IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
June 2021 Vol.:21, Issue:3

Solid Dispersion Techniques Improve Solubility of Poorly Water-Soluble Drug: A Review

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

R. H. Pawar, N. N. Bidagar,Y. N. Gavhane, M. S. Charde, R. D. Chakole*

Post Graduate Department of Pharmaceutics
Government College of Pharmacy, Vidyanagar, Karad, Dist.: Satara Pin- 415124, Maharashtra, India.

Submitted: 25 May 2021
Accepted: 02 June 2021
Published: 30 June 2021

Keywords: Solubility, Solubility Enhancement, Solid dispersion, Characterization

ABSTRACT

Solid dispersion is a unique and commonly used method for increasing solubility and dissolving rate, particularly for BCS class II medicines. The primary goal of solid dispersion development is to improve oral absorption and oral bioavailability of poorly water-soluble drugs. Solubility is the process of a solid dissolving in a liquid phase to form a homogeneous system, and it is an important metric for achieving the desired drug concentration in the systemic circulation for pharmacological response. Poorly water-soluble medicines frequently require high dosages to achieve therapeutic plasma concentrations following oral delivery. The solubility of an orally taken medication in aqueous fluids over various pH ranges determines its bioavailability. The oral bioavailability of poorly water-soluble substances is limited by the drug's insufficient dissolving rate. Various techniques are used for the improvement of the aqueous solubility, dissolution rate, and bioavailability of poorly water-soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, cosolvency, micellar solubilization, hydrotropic, etc. The goal of this review paper is to present solubilization approaches for achieving effective absorption and increased bioavailability. Because of their low solubility and dissolution rates, BCS class II medicines provide a significant challenge in the creation of pharmaceutical products.

INTRODUCTION:

The ability of a solid, liquid, or gaseous chemical substance called a solute to dissolve in a solid, liquid, or gaseous solvent to produce a homogenous solution of the solute in the solvent is referred to as solubility. A substance's solubility is mostly determined by the solvent it is dissolved in, as well as temperature and pressure. The saturation concentration of a material in a given solvent is the point at which adding more solute does not increase its concentration in the solution [1]. In most cases, the solvent is a liquid, which might be a single liquid or a mixture of two liquids. A solid solution is also a possibility, though a gaseous solution is uncommon. Oral administration is the simplest and most convenient method of drug administration. Oral dosage forms offer several advantages over other types of dosage forms, including increased stability, precise dosing, reduced volume, and ease of preparation. One of the most common and significant issues for formulation scientists in the pharmaceutical sector is the formulation of poorly soluble chemicals for oral delivery. The pharmaceutical industry has found about 40% of prospective new drugs are poorly water-soluble. Water-insoluble chemicals have a slower release rate and bioavailability. As a result, a high dose is required to get the desired effect, however, this may result in drug toxicity. So the best option for increasing the release rate is an improvement of the solubility through formulation approaches.

FACTOR AFFECTING SOLUBILITY:

The solubility of a solid is determined by its physical shape, the nature, and composition of the solvent medium, as well as the temperature and pressure of the system**.**

Particle size:

Because the surface area to volume ratio increases as a particle gets smaller, the size of the solid particle has an impact on its solubility. The bigger surface area allows for more solvent interaction. The following equation can be used to illustrate the effect of particle size on solubility. Where S is the solubility of infinitely large particles, S is the solubility of fine particles, V is molar volume, G is the surface tension of the solid, R is the radius of the fine particle (2).

Temperature:

Solubility is affected by temperature. If the solution process absorbs energy, then as the temperature rises, so will the solubility. If the solution process releases energy, the solubility decreases as the temperature rises (3). A solid solute's solubility generally increases as the temperature of the solution rises. In heated solutions, a few solid solutes are less soluble. As the temperature of the solution rises, solubility reduces for all gases (4).

Pressure:

A rise in pressure enhances solubility for gaseous solutes, while a decrease in pressure decreases solubility. Changes in pressure have almost no influence on the solubility of solids and liquids (4).

Nature of the solute and solvent:

At room temperature, only 1 gram of lead (II) chloride may be dissolved in 100 grams of water, but 200 grams of zinc chloride can. The large disparity in solubilities between these two compounds is due to variances in their nature (4).

Molecular size:

The less soluble a material is, the larger the molecule or the higher its molecular weight. Larger molecules are more difficult to solvate by surrounding them with solvent molecules. When it comes to organic molecules, the amount of carbon branching increases solubility because greater branching reduces the size (or volume) of the molecule, making it easier to dissolve it in a solvent (5).

Polarity:

Generally, non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then the positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction (5).

Polymorphs:

A solid has a defined shape and a rigid form. Although the shape or habit of a crystal of a given substance can change, the angles between the faces remain constant. A crystal is a three-dimensional grouping of atoms, ions, or molecules in a regular geometrical pattern or lattice. The unit cell is the name for this repeating pattern. Polymorphism refers to a substance's ability to crystallize in several crystalline forms (6).

