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A REVIEW ON SOLID DISPERSION: CHALLENGING ASPECT OF SOLUBILITY ENHANCEMENT OF PER ORAL POORLY SOLUBLE DRUGS

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Abstract: At least 40% of pharmaceutical companies' innovative drugs exhibit poor water solubilization properties. Therefore, the scientists' biggest problems are to make such drugs more soluble in water and more bioavailable. Therefore, the creation of solid dispersion with carriers with strong water solubility is advantageous to overcome such issues and promote dissolution. Therefore, it is discovered that using solid dispersion methods is a successful way to increase the drug's solubility when it has low water solubility. This review emphasizes many types of solid dispersion, their justifications, benefits, and drawbacks, as well as the production procedures for their limited commercialization. As a result, this technique has been recognized as a very useful tool for increasing the dissolving capabilities of poorly water-soluble pharmaceuticals.

Keywords: poorly soluble drug, solid dispersions, solid solution, amorphous state, hydrophilic, carrier, solubility, polymer, bioavailability

INTRODUCTION

Solid dispersion is a set of solid goods that contains at least two separate components i.e., a hydrophilic matrix and a hydrophobic medication. The drug may be disseminated molecularly, in amorphous particles, or crystalline particles. Riegelman and Chiou defined solid dispersion as "a dispersion involving the creation of a eutectic combination of medicine with water-soluble carriers by melting of their physical composition."Due to its simplicity and convenience, the oral route is the most widely used way to administer medication [[1]]. The oral route is a familiar and cozy way to take medication from the patient's perspective. Therefore, compared to alternative modes of delivery, oral drugs are more effective. Because of slow release, low bioavailability, and slow dissolving, which necessitates the administration of high doses to produce desired pharmacological effects [[2],[3],[4]], at least 40% of innovative drugs from the pharmaceutical sectors have poor capacity to solubilize in water. The easiest way to deal with these issues is to increase the solubility of inferior medications that are water soluble and solve the solubility problem. The method is a good tool for improving dissolution rates, solubility, and bioavailability of poorly water-soluble drugs.

Pharmaceutical research focuses on two main areas: Enhancing the permeability of weakly permeable drugs and increasing the solubility and dissolving rate of poorly water-soluble drugs to increase active agent oral bioavailability [[5],[6]]. Using solid dispersions to enhance the dissolving characteristics of poorly water-soluble medicines and their bioavailability is the main theme of this narrative review. Drugs classified as Class II in the BCS have strong membrane permeability but poor water solubility. To increase the oral absorption and bioavailability of Class II(BCS) medications, solid dispersion methods are thus particularly used. The fundamental idea behind improving a drug's poor solubility using solid dispersion is completely removing in a hydrophilic polymeric carrier, the molecules of the drug are dispersed, preserving its crystal structure [[7]].

