be identified by FTIR.

Thermal Gravimetry Analysis (TGA): TGA is a method of thermal analysis that measures the weight change as a function of time and temperature, thereby providing information about the stability of a material and the compatibility of different materials in a solid dispersion mixture. This method can provide useful information about the stability of drugs and carriers as well as the chemical and physical processes in solid dispersions to decide the preparation method and the processing parameters for solid dispersion preparation.

Other common applications in the pharmaceutical sciences include the determination of moisture and solvent content as well as decomposition, vaporization or sublimation temperatures. However, this technique is not effective for materials that do not exhibit a weight change during degradation and some processes which do not involve the loss of mass. Similar to the DSC method, TGA results are changeable and depend on the conditions of the sample and experimental process, which is difficult to compare the work of one researcher to another.

Applications of Solid Dispersions:

- ✓ To increase the solubility of poorly soluble drugs, thereby increasing the dissolution rate, absorption, and bioavailability.

- ✓ To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerization, photo-oxidation, and other decomposition procedures.
- ✓ To reduce the side effect of certain drugs.
- ✓ Masking of unpleasant taste and smell of drugs.
- ✓ Improvement of drug release from ointment creams and gels.
- ✓ To avoid undesirable incompatibilities.
- ✓ To obtain a homogeneous distribution of a small amount of drug in a solid state.
- ✓ To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- ✓ To formulate a fast release primary dose in a sustained released dosage form.
- ✓ To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- ✓ To reduce pre systemic inactivation of drugs like morphine and progesterone.

CONCLUSION: Solid dispersions are currently considered one of the most effective methods to solve the low bioavailability problem of poorly water-soluble drugs. Although some problems relating to instability and scalability remain; novel and optimized manufacturing techniques with high potential to overcome these problems are being introduced, thanks to academic and industrial researches. This review documents current efforts to overcome these problems and discusses critical aspects for a better understanding of solid dispersions.

Most of the promising NCEs are poorly water-soluble drugs, which may present a lack of therapeutic effect, because of their low bioavailability. Solid dispersions are one of the most attractive processes to improve drugs' poor water solubility. Third generation solid dispersions can improve their stability and performance by increasing drug-polymer solubility, amorphous fraction, particle wettability, and particle porosity. Moreover, new, optimized manufacturing techniques that are easily scalable are also coming out of academic and industrial research.

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