TECHNIQUES FOR SOLUBILITY ENHANCEMENT:

I. Chemical Modifications:

1. Salt Formation
2. Co-crystallization
3. Co-solvency
4. Hydrotropic
5. Solubilizing agent
6. Nanotechnology

II. Physical Modifications:

1. Particle size reduction
2. Modification of the crystal habit
3. Complexation
4. Solubilization by surfactants
5. Drug dispersion in carriers

- Solid solution
- Eutectic mixtures
- Solid dispersion

III. Other:

1) Supercritical fluid method

2) Spray freezing into liquid and Lyophilization

3) Evaporative precipitation into an aqueous solution

4) Solvent evaporation method

5) Hot melt extrusion

6) Electrostatic spinning method

7) Direct capsule filling

8) Polymeric Alteration

9) High-Pressure Homogenization

10) Lyophilization technique

11) Inclusion Complexes:

- Kneading Technique
- Co-precipitation
- Neutralization
- Co-grinding
- Spray-Drying Method
- Microwave Irradiation Method

IMPORTANCE OF SOLUBILITY:

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, cost-effectiveness, least sterility constraints, and flexibility in the design of dosage form. As a result, many of the generic drug companies are inclined more to produce bioequivalent oral drug products (7). However, the major challenge with the design of oral dosage forms lies with their poor bioavailability. The

oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, presystemic metabolism, and susceptibility to efflux mechanisms. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability. Solubility also plays a major role in other dosage forms like parenteral formulations as well (8). Solubility is one of the important parameters to achieve the desired concentration of drug in systemic circulation for achieving the required pharmacological response (9). Poorly water-soluble drugs often require high doses to reach therapeutic plasma concentrations after oral administration. Low aqueous solubility is the major problem encountered with the formulation development of new chemical entities as well as generic development. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility. More than 40% of NCEs (new chemical entities) developed in the pharmaceutical industry are practically insoluble in water. These poorly water-soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. For orally administered drugs solubility is the most important rate-limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. The problem of solubility is a major challenge for formulation scientists (10). The improvement of drug solubility thereby its oral bioavailability remains one of the most challenging aspects of the drug development process, especially for the oral-drug delivery system. There are numerous approaches available and reported in the literature to enhance the solubility of poorly water-soluble drugs. The techniques are chosen based on certain aspects such as properties of a drug under consideration, nature of excipients to be selected, and nature of intended dosage form. The poor solubility and low dissolution rate of poorly water-soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II (low solubility and high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids. As for BCS class II drugs rate-limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility, in turn, increases the bioavailability for BCS class II drugs (7, 9).

The negative effect of compounds with low solubility includes poor absorption and bioavailability, insufficient solubility for IV dosing, development challenges leading to

increasing the development cost and time, the burden shifted to the patient (frequent high-dose administration) (8). Micronized fenofibrate exhibited more than 10-fold (1.3% to 20%) increase in dissolution in at 30 minutes bio relevant media (8, 9).

SOLID DISPERSION:

Enhancing solubility can be done in several ways. Solid dispersion is one of the most effective methods for increasing solubility. Solid dispersion is a phrase used to describe a collection of solid goods made up of at least two separate components, usually a hydrophilic matrix and a hydrophobic medication. The matrix might be crystalline or amorphous; amorphous substances have better solubility than crystalline substances because no energy is required to break up the drug's crystal lattice during the dissolution process. Surrounding hydrophilic carriers may improve drug solubility and wettability.

First Generation Solid Dispersions:

Sekiguchi and Obi were the first to define solid dispersions in 1961, using the concept of eutectic mixtures. They stated that eutectic mixture formulation improves medication release rate and thereby increases the bioavailability of poorly soluble drugs. As a result, crystalline carriers were used to make first-generation solid dispersions. Eutectic mixtures are binary systems in which a poorly water-soluble medicine is combined with a highly water-soluble carrier, with the medication crystallizing only in the precise composition at the eutectic point. When a eutectic mixture is dissolved in water, the carrier dissolves quickly, releasing the drug in fine crystals. The main disadvantage of first-generation computers is their inefficiency. Solid dispersion is crystalline, meaning it has less solubility than amorphous dispersion but higher thermodynamic stability. To generate solid dispersions, crystalline carriers like urea and mannitol were initially utilized (12,14).

Second Generation Solid Dispersions:

In the second generation, amorphous carriers were used instead of crystalline carriers to disperse drugs that were largely polymers. Povidone, polyethylene glycols, and polymethacrylates are examples of wholly synthetic polymeric carriers, whereas cellulose derivatives such as cyclodextrins, hydroxypropyl methylcellulose, and others are natural product-based polymers. Amorphous solid dispersions are further classified as solid solutions, solid suspensions, or a mixture of both based on the molecular interaction between

the drug and the carrier. Amorphous carriers include polyethylene glycol, Povidone, Polyvinyl acetate, Polymethacrylate, and cellulose derivatives.

