A Review on Ternary Solid dispersion for delivery of poorly soluble drug

Ranjodh Singh, Lakshya Veer Singh, Rohan Yadav
Department of Pharmacy
MJP Rohilkhand University Bareilly. U.P.
ranjodhsingh50046@gmail.com

Abstract

At Least 40 % of novel drug in the pharmaceutical industry have poor water solubility. Improving the solubility of poorly water-soluble drugs can enhance their bioavailability. The most difficult aspect of formulation development is the solubility behavior of the drug. To solve this problem and to increase dissolution rate, development of ternary solid dispersion with carriers having good water solubility is beneficial. Studies show that the Ternary dispersions having drug, polymer and surfactant give better results in comparison to binary dispersions. Different types of polymers and surfactants are used in the formulation of Ternary solid dispersions to increase the solubility of poor soluble drugs.

Key words: dissolution rate, solid dispersions, surfactants, ternary dispersions.

Introduction

Ternary solid dispersion refers to a formulation technique that involves the dispersion of three different components in a solid matrix. By combining a drug, a polymer, and a surfactant or co-surfactant, this technique enhances the solubility and bioavailability of poorly soluble drugs. The solid dispersion matrix allows for improved dissolution rates, leading to enhanced drug absorption and therapeutic efficacy. It is commonly used in pharmaceutical research and development to overcome the challenges associated with low solubility of active pharmaceutical ingredients.[1]

There are several types of ternary solid dispersions, each with its own unique composition and purpose. Ternary solid dispersion is a formulation technique that has gained considerable attention in the field of pharmaceutical research and development. It involves the dispersion of three components, namely a drug, a polymer, and a surfactant or co-surfactant, in a solid matrix. The concept of solid dispersion dates back several decades. The initial studies in this area focused on binary systems, which consisted of a drug and a polymer. However, researchers soon realized that incorporating a surfactant or co-surfactant in addition to the drug and polymer could further enhance the dissolution and absorption of the drug. With this insight, ternary solid dispersion formulations started gaining prominence. [2-3]

The primary objective of ternary solid dispersion is to overcome the challenges associated with poor solubility of drugs. Many drugs possess aqueous solubility, which limits their dissolution and subsequent absorption in the body. Consequently, their therapeutic effectiveness is compromised. Ternary solid dispersion offers a solution to this problem by improving the solubility and release kinetics of such drugs. [4]

The drug component of ternary solid dispersion (API) is the therapeutic agent responsible for the desired pharmacological effects. The selection of the drug depends on the specific condition being treated and the desired outcomes. Examples of drugs that can benefit from ternary solid dispersion include anticancer drugs, antifungal agents, cardiovascular drugs, and many others.[5]

The polymer component plays a crucial role in ternary solid dispersion. Polymers are inert, high molecular weight substances that can act as carriers for the drug. They provide stability, control drug release, and recover the solubility of the medicine in the solid matrix. Examples of polymers in ternary solid dispersion include hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), and others. The selection of the polymer depends on factors such as compatibility with the drug, desired release profile, and stability considerations. [6-8]

The surfactant or co-surfactant component in ternary solid dispersion formulations assists in the dispersion and dissolution of the drug in the solid matrix. Surfactants have amphiphilic properties, which allow them to interact with both hydrophilic and hydrophobic components. They reduce the interfacial tension between the medicine and the polymer, facilitating homogenous dispersion. Surfactants commonly used in ternary solid dispersion include sodium lauryl sulfate (SLS), polysorbate 80 (Tween 80), and others.[9]

Various preparation methods are employed to create ternary solid dispersions. The choice of method depends on several factors, including the physicochemical properties of the drug and polymers, equipment availability, and desired characteristics of the formulation.

Oral route is safe ,easy, most effective for drug delivery due its simplicity and convenience.However, In the pharmaceutical industry, at least 40% of new drugs have problems such as poor water solubility, sluggish release, slow dissolution, and poor bioavailability, requiring dosages large enough to produce the desired pharmacological effects It is feasible to increase the oral bioavailability of certain medications while lowering their negative effects.

Drug that are poorly water-soluble dissolve in solid dispersion is term used to describe the dispersion of one or two active materials in an inert (hydrophilic) carrier at the solid state following either the melting (fusion) method or solvent approach [10, 11, 12, 13]

When the term "solid dispersion" first appeared in the 1970s, it referred a collection solid products with two distinct ingredients, often hydrophilic matrix or hydrophobic substance. Improving, dissolving dissolution the drug can increase the bioavailability of oral medications, especially those with low dissolution a aqueous solubility

In contrast to the traditional binary solid dispersion, which contains a medicine dispersed in a single polymer matrix, the latest development of "ternary solid dispersion" contains. three components. The three components of ternary solid dispersion are API, polymer, and additive The third element is typically a surface-active substance that regulates the drug's solubility stability profile.