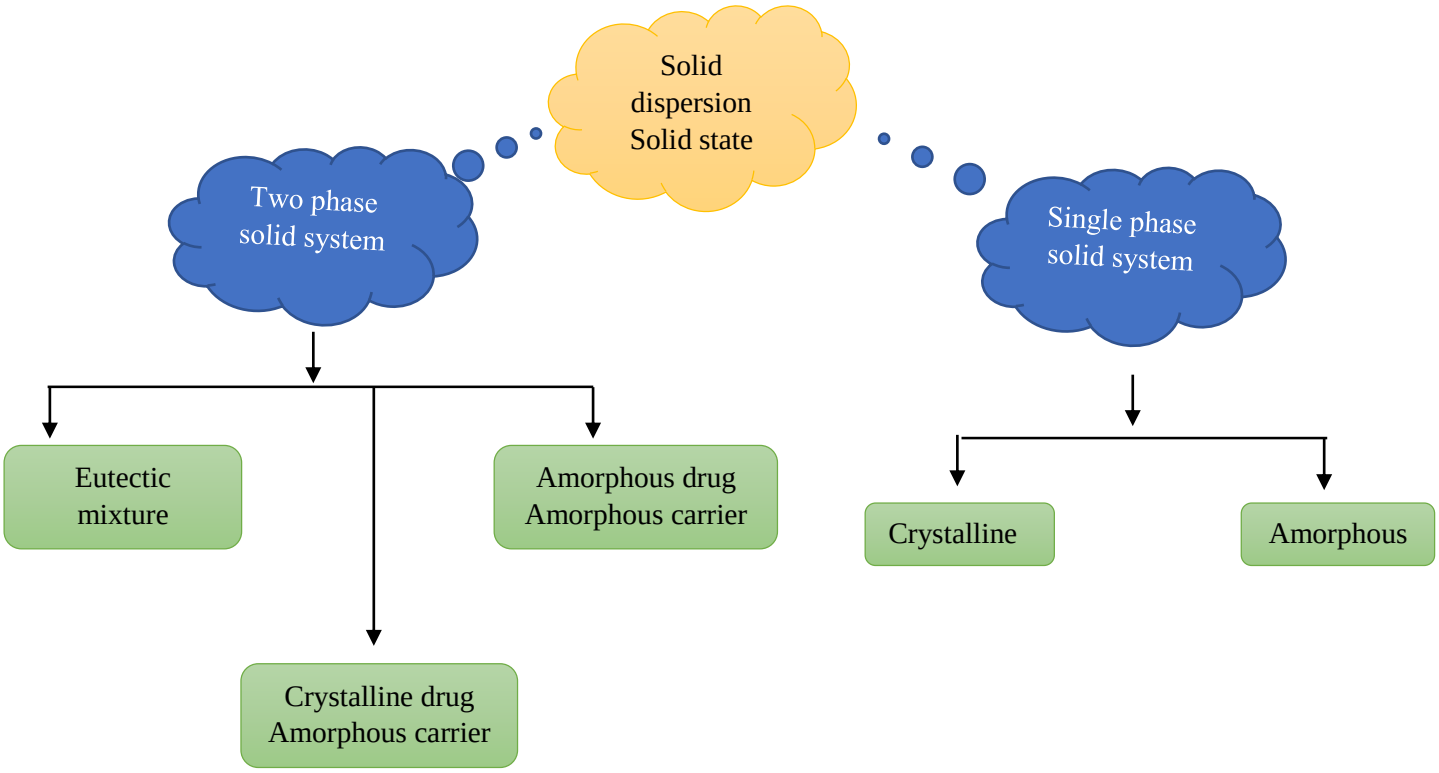

Fig 1: Solid Dispersion Classification

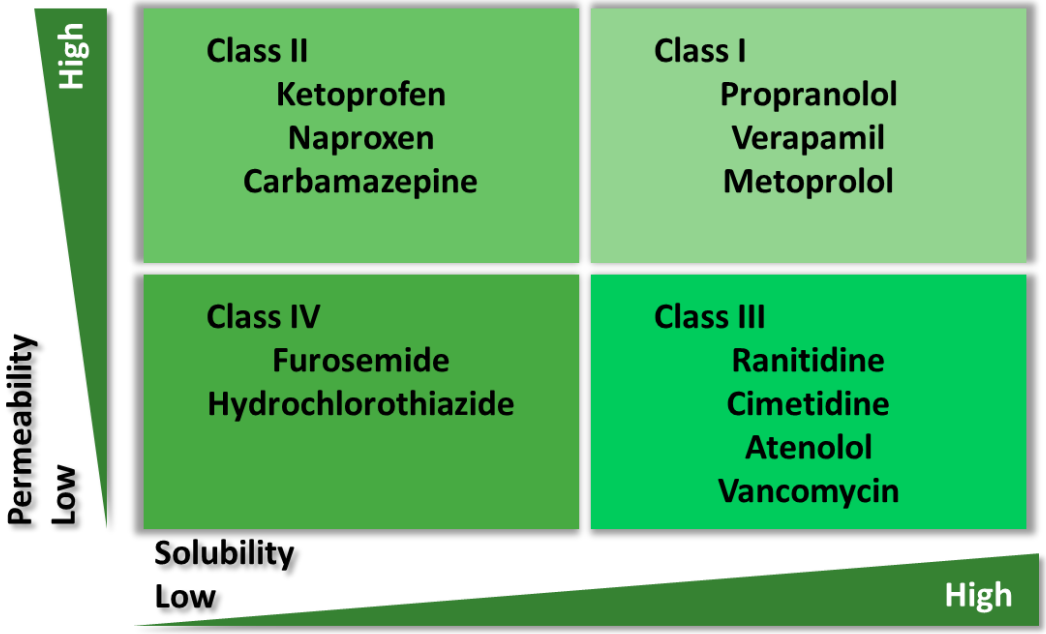

Fig 2: BCS Classification System

TYPES

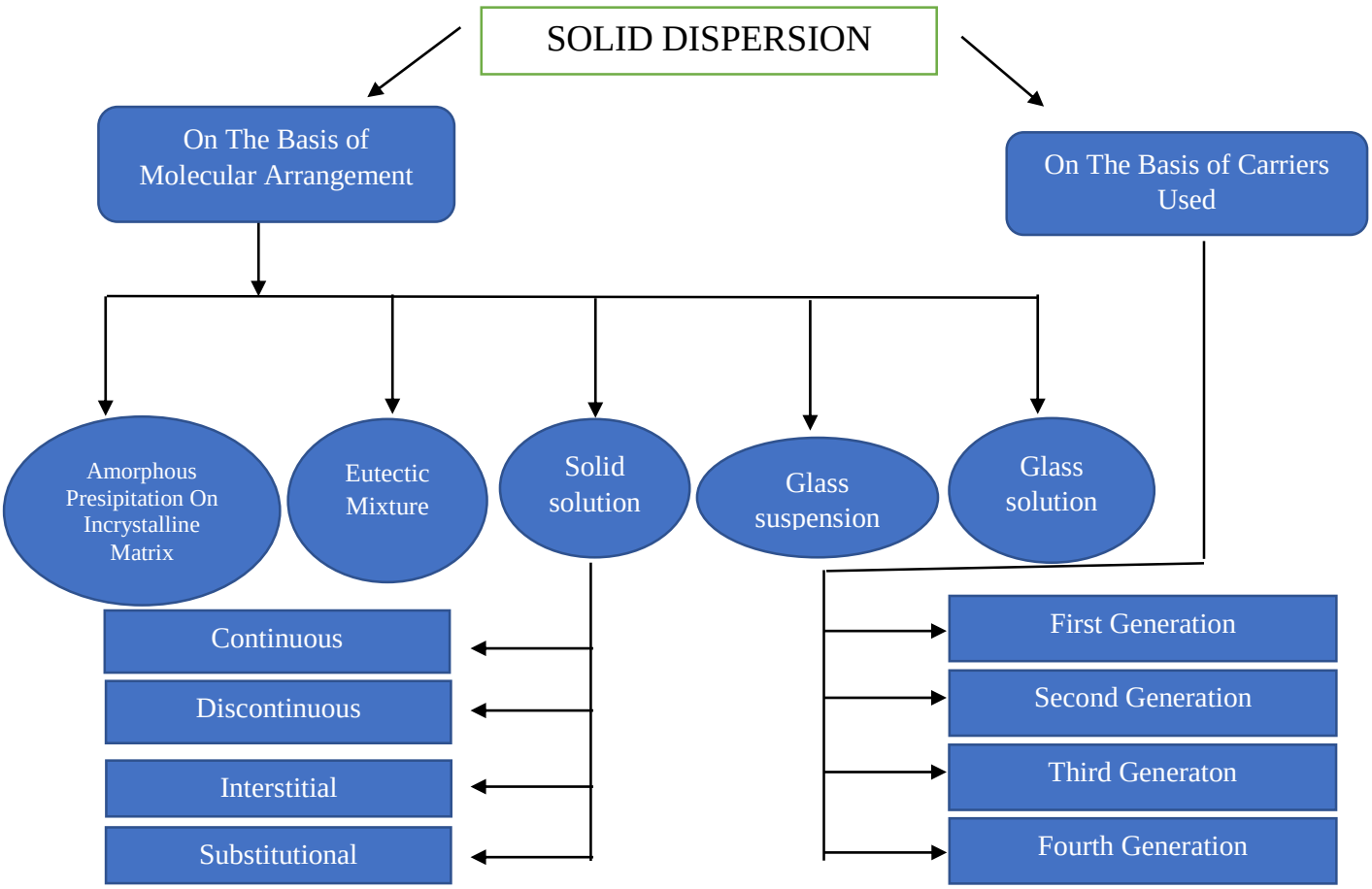

Fig 3: Types

1) Eutectics Mixtures:
Two chemicals that are entirely miscible in liquid state but only to a very small amount in the solid state make up the simple eutectic combination. A solid-solid solution is created by rapidly solidifying two components that were fused and exhibit 100% liquid miscibility [[5],[8],[9]].