Third Generation Solid Dispersions:

A polymer mixture or a carrier is used as the carrier in third-generation solid dispersion surfactants. If the carrier has surface-active or self-emulsifying properties, the dissolving profile of a poorly soluble medicine can be improved, resulting in increased bioavailability. Solid dispersion carriers include surfactants like poloxamer 407, gelucire 44/14, compritol 888 ATO27, and inulin.

Advantages:

For a variety of reasons, solid dispersion technology improves the solubility of weakly water-soluble pharmaceuticals. The reasons for solid dispersion, as well as the advantages of solid dispersion, are listed below (15).

• Particles with reduced particle size:

After inert carrier or matrix dissolution, solid dispersion is the final stage of particle size reduction, in which the medication is molecularly distributed in the dissolving media. Because a wide surface area is formed, the medicine that is weakly water-soluble dissolves faster and has higher bioavailability.

• Particles with improved wettability:

The drug's wettability improves its solubility, which can increase bioavailability.

• Particles with higher porosity:

It has been discovered that particles in solid dispersions have a higher degree of porosity, which is depending on the carrier's properties. When linear polymers are utilized, the resulting solid dispersion is larger and more porous than when reticular polymers are utilized. The porous structure of the particle speeds up the dissolving process.

• Drugs in the amorphous state:

Poorly water-soluble crystalline medications have a higher degree of solubility in the amorphous state. Drug release is higher in the amorphous state because no energy is required to break up the crystal lattice during the dissolving process.

Disadvantages:

Solid dispersion has several disadvantages, the most significant of which is its instability. Several systems have indicated changes in crystallinity and a decrease in dissolution rate as a result of aging. Phase separation, crystal formation, or a change from a metastable to a stable crystalline state can occur as a result of absorbing moisture, reducing medicine solubility (18,19)**.** Due to moisture and temperature, solid dispersions degrade faster than physical combinations. It might be tough to manage at times due to its tackiness (18).

Limitation of Solid Dispersion:

Although there has been a lot of interest in solid dispersion research over the last four decades, practical use is restricted. Solid dispersion issues are complicated.

- ❖ The physical and chemical stability of drugs and vehicles,
- ❖ Method of preparation.
- ❖ Reproducibility of its physicochemical properties,
- ❖ Formulation of solid dispersion into dosage forms, and
- ❖ Scale-up of manufacturing processes (16).

Types of Solid Dispersion: (15, 17).

1. Binary Solid Dispersion: It consists of a drug and a polymeric carrier.
2. Ternary Solid Dispersion: It consists of the drug, a polymeric carrier, and a surfactant.
3. Surface Solid Dispersion:

Surface solid dispersion is formulated with polymers such as polyvinyl pyrrolidone, polyethylene glycol, and polyvinyl pyrrolidone-vinyl acetate copolymer by fusion technique to improve its solubility. It is appropriate to classify various systems of solid dispersion based on their major fast release mechanisms.

Solid dispersions into the following six representative types Based on their molecular arrangement,

Type 1- Simple eutectic mixture.

Type 2 - Amorphous precipitations in the crystalline matrix.

Type 3 - Solid solutions

Type 4 - Glass suspension

Type 6 - Glass solution

1. Simple Eutectic Mixtures

These are made by quickly solidifying a fused melt of two components with perfect liquid miscibility and little solid-solid solubility. In terms of thermodynamics, such a system is a physically blended mixture of its two crystalline components. As a result, a eutectic's X-ray diffraction pattern is an additive composite of two components. Griseofulvin and Tolbutamide with PEG 2000 are examples of chloramphenicol-urea, paracetamol-urea, and chloramphenicol-urea.

2. Solid Solutions

In a solid solution, the two components crystallize together in a homogeneous one-phase system. The particle size of the medication is reduced to its molecular size in a solid solution. As a result, a solid solution dissolves more quickly than a eutectic combination. There are two ways to categorize solid responses. They can be classified as continuous or discontinuous based on the degree of miscibility between the two components, or as substitutional, interstitial, or amorphous based on how the solvate molecules are disseminated in the solvent. In the solid-state, continuous solid solutions have two components that are miscible in all amounts. This means the bonding strength between the two components is stronger than the bonding strength between the molecules of each component individually. In discontinuous solid solutions, each component's solubility in the other component is limited. Solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the interstices between the solvent molecules in substitutional crystalline solid dispersions. The dissolved molecules in interstitial crystalline solid dispersions fill the interstitial gaps between the solvent molecules in the crystal lattice. The solute molecules are scattered molecularly yet irregularly inside the amorphous solvent in amorphous crystalline solid dispersions.

3. Glass Solutions and Suspensions

A glass solution is a homogeneous glassy system containing a dissolved solute. Glass suspensions are made up of precipitated particles suspended in a glassy solvent. The glassy state is characterized by transparency and brittleness below the glass transition temperature. Glasses do not have a definite melting point; instead, as they are heated, they soften progressively. The lattice energy in glass solutions, which acts as a barrier to rapid dissolution, is much lower than in solid solutions.

4. Amorphous Precipitations in a Crystalline Carrier

The difference between this set of solid dispersions and a simple eutectic mixture is that the substance precipitates out in an amorphous form in the former and a crystalline form in the latter. Sulfathiazole precipitated in an amorphous form in crystalline urea.