A significant surge in interest in adding a surface-active agent to solid dispersion and significant improvement in drug dissolution was reported ternary solid dispersion study of dissolving one or more ingredients in a solid state in an inert matrix to increase the dissolution rate, complete drug release, modify the product, improve s olubility and stability, and release drugs ..
Ternary solid dispersion is defined as the product dispersion of two different compositions of active ingredients. With this advancement, almost any absorption problem can be overcome. This third component may be another polymer, a surfactant, an excipient, other chemical com pounds, or a carrier that will increase solubility and ultimately increase separation and bioava ilability.[14]

. The development of numerous techniques to enhance these qualities includes the production of salts, other technique To resolve these one of the best choices is using the solid dispersion method to enhance water solubility, the rate of dissolution and thus bioavailability of pharmaceuticals. With low solubility Enhancing the solubility and rate of dissolution of drugs that dissolve slowly in water and improving the permeability of drugs that are poorly permeable are the two fields of pharmaceutical study that are focused on increasing the active agent's oral bioavailability.

Types of solid dispersion

1-Binary solid dispersion- polymer and a medication are mix to form a binary solid dispersion.

2-Ternary solid dispersion-Drug, polymeric carrier, and surfactant are all present in a ternary solid dispersion.

3-Surface solid dispersion-Polymers and copolymers make up the surface solid dispersion. It is created using a fusion process to improve the solubility of a medicine that isn't very soluble

1. Drug-Polymer-Surfactant: This type consists of a drug, a polymer, and a surfactant. The drug is the active pharmaceutical ingredient, the polymer enhances stability and solubility, and the surfactant aids in the dispersion process and dissolution of the drug

2. Drug-Polymer-Polymer: In this type, two different polymers are used along with the drug. The combination of polymers can provide controlled drug release, improved stability, and enhanced solubility.

3. Drug-Polymer-Cosolvent: This type includes a drug, a polymer, and a cosolvent. The cosolvent is typically a water-miscible organic solvent that helps to increase the drug's solubility and improve its dispersion in the polymer matrix[15]

Carriers used in individual products –

S.NO	Category	Carrier
1	Sugar	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose
2	Acid	Citric acid, succinic acid
3	**P**olymer Product	Polyvinyl pyrrolidine (PVP), polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), methyl cellulose (MC), hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, pectin, galactomannan
4	Insoluble or enteric Polymer	Hydroxy propyl methyl cellulose phthalate (HPMCP), eudragitL100, eudragit E100,eudragit RL, eudragit RS
5	Surfactant	Polyoxymethylene stearate, poloxamer 188, deoxycholic acid, tweens, spans
6	Other	Pentaerythritol, pentaerythrityl tetraacetate, urea, urethane, hydroxy alkyl xanthine

Different generation carriers:[16,17]

First Generation carriers	Second Generation carriers	Third Generation carriers
Crystallization mate rials: urea, sugar, or ganic acids	Synthetic products contain povidone. (PV P), polyethylene glycol (PEG) and polyme thacrylate. Polymerbased natural materials often cont ain cellulose. Hydroxypropyl methylcellul ose (HPMC), Derivatives such as ethyl cellulose or hydr oxypropyl cellulose or starch derivatives s uch as cyclodextrin	Surface active, self-emulsifying carriers: P oloxamer 408, Tween 40/ Geluire

Method of Preparation Solid Dispersion

1. Melting Method:

In this way, the drug, polymer, and surfactant/co-surfactant are melted together. [18, 19]

2. Spray Drying Method:

In this method, a solution or suspension of the drug, polymer, and surfactant/co-surfactant is atomized and sprayed into a heated chamber. The solvent evaporates rapidly, leaving behind solid particles that form a solid dispersion.[20]

3. Solvent Evaporation Method:

The drug, polymer, surfactant/co-surfactant are mixed in a common solvent. The solution is then poured into a mold or on a substrate, and the solvent is allowed to evaporate slowly, resulting in the development of a solid dispersion.

