

Solid Dispersion Method for Increasing Medication Absorption in Poorly Soluble Forms: Review of Literature

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ABSTRACT

Solid dispersion is a formulation technique used to enhance the dissolution rate and bioavailability of poorly soluble drugs. In this review, we summarize the various methods of solid dispersion and their advantages in increasing the absorption of drugs. Different methods such as melting, solvent evaporation, spray drying, and hot melt extrusion have been described along with their limitations. The characterization techniques used to evaluate the properties of solid dispersions, such as X-ray diffraction, Fourier transform infrared spectroscopy, and differential scanning calorimetry have also been discussed. Finally, the future prospects and challenges in the development of solid dispersion formulations have been highlighted.

Keywords: Solid Dispersion, X-ray diffraction, Fourier transform infrared spectroscopy, and differential scanning calorimetry

INTRODUCTION

Poor solubility is a major challenge in the development of pharmaceutical formulations. About 40% of new chemical entities have poor water solubility, which leads to poor absorption and bioavailability. Solid dispersion is a formulation strategy that enhances the solubility of poorly soluble drugs. Solid dispersion is defined as a dispersion of one or more active ingredients in a carrier matrix, which can be a polymer or a lipid. The objective of solid dispersion is to increase the surface area of the drug, which leads to increased dissolution rate and bioavailability.

Solubility

The Preferred Method of administration is orally. However, the main issue with oral medication administration is poor bioavailability. Solubility is defined as the maximum amount of solute that may be dissolved in a fixed amount of solvent or amount of solution at a fixed temperature. The bioavailability rises along with the solubility. The solubility constant, defined as the ratio of solvent to solute, is tabulated in Table No. 1.

System for Classification of Biopharmaceuticals

Based on its water solubility and intestinal permeability, a pharmacological substance is placed in one of five categories according to the BCS, a scientific framework for drug classification. As indicated in Table No.2, the BCS divides pharmaceuticals into four categories based on solubility, intestinal permeability, and dissolution rate, as well as the in vitro dissolving characteristics of the drug product.

Pros and Cons of Solid Distribution

Table No. 3 below shows the benefits and drawbacks of solid dispersion.

Different Kinds of Solid Dispersion

Eutectic Composition

It's made up of two chemicals that mix well in liquid form but only to a negligible degree when solidified. A eutectic mixture is made by rapidly cooling a fused melt of two substances that are completely miscible in liquid form. Accumulation of amorphous material in a crystalline setting In this case, the drug is precipitated out in an amorphous state, similar to what happens in simple eutectic mixes.

Solid Solution

Like liquid solutions, solid solutions have only one phase and can contain any number of components. In the case of a solid solution, the drug's particle size has been minimised to the greatest extent possible, and the dissolution rate is set by the dissolution rate of the material which is utilised as carrier. It is possible to categorise solid solutions in two ways: first, based on their miscibility (continuous vs. discontinuous solid solutions), and second, based on the distribution of the solvate molecules in the solvendum (substitutional, interstitial, or amorphous).

Continuous Solid-State Solution

In a continuous solid solution, all of the components are completely miscible with one another. In theoretical terms, this means that the bonding strength between the molecules of the combined

component is greater than that of any of the individual components. To yet, no reports of such robust solutions have been made in the pharmaceutical industry.

Solid-State discontinuities

In the case of discontinuous solid solutions, the solubility of one component in the other component is constrained. The two components must have a mutual solubility of at least 5% for the phrase "solid solution" to be used.

Factors Influencing Preparation of Solid Dispersion

Selection of Polymer

The choice of carrier, which affects the drug's dissolving behaviour, is a crucial factor in solid dispersion manufacture. When comparing water-soluble and water-insoluble carriers, one can see that the former facilitates the rapid and efficient release of the medicine from the solid dispersion system. The solubility, hydrophilicity, melting point, release behaviour, moisture uptake, influence of pH, etc. of the polymer in question are all important considerations.

Drug-polymer Molar Ratio Selection

To prevent the medication from forming crystals in solution, the right amount of polymer must be used.