Compound or Complex formation

The drug and matrix interact intensely in aqueous media, such as cyclodextrins, and form complexes. A low association constant is necessary for dissolution enhancement. When preparing solid dispersion, a low or moderate quantity of carrier is used., the creation of soluble complex may occur. Drug dissolution may be aided by the creation of a solid solution when a large fraction of carrier is used.

Common Methods Used for Preparation of Solid Dispersion:

Various methods are used for the preparation of a solid dispersion system. These methods are given below(19,21).

1. Melting method
2. Solvent methods
3. Melting solvent method (melt evaporation)
4. Melt extrusion methods
5. Lyophilization techniques
6. Melt agglomerations Process
7. The use of surfactant

8. Electrospinning

9.Super Critical Fluid technologies

1. Melting method:

Melting or fusing is the process of preparing a physical mixture of medication and a water-soluble carrier and heating it until it melts. The melting slurry is then immediately solidified in an ice bath while being vigorously stirred. The final solid mass is crushed, pulverized, and sieved. Appropriately this has undergone many modifications in 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. In addition, by fast cooling, a melt from a high temperature, a super-saturation of a solute or medicine in a system can typically be achieved. The solute molecule is halted in the solvent matrix by the instantaneous solidification process at these conditions. When employed for simple eutectic mixtures, the quenching process produces a much finer dispersion of crystallites. Many chemicals, medicines, and transporters, on the other hand, may disintegrate during the high-temperature fusion process. During the fusion process at high temperatures, it may potentially cause evaporation of volatile medication or volatile carrier. To avoid oxidative destruction of the medication or carrier, some solutions include heating the physical mixture in a sealed container or melting it under a vacuum or in the presence of an inert gas such as nitrogen.

2. Solvent method:

This approach involves dissolving the physical mixture of drug and carrier in a common solvent, which is then evaporated until a clear, solvent-free film is left. After that, the film is dried to a consistent weight. The fundamental advantage of the solvent approach is that due to the relatively low temperatures necessary for the evaporation of organic solvents, thermal degradation of medications or carriers can be avoided. However, some disadvantages are associated with this method such as

1) The higher cost of preparation.

2) The difficulty in completely removing liquid solvent.

3) The possible adverse effect of traces of the solvent on the chemical stability.

4) The selection of a common volatile solvent.

5) The difficulty of reproducing crystal form.

6) In addition, supersaturation of the solute in the solid system cannot be attained except in a System showing highly viscous properties.

3. Melting solvent method (melt evaporation): (21)

• Solid dispersions are made by dissolving the medication in a suitable liquid solvent and then integrating the solution directly into a polyethylene glycol melt, which is subsequently evaporated until a clear, solvent-free film is left. After that, the film is dried to a consistent weight. Liquid chemicals in the range of 5–10% (w/w) can be added into polyethylene glycol 6000 without significantly reducing its solid properties. Possibly the chosen solvent or dissolved medicine will not mix with the polyethylene glycol melt.

• The liquid solvent may also affect the polymorphic form of the medication, which precipitates as a solid dispersion. The advantages of both the fusion and solvent evaporation procedures are combined in this technique. Practically, it is limited to medications with a modest therapeutic dose, such as less than 50 mg.

4. Melt extrusion method:

• A twin-screw extruder is commonly used to process the drug/carrier mixture. Extruded and formed as tablets, granules, pellets, sheets, sticks, or powder. The drug/carrier mix is melted, homogenized, and then extruded and shaped as tablets, granules, pellets, sheets, sticks, or powder. After that, the intermediates can be converted into traditional tablets. The drug/carrier combination is only exposed to a higher temperature for around 1 minute with the hot melt extrusion method, which allows for the processing of thermally labile pharmaceuticals.

• Solid dispersion by this method is composed of active ingredients and carriers and prepared by hot stage extrusion using a co-rotating twin-screw extruder. The concentration of drugs in the dispersions is always 40% (w/w). The screw configuration consists of two mixing zones and three transport zones distribute over the entire barrel length, the feeding rate is fixed at 1 kg/h and the screw rate is set at 300 rpm. The five temperature zones are set at 100, 130, 170, 180, and 185^{o}C from feeder to die. The extrudes are collected on a conveyer belt after cooling at room temperature. Using a laboratory cutting mill and sieve, samples are processed for 1 minute to remove particles larger than 355 microns.

5. Lyophilization Technique: (21,22)

Heat and mass are transferred to and from the product being prepared during lyophilization. This method was offered as a viable alternative to solvent evaporation. Lyophilization is a molecular mixing procedure in which the drug and carrier are mixed in a shared solvent, frozen, then sublimed to produce a lyophilized molecular dispersion.

Vial freeze-drying

Dissolve the drug in the solvent at a fixed concentration. Dissolve the carrier in water. Mix both the solutions in a ratio of 40/60 v/v. Subsequently immerses the mixture in liquid nitrogen until it gets fully frozen. Various concentrations of drug in the resulting solid dispersions are obtained by adjusting carrier concentrations while maintaining drug concentration constant. Then lyophilize the frozen solution by lyophilized. Lyophilization is performed according to a two-step procedure,

1) For the first day, set the pressure to 0.22 mbar and the shelf temperature to (-350C).