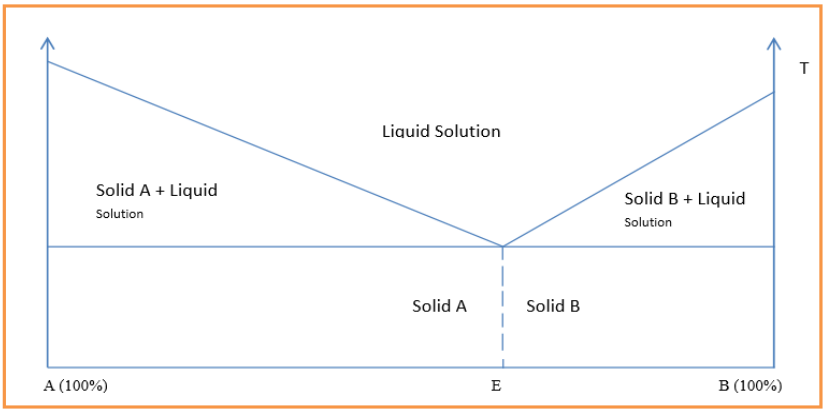

Fig 4: Eutectics mixtures [[5],[8],[9]]

2) Amorphous solid solution:
Medication precipitates out in an amorphous form here, as opposed to simple eutectic mixes [[5],[10],[11]].

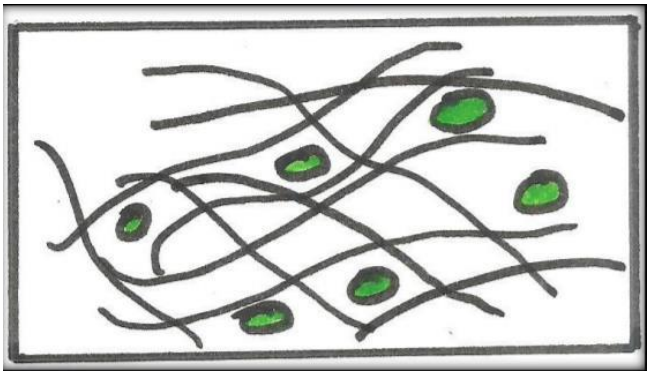

Fig 5: Amorphous solid solution [[5],[10],[11]]

3) Solid solution:

The same applies to solid solutions, regardless of the number of components. Solid solutions have only one phase, similar to liquid solutions. Drug particle sizes, or the dimensions of individual molecules, are reduced to an absolute minimum by the carrier's rate of dissolution in solid solutions. Third, based on their diffusibility (continuous vs. discontinuous solid solutions) (interstitial/amorphous, substitutional) [[5]]

a) Continuous solid solution:

Solid solutions are continuous solutions in which all components are miscible. According to theory, the molecules of the two components have a stronger relationship than the molecules of their components. This form of solid solutions has not yet been documented in the pharmaceutical sector [[5],[12]].

b) Discontinuous solid solutions:

As a result of discontinuous solid solutions, one component is restricted in its solubility in the other. According to Goldberg et al., solid solutions should only be referred to when they have a combined solubility greater than 5% [[5],[12]].

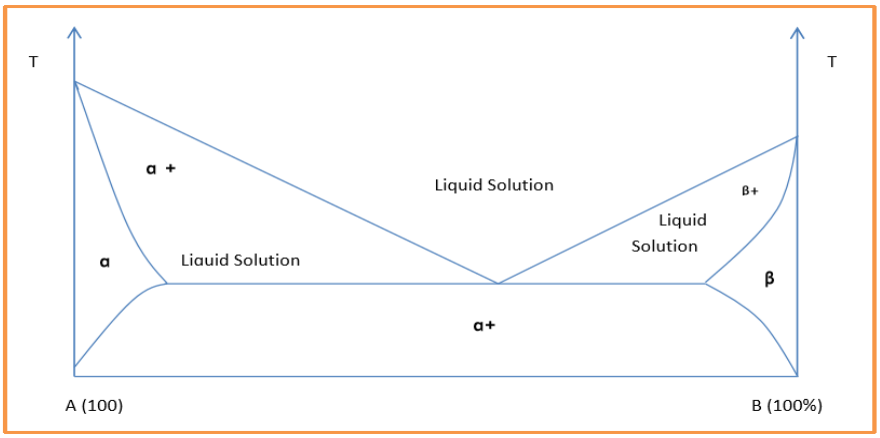

Fig 6: Discontinuous solid solution [[5],[12]]

c) Substitutional solid dispersions:
A substitution is feasible only when the solute molecule size differs from the solvent molecule size by around 15% or less. Crystal structures of solid solutions typically contain solute molecules that either fit between or substitute for solvent molecules [[5]].