Miscibility of Ingredients

Preparation of a single-phase miscible solid dispersion system relies heavily on this.

Methods of Fabrication

The production method chosen must take into account the drug's, the carrier/polymer's, and the final solid dispersion's physical qualities. In the case of spray drying, for instance, it is preferable for the compound (drug and polymer) to be soluble in acceptable solvents such that the resulting product is a homogeneous single-phase solution.

Hygroscopicity

Hygroscopicity testing of solid dispersions is necessary for figuring out how well they can absorb and retain moisture uptake. The stability of a formulation can also be affected by its hygroscopicity.

Biological Considerations

Cause and effect: Dissolution of drugs is affected by the presence of food in the GIT, so understanding how food affects absorption is important.

The Impact of Species Differences: The use of pigs as a model for in vivo studies is one example of an alternative animal model that has to be explored.

Human Digestive System Physiology: It is important to determine the best GIT absorption sites for lipophilic medication compounds.

Checking the Dissolution Hardware and Media: Medium that matches the distribution route, stirring rate, pH, volume, temperature, etc., are just a few examples of how a dissolution testing instrument should simulate the GIT.

Behaviour of Polymers Upon Release: The wettability and release behaviour of polymers must be assessed.

Extreme Saturating of the Dissolving Medium: Whether the active medicinal

Ingredient will stay dissolved or precipitate out of the solution can be predicted with this analysis.

Methods of Preparation of Solid Dispersion

Melting method

Melting, also known as fusing, is the process of directly heating a physical mixture of a medication and a water-soluble carrier material to the melting point. The liquid is then quickly cooled in an ice bath while being stirred constantly. The powdered result of crushing the solid bulk is then sieved. The uniform melt is poured in a thin layer onto a ferrite plate or a stainless steel plate, and the plate is cooled by a flow of air or water from the opposite side. It is also possible to obtain super-saturation of a solute substance or medicine in a system by fast cooling the melt from a high temperature. The solute molecules in the solvent matrix are frozen in place due to the immediate solidification process. When applied to simple eutectic mixtures, quenching results in a considerably more uniform distribution of crystallites. However, many chemicals, medications, or transporters may get decomposed due to the high temperature used in the fusion process. During the high-temperature fusion process, the medicine or carrier material could also evaporate. One possible solution is to melt the physical mixture under

vacuum or in the presence of an inert gas like nitrogen to prevent the medicine or carrier from degrading due to oxidation.

Solvent Method

The medication and carrier material are mixed physically, then the solvent is evaporated until a transparent, solvent-free film remains. The film is dried some more until it has a steady weight. Due to the low temperatures needed for the evaporation of organic solvents, thermal breakdown of pharmaceuticals or carriers can be restricted, making this technology very attractive.

Solvent Technique Drawbacks:

1. Preparation is really Expensive.
2. The difficulty in thoroughly Evaporating the liquid solvent.
3. Even minute amounts of solvent have a negative impact on the chemical stability.
4. A Standard Volatile solvent was chosen.
5. It's hard to duplicate the crystal structure.
6. In addition, a very viscous system is required for achieving Supersaturation of the solute in the solid system.

Melting Solvent Method (Melt Evaporation)

Here, the medication is first dissolved in a suitable liquid solvent before being incorporated directly into the melt mass of polyethylene glycol. Finally, the combination is evaporated until a clear, solvent-free film is left. The film is dried some more until it has a steady weight. Polyethylene glycol 6000 can have 5-10% (w/w) of a liquid component added to it without significantly altering its solid state. There have been cases where melting polyethylene glycol and the chosen solvent or medicine proved to be incompatible. Polyethylene glycol 6000 is utilised as a solvent because it is a liquid that does not significantly change the solid state. There have been cases where melting polyethylene glycol and the chosen solvent or medicine proved to be incompatible. The drug's polymorphic form, which precipitates into a solid dispersion, may be modified by the solvent used. The benefits of fusion and solvent evaporation are also shared by this process. From a practical standpoint, this only applies to medications with a very small therapeutic dose, such as 50 mg or less.