2) Lower the pressure to 0.05 mbar and elevate the shelf temperature to 200 degrees. Keep these conditions in place for another day. Place the samples in a vacuum desiccator over silica gel at room temperature for at least 1 day after taking them from the freeze drier.

Spray freeze-drying

Dissolve the medication in a fixed-concentration solvent and the carrier in water. In a 40/60 v/v ratio, mix the solution. Using a nozzle, spray the solutions into liquid nitrogen. Set the liquid feed rate and the airflow for atomization. Place the nozzle's exit approximately 10 cm above the liquid nitrogen. To keep the solution inside the nozzle from freezing, hot water is pushed through the nozzle's jacket. Transfer the resulting suspension (liquid nitrogen-frozen droplets of the solution) to the lyophilized. The lyophilization process begins once all liquid nitrogen has evaporated.

6. Melt Agglomeration Process

• This method has been used to make solid dispersions in which the binder serves as a carrier. Furthermore, solid dispersions are made by heating the binder, drug, and excipient to a temperature above the binder's melting point (melt-in process) or spraying a drug dispersion in a molten binder on the heated excipient (spray-on process) with a high shear mixer.

Because it is easier to control the temperature and a higher binder content can be integrated into the agglomerates, the rotary processor may be preferred to the high melt agglomeration.

• In the preparation of solid dispersion by melt agglomeration, the effect of binder type, manufacturing method, and particle size are essential criteria. With PEG 3000, Poloxamer 188, and gelucire 50/13, it was discovered that the melt-in process produces higher dissolving rates than the spray-on approach, which was linked to the immersion mechanism of agglomeration formation and growth. Furthermore, the melt-in method ensures that the medication is distributed uniformly throughout the agglomeration.

7. Melt Agglomeration Process

• Larger particles cause agglomerates to densify, but small particles cause total adherence to the bulk to the bowl immediately after melting due to fine particle distribution and coalescence.

• The importance of surfactant systems in solubilization is critical. Surfactant adsorption on solid surfaces can change their hydrophobicity, surface charge, and other important qualities that control interfacial processes as flocculation/dispersion, flotation, wetting, solubilization, detergency, and improved oil recovery and corrosion inhibition.

• Surfactants have also been linked to solvation/plasticization, which results in lower melting temperatures for active medicinal components, as well as lower glass transition temperatures and combined glass transition temperatures for solid dispersions. Surfactants have caught the attention of researchers for the manufacture of solid dispersions due to their distinctive features.

8. Electrospinning

• Electrospinning is a method for producing solid fibers from a polymeric fluid stream solution or melt that is delivered through a millimeter-scale nozzle. A high electrostatic field is applied to a conductive capillary attached to a reservoir containing a polymer solution or melt and a conductive collection screen in this method Charge species accumulating on the surface of a pendant drop collapse the hemispherical shape into a conical shape when the electrostatic field intensity is increased up to but not surpassing a critical value (commonly known as Taylor cone).

• When the critical value is exceeded, a charged polymer jet is ejected from the cone's apex (as a way of relieving the charge built-up on the surface of the pendant drop). The electrostatic force carries the ejected charged jet to the collection screen. The charged jet's thinning along its passage to the collection screen is due to the Columb repulsion force. The charged jet's thinning down is limited. The charged jet is dried as the viscosity rises.

• Because it is the easiest and cheapest method for preparing solid dispersions in the future, this technology offers significant potential for the manufacture of Nanofibers and controlling the release of medicines.

9. Super Critical Fluid Technology

• Carbon dioxide is employed as an antisolvent for the solute but as a solvent for the organic solvent in supercritical fluid antisolvent procedures. Various writers used different acronyms to describe micronization processes: aerosol solvent extraction system, aerosol solvent extraction system, aerosol solvent extraction system, aerosol solvent extraction system, aerosol solvent extraction system, aerosol solvent extraction system aero precipitation using a compressed fluid antisolvent, a gas antisolvent, and a solution improved supercritical fluid dispersion and supercritical antisolvent dispersion.

• The SAS procedure entails spraying a solution containing the solute and an organic solvent into a continuous supercritical phase that is flowing at the same time.

Although a little amount of carbon dioxide remains strapped inside the polymer after the process is complete, using supercritical carbon dioxide is favorable since it is much easier to extract from the polymeric materials when the procedure is complete; it offers no harm to the patient.

• In addition, carbon dioxide's ability to plasticize and swell polymers can be used, and the procedure can be done at room temperature.

• Furthermore, supercritical fluids are utilized to reduce the melting temperature of the dispersed active ingredient, lowering the temperature of the melt dispersion process. The solubility of the lighter component (dense gas) in the forming phase is the cause of this decrease (heavier component).