It is important to consider factors such as compatibility, stability, and processing conditions when selecting the appropriate method of preparation.[21]

4. Fusion method-

It is a variation on the co-melting technique. The carrier is put inside a porcelain dish and cooked in a steam bath until it melts. Using a glass rod and a properly measured amount of medication, an organic solvent is dissolved in hydroxyl propyl methyl cellulose (used as a carrier) to create a clear, translucent gel. The medicine is then sonicated dissolve it in the gel. Under vacuum, organic solvent evaporates. By using a mortar and pestle and a sieve, solid dispersions are condensed in size. Little amount is gradually injected into a molten carrier. After the medicine has been completely distributed throughout the carrier, the dish is taken out of the steam bath and set aside to cool at room temperature until its contents have solidified. The resultant solid dispersion is next ground and sieved. This technique helps prevent the heat degradation of drugs.[22]

5. Kneading techniques-

This technique turns the carrier into paste by allowing water to permeate it. The drug is then added and mixed for a specific amount of time, then dried and, if necessary, put over a sieve. Drug and compound that are moisture-sensitive cannot be processed using this technology; thermolabile medicines can be processed using it.[23]

6. Co-precipitation method-

The specific quantity of drug is mix to the carrier liquid. System is shielded from light and kept in magnetic agitation. By vacuum filtration, the precipitate is separated, then dried at room temperature.[24]

7. Gel entrapment technique-

An organic solvent is dissolved in hydroxyl propyl methyl cellulose (used as a carrier) to create a clear, translucent gel. The medicine is then sonicated for a brief length of time to dissolve it in the gel. Under vacuum, organic solvent evaporates. using a mortar and pestle and a sieve, solid dispersions are condensed in size.[25]

8. Electro-spinning method-

A polymeric liquid stream fed by a millimeter-sized delivery device generates solid fibres. The nozzle scale. It mostly entails applying a high electrostatic field to a conductor coupled to a reservoir holding a polymer solution or melt and a catalyst.

Testing for conductive I collection. Charge species collected on the surface of a pendant drop destabilised the hemispherical shape, causing the electrostatic field intensity to rise to but not exceed a critical level. It is the easiest and cheapest way to create explosives technology used to make solid dispersion in subsequent studies, and it has considerably more potential for generating nano fibers and managing the release of drugs.[26,27,28,]

9. Supercritical fluid (SCF) method-

The ultra-critical fluid anti-solvent technique is a method that employs carbon dioxide anti-solvent for the solute. Drug particles can be recrystallized at significantly smaller particle sizes after being solubilized in supercritical fluid. The flexibility and accuracy of the supercritical fluid technology allow for the micronation of pharmaceutical particles within a limited r particle size range, down to the sub-micron level.The present supercritical fluid technologies may produce and demonstrate nano-particular suspensions of particles with a diameter of 5000 nm or less. Spraying the solution containing the solute and the organic diluent into the simultaneously growing nonstop supercritical phase was done.[[29]

Evaluation tests;

Ternary solid dispersion are conducted to assess their performance and determine their suitability for use. Here are some common evaluation tests:

Bulk Density

Tapped Density

Compressibility index

Hauser s ration

Angle of Repose

Drug Content and Uniformity:

The drug content is measured to ensure that the desired amount of the active pharmaceutical ingredient is present in the solid dispersion. Uniformity tests are also performed to check for uniform distribution of the drug within the matrix.[30]

Solubility and Dissolution:

Ternary solid dispersion is evaluated using techniques such as shake-flask method or HPLC analysis. Dissolution tests are conducted to assess the amount of drug release from ternary solid dispersion.

Physical Characterization:

Various physical characterization techniques are employed to examine the solid dispersion. These may include particle size analysis, surface morphology observation through methods like (scanning electron microscopy (SEM), X-ray diffraction (XRD)) to determine crystallinity, and differential scanning calorimetry (DSC) to investigate thermal behavior.

Stability Studies:

Stability tests are performed to evaluate the long-term stability of ternary solid dispersion, including factors such as drug degradation, changes in physical properties, and drug release over time. These tests typically involve subjecting the formulation to accelerated and real-time stability conditions.

Pharmacokinetic Studies:

In vivo and vitro studies are conducted to assess the pharmacokinetic behavior of the solid dispersion, including parameters such as drug absorption, distribution, metabolism, and excretion.

Fourier transform infrared spectroscopy (FT-IR):

FTIR can be used to find the interaction between the chemical state and the carrier of the Con ventional KBr spectrophotometer.