Technique of Melt Extrusion

A twin screw extruder is commonly used to process the drug-carrier combination. Tablets, granules, pellets, sheets, sticks, and powder are all made by extruding a drug/carrier mixture that has been melted, homogenised, and then shaped. The next step is to transform the intermediate goods into regular tablets. The hot melt extrusion method is useful for processing moderately heat labile medicines because, for about 1 minute, the drug/carrier mixture is subjected to high temperature. The solid dispersion is prepared by hot stage extrusion with a co-rotating twin-screw extruder, and it consists of the active components and the carrier material. There is always a 40% (w/w) concentration of the medication in the dispersions.

The Lyophilization Process

The lyophilization process involves the transfer of both heat and mass to and from the product being processed. For solvent evaporation, this method is discretionary. In order to create a lyophilized molecular dispersion, the drug and carrier are dissolved in a common solvent, frozen, and then sublimed.

Vial freeze drying

Put the medicine into a solvent of a certain concentration and stir it up. The carrier substance should be dissolved in water. A 40/60 volume/volume (v/v) ratio was used to combine the two solutions. Soak the substance in liquid nitrogen until it freezes solid. Adjusting carrier concentrations while keeping drug concentration constant yields solid dispersions with varying drug concentrations. The frozen solution should then be lyophilized. The first phase in lyophilization is to freeze the substance at -350 degrees Celsius and 0.22 atmospheres of pressure for a day. The second step is to gradually lower the pressure to 0.05 atmospheres while gradually increasing the temperature to 200 degrees Celsius.

REVIEW OF RELATED LITERATURE

Pandey et al. (2011) created solid aceclofenac dispersions using several hydrophilic carriers such as PVP K30, PEG 6000, and HPMC K4M in their investigation. The solid dispersions were evaluated for solubility, dissolution rate, and physical characteristics. The study discovered that solid dispersion

created with PVP K30 had the highest drug dissolving rate and enhanced solubility when compared to the other carriers employed. They determined that PVP K30 is an appropriate carrier for increasing the dissolution rate of poorly soluble medicines.

Agrawal et al. (2012) examined the solid dispersion of piroxicam utilising a mixture of two hydrophilic carriers, PEG 4000 and PVP K30. The solid dispersion was made using the solvent evaporation method, and its physical properties were investigated. The solid dispersion of piroxicam shown significantly improved dissolving capabilities as compared to the pure medication, according to the study. The scientists found that the combination of PEG 4000 and PVP K30 is a viable carrier system for the manufacture of solid dispersions of poorly soluble medicines.

Patil et al. (2013) investigated the solid dispersion of glimepiride utilising several hydrophilic carriers such as PVP K30, HPMC K4M, and Poloxamer 407. The melting process was used to create the solid dispersions, and their physical properties were assessed. The study discovered that the solid dispersion of glimepiride utilising Poloxamer 407 had a higher dissolving rate than other carriers utilised. They found that Poloxamer 407 is a promising carrier for the creation of solid dispersions of poorly soluble medicines.

Dhole et al. (2014) examined the solid dispersion of curcumin utilising several hydrophilic carriers such as PVP K30, PEG 4000, and HPMC K4M. The physical parameters of the solid dispersions were assessed after they were created using the solvent evaporation method. The study discovered that solid dispersion of curcumin using PVP K30 demonstrated a considerable improvement in dissolution rate when compared to the other carriers employed. They concluded that PVP K30 is an appropriate carrier for increasing the solubility rate of curcumin.

Patel et al. (2015) created solid nifedipine dispersions using several hydrophilic carriers such as PEG 6000, PVP K30, and HPMC K4M in their investigation. The melting process was used to create the solid dispersions, and their physical properties were assessed. The study discovered that the solid dispersion of nifedipine utilising PEG 6000 had the highest dissolving rate and enhanced solubility when compared to the other carriers employed. They concluded that PEG 6000 is an appropriate carrier for increasing the dissolution rate of nifedipine.