10. Spray Drying

Using water, dissolve the various amounts of carriers. Then, in the solution, scatter the 10 gm of medication that has been pre-sieved through a 60-mesh screen. The resulting dispersion is spray-dried at an intake temperature of about 120^0C and an exit temperature of about 65-70^0C at a flow rate previously determined with a peristaltic pump. Adjust the spray pressure if necessary. At the aspirator, keep the drying air flow rate constant. Collect each resulting powder using a cyclone separator and transfer it to glass vials after spray-drying.

11. High- pressure homogenization

High-pressure homogenization is the process of dispersing a medication powder in an aqueous surfactant solution and sending it through a high-pressure homogenizer to produce Nano suspensions. The cavitation force is strong enough to dissolve the medication from micro to nanoparticles. The particle size is determined by the pharmacological substance's hardness, processing pressure, and the number of cycles used. This approach, however, may only be used to break up fragile drug candidates into nanoparticles.

12. Polymeric alteration

Polymorphs are distinct crystalline forms of a medication that may have distinct characteristics. Physical and chemical stability, shelf-life, melting point, vapour pressure, intrinsic solubility, dissolving rate, shape, density, and biological activity, as well as bioavailability, may differ amongst polymorphs. To ensure reproducible bioavailability of the product across its shelf-life under a variety of real-world storage settings, it is desirable to design the most thermodynamically stable polymorph of the medicine.

13. Inclusion complexes (21).

1. Kneading technique

By mixing the drug and polymer with a tiny amount of the solvent, water, a thick paste is formed, which is then dried at 450°C in an oven. Place the bulk in the desiccator after passing it through sieve No. 30.

2. Co-precipitation

Add the needed amount of medication to the cyclodextrin solution. Protect the system from light and keep it under magnetic agitation with controlled process parameters. To prevent the

loss of the structural water from the inclusion complex, vacuum filter the produced precipitate and then dry it at room temperature.

3. Neutralization

Add the medication to an alkaline solution, such as sodium or ammonium hydroxide. Then, to dissolve the joint medication, add a solution of eta-Cyclodextrin. After a few seconds of agitation, a clear solution is obtained. Then, using HCl solution, neutralize it until the equivalence point is reached. At this point, a white precipitate appeared, which corresponded to the inclusion complex's formation. The precipitate is next filtered and dried to complete the process.

4. Co-grinding

Weigh the medication and carriers separately and combine them with one mL of water. Pass the moist bulk through a 44-mesh sieve, then spread the granules in Petri dishes and dry at 60°C under vacuum until a consistent weight is achieved. Keep the granules in desiccators until they are needed for more research.

5. Spray-drying method

Dissolve the medication and the requisite stoichiometric amount of carrier material, such as -Cyclodextrin, in a suitable solvent. To make a clear solution, combine the solutions using sonication or another suitable method. Using a spray dryer, dry it.

6. Microwave irradiation method

In a microwave oven, the drug and cyclodextrin combination is reacted to create inclusion. It is a revolutionary method for industrial-scale preparation since it has a shorter reaction time and a higher product yield.

CHARACTERIZATION OF THE SOLID DISPERSION SYSTEM:(12, 21, 23)

In solid dispersions, the medication in the matrix can take on a variety of molecular configurations. The molecular arrangement in solid dispersions has been studied using a variety of approaches the most effort, however, has gone into distinguishing between amorphous and crystalline materials. There are a variety of approaches for detecting the amount of crystalline material in dispersion.

• Hot stage microscopy

• Differential scanning calorimetry

• Powder X-ray diffraction

• NMR 1H Spin lattice relaxation time

Drug carrier interactions

• FT-IR spectroscopy

• Raman spectroscopy

• Solid-state NMR

Physical Structure

• Scanning electron microscopy

• Surface area analysis

• Surface properties

• Dynamic vapor sorption

• Inverse gas chromatography

• Atomic force microscopy

• Raman microscopy

Amorphous content

• Polarized light optical microscopy

• Hot stage microscopy

• Humidity stage microscopy

• DSC (MTDSC)

• ITC

• Powder X-ray diffraction

Stability

• Humidity studies

• Isothermal Calorimetry

• DSC (Tg, Temperature recrystallization)

• Dynamic vapor sorption

• Saturated solubility studies

Dissolution enhancement

• Dissolution

• Intrinsic dissolution

• Dynamic solubility

• Dissolution in bio-relevant media

PRACTICAL LIMITATION IN TECHNIQUES:

Problem Related (20)

1. Problem concerned with dosage form development Poor Flow and Compressibility:

Solid dispersion is typically found to be difficult in sieving and pulverization. The compressibility and stability of solid dispersion are similarly poor (17, 24). The in-situ drug granulation approach is utilized to solve this problem. The excipients (CaHPO4 and sodium starch glycolate) were pre-heated and then rotated at 70°C in a water-jacketed blender. The granules were then passed through a 20-mesh sieve and allowed to solidify at 25°C for 12 hours after the drug carrier mixture was melted at 100°C and added to the moving powder. The granules are then combined with greater magnesium content (1 %) and compacted into tablets. In addition, it was discovered that wet granulation was not an option for generating a tablet formulation for the solid dispersion since water could disturb its physical structure.