Particle method. [30, 31, 32, 33]

Scanning electron microscopy (SEM):

SEM can be used to determine the morphology and particle size of materials and chemicals. The drug in the carrier matrix is visible. The application of electron microscopy is generally li mited to high performance chemicals.[34]

Differential scanning calorimetry (DSC);

To determine the glass transition temperature of an amorphous drug in the TSD system, examine the intermolecular interactions between drugs and excipients.[35]

Powder x ray diffractometry (PXRD);

To investigate the amorphization of medicines in the TSD system[36]

Thermogravimetric analysis (TGA);

To determine the composition of every component in the TSD system.[37]

Solid-state NMR;

To investigate the molecular state of the medication in the TSD system.[38]

Dielectric spectroscopy;

Measure the molecular mobility of medicines in the TSD system.[39,40]

Dynamic Light Scattering(DLS);

The study aims to examine the particle size distribution of pharmaceuticals in the TSD system after dispersion in water. Size and PDI values[41]

TEM and Cryo-TEM Measurements;

To assess drug morphology in the TSD system following dispersion in water. Size and form of nanoparticles [42,43]

Atomic Force Microscopy (AFM) Measurements;

To determine the topography and stiffness of the TSD system in an aqueous solution. Nanoparticles' size, shape, contact location, and force.[44]

Solution-State 1H NMR;

To investigate the hydrogen-bonding interactions between pharmaceuticals and excipients in the solution phase. Shifting the peak to the protected area in the NMR[45]

Zeta Potential;

To investigate the stability of amorphous pharmaceuticals in the TSD system following their dispersion in water. The charge and surface zeta potential of the TSD system at the solution stage[46]

In vitro Drug release

Drug release studies ternary solid dispersions. Aliquots of amount are taken at various times replaced with the equal volume of dissolution medium. Absorbance are measured with a UV spectrophotometer.

These measurements help determine the quality and performance of ternary solid dispersion f ormulations, providing important information for further development and improvement.[47]]

Advantages of ternary solid dispersion:

1. Enhanced solubility: Ternary solid dispersions increase the solubility bcs class ii drug and effectiveness.

2. Improved stability: Solid dispersions can protect drugs from degradation by providing a stable matrix, enhancing the shelf life of the pharmaceutical product.

3. Controlled drug release: Ternary solid dispersions can be formulated to control the release rate of drugs, allowing for controlled and sustained release profiles.

4. Increased dissolution rate: The dispersion of drugs in a solid matrix can significantly improve their dissolution rates, leading to faster drug absorption and onset of action.

5. Formulation versatility: Ternary solid dispersions offer flexibility in formulation design, allowing for the incorporation of various drug-polymer-surfactant combinations to address specific drug delivery challenges.

Limitation of ternary solid dispersion:

1. Formulation complexity: Developing ternary solid dispersions can be challenging due to the need for careful selection and optimization of the drug, polymer, and surfactant/co-surfactant components.

2. Manufacturing scale-up: Scaling up the production of solid dispersions can be complicated, as the process parameters and conditions may require adjustments to ensure consistent and reproducible results.

3. Drug-polymer interactions: The compatibility between the drug and polymer/surfactant components must be considered, as certain interactions may affect drug stability or release characteristics.

4. Cost: The formulation and production of ternary solid dispersions can be more expensive compared to traditional dosage forms due to the additional materials and processing steps involved.

5. Regulatory considerations: Depending on the region and specific drug, additional regulatory requirements may be needed for the approval and commercialization of solid dispersion-based products.

It is essential to weigh these advantages and disadvantages when considering the use of ternary solid dispersions for drug delivery, as they can affect formulation development, manufacturing, and regulatory aspects.

Application of the solid dispersion-

- It is mostly used to provide homogenous medication distribution in modest amounts of solid state.
- It aids in stabilizing the unstable dosage form.
- It is utilized to administer the substance as a solid dosage form whether it is liquid or gaseous.
- quick release as well as release Sustained dosage forms for primary doses are possible. [48,49]

Conclusion

Solid dispersions and Ternary solid dispersions the ideal option for increasing the solubility of the weakly water soluble BCS-II medication. The oral bioavailability and release amount of weakly water-soluble medicines utilizing solid dispersion be careful carrier selection. It is too possible alter the drugs release pattern by delaying or slowing, it in this method three component drug, polymer surfactant they different types of polymers and surfactant increase the solubility of drug. Difficult ways to expand the solubility of poorly water-soluble Bcs class II drugs and to increase their bioavailability is through the way of solid dispersion and Ternary solid dispersion. Thus, it is necessary.to solve several issues with medication stability and flow. Characteristics. As a results, the least poisonous, most biocompatible, and most widely accessible

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ranjodhsingh50046@gmail.com