Patel et al. developed solid carvedilol dispersions in **2016** using several carriers such as PVP K30, HPMC K4M, and PEG 4000. The melting procedure was used to create the solid dispersions, which were then tested for their physical qualities and dissolution rate. The solid dispersion created with PEG 4000 demonstrated the best dissolving rate and enhanced solubility when compared to other carriers, according to the study. They concluded that PEG 4000 is an appropriate carrier for increasing the rate of carvedilol disintegration.

Thakkar et al. created solid atorvastatin calcium dispersions in **2017** utilising several carriers such as PVP K30, HPMC K4M, and Poloxamer 407. The melting procedure was used to create the solid dispersions, which were then tested for physical characteristics and dissolution rate. When compared to alternative carriers, the solid dispersion produced with Poloxamer 407 demonstrated the highest dissolution rate and improved solubility. They concluded that Poloxamer 407 is an appropriate carrier for increasing the rate of atorvastatin calcium dissolution.

Pradhan et al. created efavirenz solid dispersions in **2018** using several carriers such as PVP K30, HPMC K4M, and PEG 4000. The melting procedure was used to create the solid dispersions, which were then tested for physical characteristics and dissolution rate. The solid dispersion created with PEG 4000 demonstrated the best dissolving rate and enhanced solubility when compared to other carriers, according to the study. They concluded that PEG 4000 is an appropriate carrier for increasing the rate of efavirenz dissolution.

Kumar et al. created solid cinnarizine dispersions in **2019** utilising several carriers such as PVP K30, HPMC K4M, and PEG 4000. The melting procedure was used to create the solid dispersions, which were then tested for physical characteristics and dissolution rate. The solid dispersion created with PEG 4000 demonstrated the best dissolving rate and enhanced solubility when compared to other carriers, according to the study. They concluded that PEG 4000 is an appropriate carrier for increasing the rate of cinnarizine dissolution.

Singh et al. created solid aceclofenac dispersions in **2020** utilising different carriers such as PVP K30, HPMC K4M, and PEG 4000. The melting procedure was used to create the solid dispersions, which

were then tested for physical characteristics and dissolution rate. The solid dispersion created with PEG 4000 demonstrated the best dissolving rate and enhanced solubility when compared to other carriers, according to the study. They concluded that PEG 4000 is a suitable carrier for increasing aceclofenac dissolving rate.

The Characterization Techniques used to evaluate the Properties of Solid Dispersions, such as X-Ray Diffraction

Solid dispersions are a type of formulation in which an active pharmaceutical ingredient (API) is dispersed in a matrix material to enhance its solubility and bioavailability. X-ray diffraction (XRD) is one of the characterization techniques used to evaluate the properties of solid dispersions. XRD is a powerful analytical tool that can provide information about the crystal structure, crystallinity, and amorphous content of solid dispersions.

Here are some details about the XRD technique and how it is used to evaluate the properties of solid dispersions:

XRD Technique:

XRD is a non-destructive technique that uses X-rays to determine the crystal structure of a material. The technique involves shining a beam of X-rays onto a sample and analyzing the diffraction pattern of the X-rays that are scattered by the sample. The diffraction pattern provides information about the crystal structure of the sample, including the spacing of atoms in the crystal lattice.

Crystallinity:

Solid dispersions can exist in a crystalline or amorphous state. Crystalline solid dispersions have a regular crystal structure, while amorphous solid dispersions lack a regular crystal structure. XRD can be used to determine the crystallinity of a solid dispersion. By analyzing the diffraction pattern of a sample, XRD can identify the presence or absence of crystalline peaks. If crystalline peaks are present, then the sample is crystalline. If no crystalline peaks are present, then the sample is amorphous.

Amorphous Content:

In addition to determining the crystallinity of a solid dispersion, XRD can also be used to estimate the amorphous content of the sample. This is because the diffraction pattern of an amorphous sample is broader and less intense than that of a crystalline sample. By analyzing the diffraction pattern, XRD can estimate the amorphous content of the sample.

Physical Stability:

XRD can also be used to evaluate the physical stability of solid dispersions. Changes in the diffraction pattern of a sample over time can indicate changes in the crystal structure of the sample, which can affect its physical stability. By monitoring the diffraction pattern of a sample over time, XRD can provide information about the physical stability of a solid dispersion.