Sticking of Granules of Solid Dispersion to Die and Punches: -

To avoid the problem of solid dispersion sticking to dies and punches during compression, little pieces of grease-proof paper were inserted between the metal surface and the granules.

Direct contact between the metal surface and the granules is avoided as a result of this. Filling drug-PEG melts in a hard gelatin capsule is one of the novel approaches, however, caution must be taken because the temperature of the drug PEG melt should not surpass 70°C while filling.

2. Problem concerned with scale-up and manufacturing

Condensation of Moisture over Solid Dispersion During Cooling: - There is a possibility of condensation of moisture over solid dispersion during evaporation. A continuous cooling operation, such as cooling on a surface moving belt or rotating belt, is used to overcome this.

Reproducibility of Physicochemical Properties: -

The physicochemical features of solid dispersions created may be strongly influenced by the production conditions for solid dispersion. Many researchers found that the heating rate, the highest temperature employed, duration spent at a high temperature, cooling method, and rate, pulverization process, and particle size all had a significant impact on the properties of solid dispersions made by using the melt method. The solid's powder X-ray diffraction patterns.

3. Problem concerned with Stability

A certain portion of the drug may stay molecularly distributed in the carrier in a solid dispersion generated by the hot-melt method. If the concentration of such medication is high, phase separation can occur, in which the crystalline and amorphous phases separate. As a result, polymers such as PVP, HPMC, and HPMCAC are increasingly often employed. By preventing drug crystallization at low humidity, the polymer works as a stabilizer in the manufacture of solid dispersion. Reduced nucleation rate is a crystallization-prevention mechanism. The kinetic barrier to nucleation is increased by this polymer, which affects nucleation kinetics. The rate at which a polymer performs as an efficient barrier is proportional to its concentration and independent of its physicochemical qualities.

NEWER AND NOVEL TECHNIQUES: (25)

Newer and novel drug delivery technologies developed in recent years for solubility enhancement of insoluble drugs are

- Size reduction technologies

- Nanoparticle Technology
- Nanocrystal Technology
- Nanosuspension
- Cryogenic Technology
- Supercritical Technology
- Lipid-based delivery system.
- Microemulsion Technology
- Self-Dispersing Lipid Formulation (SDLF)
- Micellar technologies
- Mixed Micelle
- Polymeric Micelle
- Porous Microparticle technology

APPLICATIONS OF SOLID DISPERSIONS:(24)

1. To increase the dissolving rate, absorption, and bioavailability of poorly soluble medicines by increasing their solubility.

2. To protect unstable pharmaceuticals from degradation processes such as hydrolysis, oxidation, recrimination, isomerization, photo-oxidation, and others.

3. To lessen the negative effects of some medications.

4. The masking of the drug's disagreeable taste and odour.

5. Drug release from ointment, creams, and gels is improved.

6. To avoid undesired incompatibilities.

7. To achieve a uniform dispersion of a little amount of medication in solid form.

8. To administer liquid or gaseous chemicals in a solid dose (up to 10 %).

9. To create a sustained-release version of a fast-acting primary dose.

10. Using poorly soluble or insoluble carriers to create a prolonged release strategy for soluble medicines.

11. Pre-systemic inactivation of medicines like morphine and progesterone should be reduced.

CONCLUSION:

Because dissolving is the rate-limiting step, new chemical entities' poor solubility reduces their oral bioavailability. As a result, the primary issue for formulation scientists is to improve solubility and bioavailability. Many strategies have been used to improve solubility, one of which is solid dispersion. The use of solid dispersion to improve solubility has been around for a decade. However, the commercialization of this technology will necessitate the resolution of issues such as scale-up, cost-effectiveness, and drug instability. Solid dispersion technology is an effective technique for improving the solubility of poorly soluble pharmaceuticals, but more study is needed to better use it on an industrial scale.

ACKNOWLEDGMENTS:

The authors of this review article are thankful to the Principal, Government College of Pharmacy, Karad for allowing us to present this paper. We are also thankful to AICTE for providing a research fellowship to complete our research work and convert our research work into publications.

REFERENCES:

1) P S Argade, D DMagar, R B Saudagar. Solid Dispersion: Solubility Enhancement Technique for poorly water-soluble Drugs Journal of Advanced Pharmacy Education & Research Oct-Dec 2013 Vol 3 Issue 4,437.
2) Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions.Eur. J. Pharm. Biopharm. 50, 47–60.
3) Amidon, G.L., Lenneranas, H., Shah, V.P., Crison J.R., 1995. A theoretical basis for a biopharmaceutical drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability. J. Pharm. Res. 12(3), 413-420.
4) Amin, K., Dannenfelser, R.M., Zielinski, J., Wang, B., 2004. Lyophilization of polyethylene glycol mixtures, J. Pharm. Sci. 93, 2244- 2249.
5) Yalkowsky, S.H., Roseman, T.J., 1981. Solubilization of drugs by cosolvents. In: Yalkowsky, S.H. Ed. Techniques of Solubilization of Drugs. Dekker, New York.
6) Ahuja, N., Katare, O.P., Singh, B., 2007. Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. Eur. J. Pharm. Biopharm. 65, 26-38.
7) S. R. K. Yellela, “Pharmaceutical technologies for enhancing oral bioavailability of poorly soluble drugs,” Journal of Bioequivalence & Bioavailability, vol. 2, no. 2, pp. 28–36, 2010.