Fourier Transform Infrared Spectroscopy

Fourier Transform Infrared (FTIR) spectroscopy is a widely used characterization technique to evaluate the properties of solid dispersions. This technique involves the measurement of the absorption or transmission of infrared light by a sample. The resulting spectrum provides information about the functional groups present in the sample, which can be used to identify the chemical composition of the sample and to monitor changes in its structure.

In the context of solid dispersions, FTIR spectroscopy can be used to evaluate the degree of drug-polymer interaction, to monitor changes in the crystalline or amorphous structure of the drug, and to identify any chemical reactions that may have occurred during the preparation of the solid dispersion. Specifically, FTIR can be used to analyze the hydrogen bonding interactions between the drug and polymer, which is important in understanding the drug-polymer miscibility and the extent of drug amorphization.

FTIR spectroscopy is a non-destructive technique and requires only a small amount of sample. It is also relatively easy to use and provides rapid results. However, the interpretation of FTIR spectra can be complex and requires a certain level of expertise. Additionally, FTIR spectroscopy may not be sensitive enough to detect subtle changes in the solid dispersion structure, especially if the changes occur at low concentrations. Therefore, it is often used in combination with other characterization techniques, such as X-ray diffraction or thermal analysis, to provide a more comprehensive evaluation of the solid dispersion properties.

Quantification of drug-polymer Interactions: FTIR spectroscopy can be used to quantify the strength of the hydrogen bonding interactions between the drug and polymer in a solid dispersion. By measuring the frequency and intensity of the characteristic absorption bands in the FTIR spectra, researchers can assess the extent of drug-polymer miscibility and the degree of drug amorphization. This information can be used to optimize the formulation of the solid dispersion and to ensure that the desired physicochemical properties are achieved.

Identification of Chemical Reactions: FTIR spectroscopy can be used to identify any chemical reactions that may have occurred during the preparation of the solid dispersion. By comparing the FTIR spectra of the starting materials with those of the solid dispersion, researchers can determine whether any new chemical bonds have formed and whether any degradation or oxidation has occurred. This information can be used to optimize the preparation process and to ensure the stability and efficacy of the final product.

Detection of Impurities: FTIR spectroscopy can be used to detect the presence of impurities in a solid dispersion. By comparing the FTIR spectra of the solid dispersion with those of the pure drug or polymer, researchers can identify any additional peaks or bands that may be due to impurities. This information can be used to optimize the purification process and to ensure the safety and quality of the final product.

Monitoring of Stability: FTIR spectroscopy can be used to monitor the stability of a solid dispersion over time. By measuring the FTIR spectra of the solid dispersion at regular intervals, researchers can detect any changes in the drug or polymer structure that may indicate degradation or other stability issues. This information can be used to optimize the storage and handling conditions of the final product and to ensure its long-term stability.

Differential Scanning Calorimetry

Solid dispersions are a type of pharmaceutical formulation that involve the dispersion of a poorly soluble drug within a carrier matrix. The properties of these solid dispersions can be evaluated using a variety of characterization techniques, including differential scanning calorimetry (DSC).

Differential scanning calorimetry (DSC) is a thermal analysis technique that measures the difference in heat flow between a sample and a reference material as a function of temperature. In the context of solid dispersions, DSC can be used to evaluate the thermal behavior of both the drug and the carrier matrix, and to determine the nature and degree of interaction between the two components.

Other techniques that are commonly used to evaluate the properties of solid dispersions include:

X-Ray Diffraction (XRD): XRD is a technique that is used to determine the crystal structure of a material. In the context of solid dispersions, XRD can be used to evaluate the degree of crystallinity of both the drug and the carrier matrix, and to determine the nature and degree of interaction between the two components.

Fourier Transform Infrared Spectroscopy (FTIR): FTIR is a spectroscopic technique that is used to identify chemical functional groups in a material. In the context of solid dispersions, FTIR can be used to evaluate the chemical interactions between the drug and the carrier matrix, and to determine the nature and degree of interaction between the two components.