8) K. H. Edward and D. Li, "Solubility," in Drug Like Properties: Concept, Structure, Design and Methods, from ADME to Toxicity Optimization, p. 56, Elsevier, 2008.
9) D. Sharma, M. Soni, S. Kumar, and G. D. Gupta, "Solubility enhancement—eminent role in poorly soluble drugs," Research Journal of Pharmacy and Technology, vol. 2, no. 2, pp. 220–224, 2009. [14] A. Kumar, S. K. Sahoo, K. Padhee, P. S. Kochar, A. Sathapathy, and N. Pathak, "Review on solubility enhancement techniques for hydrophobic drugs," PharmacieGlobale, vol. 3, no. 3, pp. 001–007, 2011.
10) Md. Armin Minhaz, Md. Mofizur Rahman, Md. QamrulAhsan, Md. HabiburRahman, Md. RaihanChowdhury. Enhancement of solubility and dissolution properties of clonazepam by solid dispersions. Int. J. of Pharm. & Life Sci.,2012;3(3):1510-1518.
11) J. C. Chaumeil, "Micronization: a method of improving the bioavailability of poorly soluble drugs," Methods and Findings in Experimental and Clinical Pharmacology, vol. 20, no. 3, pp. 211–215, 1998.
12) Patel PB, Prajapati ST, Patel NR, Patel NN, Patel CN. Solid Dispersion: A Method of Improving Bioavailability and Taste Masking. Inventi Rapid: Pharm Tech Vol. 2012; Issue 4.
13) Patidar K, Sharma S, Soni M, Kshirsagar MD, Saini V. Preparation and Characterization of Hydrotrophic Solid Dispersions of Indomethacin. Inventi Rapid: Pharm Tech. Vol. 1, Issue 3.
14) Wairkar SM, Gaud RS. Solid Dispersions: Solubility enhancement technique for poorly soluble drugs. International Journal of Research in Pharmaceutical and Biomedical Sciences, Jul– Sep 2013; 4 (3):847-854.
15) Remington- The Science & Practice of Pharmacy, Published by Lippincott Williams & Wilkins, 21st Edn., 229-230
16) Chavan S, Patel K, Shelar D, Vavia P. Preparation of Oxcarbazine Solid Dispersion by Hot Melt Extrusion for Enhanced Dissolution: Doenstream Processing to tablets. Am. J. PharmTech Res, 2013;3 (1).
17) Ingle US, Gaikwad PD, Banker VH, et al. A Review on solid dispersion: A dissolution enhancement technique. International Journal of Research in Ayurveda & Pharmacy,2011;2 (3):751-757.
18) Seth NS, "Formulation and evaluation of solid dispersion of olanzapine," Int. J. Pharm. Sci. Res., 2011;2(2):691-697.
19) Nagender Reddy CH, Anil Reddy T, Srinivasan S. Review on: Better solubility enhancement of poorly water-solubledrugs. International Journal of Inventions in Pharmaceutical Sciences,2013;1 (4):267- 273.
20) Md. Armin Minhaz, Md. Mofizur Rahman, Md. QamrulAhsan, Md. HabiburRahman, Md. RaihanChowdhury. Enhancement of solubility and dissolution properties of clonazepam by solid dispersions. Int. J. of Pharm. & Life Sci.,2012;3(3):1510-1518.
21) Eun-Jung Kim, et al. Preparation of solid dispersion of felodipine using a solvent wetting method. European Journal of Pharmaceutics and Biopharmaceutics,2006;64:200-205,
22) X. Wang, Michel A, and Van den Mooter G, "Solid state characteristics of ternary solid.
23) SangadaKirankumarNanjibh , Jigar Vyas, Upadhyay UM, Sanjay BamaniyaInventi Rapid: Pharm Tech 2011;2.
24) P S Argade, D D Magar 2, R B Saudagar Solid Dispersion: Solubility Enhancement Technique for poorly water-solubleDrugsJournal of Advanced Pharmacy Education & Research Oct-Dec 2013 Vol 3 Issue 4,437.
25) Rohini P, KiranKadali SDVS, BhagvanRaju M, Pavan Kumar K. Studies on dissolution enhancement of Itraconazole using water-soluble carriers. Inventi Rapid: Pharm Tech,1(1).
26) Dhirendra K, Lewis S, Udupa N, Atin K. Solid Dispersion: A Review. Pak. J. Pharm, April 2009; Vol.22(2):234-246.
27) Sambath L, Kottai Muthu A, Ashis Kumar M, et al. Formulation and evaluations of Naproxen sustained release tablets using Naproxen solid dispersion. InventiS Rapid: Pharm Tech 2013.