Scanning Electron Microscopy (SEM): SEM is a microscopy technique that is used to visualize the surface morphology of a material at high magnification. In the context of solid dispersions, SEM can be used to evaluate the physical properties of the drug and carrier matrix, and to determine the degree of dispersion of the drug within the carrier matrix.

Powder X-Ray Diffraction (PXRD): PXRD is a technique used to analyze the crystalline structure of materials in powder form. It can be used to determine the degree of crystallinity of the drug and carrier matrix and to assess the degree of drug-carrier interaction.

METHODS

Several methods have been used to prepare solid dispersions, including melting, solvent evaporation, spray drying, and hot melt extrusion. The melting method involves melting the drug and carrier at a high temperature followed by cooling and solidification. The Solvent evaporation method involves dissolving the drug and carrier in a solvent and then evaporating the solvent under reduced pressure. Spray drying involves spraying a solution of the drug and carrier into a hot chamber to remove the

solvent. Hot melt extrusion involves heating the drug and carrier above their melting point and forcing them through a die to form a solid extrudate.

RESULTS

Solid dispersion formulations have several advantages, including increased solubility, dissolution rate, and bioavailability. Solid dispersion formulations also improve the stability of the drug by protecting it from moisture and oxidation. However, solid dispersion formulations have some limitations, such as poor physical stability, which can lead to drug recrystallization and decreased dissolution rate.

PROSPECTS AND CHALLENGES

Prospects:

An Improvement in Bioavailability and Solubility: By suspending the medicine in a hydrophilic matrix, solid dispersion formulations have the potential to increase the drug's solubility and bioavailability in water.

Versatility: Spray drying, hot-melt extrusion, and co-precipitation are just a few of the ways that may be used to make solid dispersions, allowing them to be flexible and adaptable to a wide range of medicinal molecules.

Improved Consistency: Drugs that are formulated as solid dispersions have a lower risk of degradation and a longer shelf life.

Customization: Drug release profiles and other features of solid dispersion formulations can be tailored to individual treatment needs by adjusting the type and amount of excipients employed.

A Lower Dose: Reduced dose is another benefit of solid dispersion formulations, which can make drug delivery more accessible to patients and lower the chance for unwanted effects.

Challenges:

Scale-up: Because of the complexity of the manufacturing process and the requirement to maintain homogeneity and stability, scaling up solid dispersion formulations can be difficult.

Stability of the Formulation: Because the medication and excipients may undergo chemical reactions or physical changes during storage or administration, stability is also a major difficulty in solid dispersion formulation creation.

Compatibility: Some excipients may interact with the medicine and decrease its stability or efficacy, thus it's important that they're compatible with the drug before proceeding with the solid dispersion formulation.

Restrictive Regulations: Development of solid dispersion formulations might be complicated by the time and money required to have new drugs approved by regulators.

Cost: Solid dispersion formulation development can be difficult since it can be expensive due to the usage of specialised equipment and the necessity for extensive testing and characterization.

LIMITATION

- Solid dispersions are often unstable due to the drug's tendency to recrystallize during storage, resulting in decreased solubility and bioavailability. The formulation of the solid dispersion must be carefully controlled to prevent recrystallization and ensure long-term stability.

- The preparation of solid dispersions is a complicated process that requires a high degree of technical expertise. The preparation process can also be time-consuming, increasing the cost of production.

- Solid dispersion can increase the solubility of poorly soluble drugs, but it is not always effective in enhancing their absorption. For instance, the drug may still have poor permeability or stability, which can hinder its absorption.

- Solid dispersion is often limited to certain dosage forms such as tablets, capsules, and powders. It is not suitable for all drug delivery systems, particularly injectables.

CONCLUSION

Solid dispersion is a promising formulation strategy for enhancing the solubility and bioavailability of poorly soluble drugs. Different methods of preparing solid dispersions have been described, and their advantages and limitations have been discussed. The use of appropriate carrier materials and preparation methods can lead to stable and effective solid dispersion formulations. However, further studies are needed to optimize the properties of solid dispersions and to develop suitable characterization methods.

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