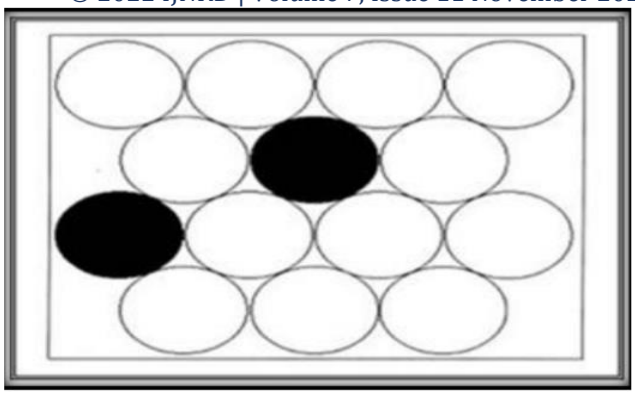

Fig 7: Substitutional solid solution [[5]]

d) Interstitial solid solutions:

As dissolved molecules fill in the gaps between solvent molecules in interstitial solid solutions, they are called interstitial solid solutions. The difference in molecular diameter between the solvent and the solute should not exceed 0.59[[5],[12]].

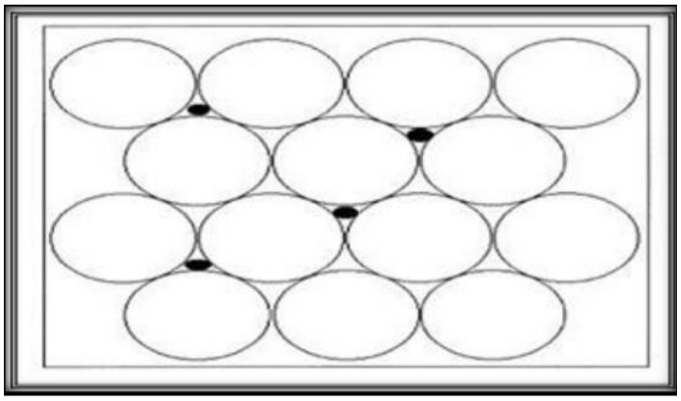

Fig 8: Interstitial solid solution [[5],[12]]

4) Glass solution and suspensions:

It is a homogeneous glassy solution that consists of a solute dissolved in a glass carrier. Mixed suspensions of precipitated particles in glass solvents are called glass suspensions. In glass suspension and solution, lattice energy is substantially smaller [[5],[12],[11]].

Advantages:

- ✓ A carrier increases solubility by reducing the particle size and therefore increasing the surface area of the particles in a formulation [[13],[14]].
- ✓ The dissolving characteristic of a medication candidate rose along with its wettability. Solid dispersion makes medication more wettable [[13],[14]].
- ✓ The porosity of the medication is increased by solid dispersion. The improvement in solubility is also a result of this trait of the medication [[13],[15],[16]].
- ✓ The insoluble medication is transformed into an amorphous state by solid dispersion, which causes a greater degree of solubility. The medication candidates are simple to release in their amorphous condition since crystal lattice disintegration doesn't require any energy to break [[13],[17],[18]].
- ✓ When making oral disintegrating tablets using the solid dispersion approach, hydrophilic carriers like PEG and super disintegrants like croscarmellose sodium are utilized, both of which increase water dissolution [[19],[20]].

Disadvantages:

- ✓ Solid dispersion has limitations including inadequate production scale-up [[19]].
- ✓ Due to a tackiness issue, it can occasionally be challenging to handle [[13]].
- ✓ Instability is a significant drawback of solid dispersion technology. The majority of carriers employed in the formulation are polymers, which quickly absorb moisture. As a result, phase separation develops, which causes instability [[21],[22]].
- ✓ Amorphous drugs can recrystallize and/or transition between the polymers that cause stability issues can take place [[22],[23]].

Application:

- It boosts the absorption and bioavailability of the medicine by making poorly soluble pharmaceuticals more soluble and, as a result, increasing the rate at which they dissolve.
- To protect unstable medications from numerous degradation processes including hydrolysis, oxidation, etc.
- To lessen the negative effects of specific medications.
- Covering up the smell and taste of narcotics.
- To prevent unwelcome incompatibilities.
- To achieve uniform dispersion of a little quantity of medication in solid form.
- The solid dose of liquid (up to 10%) or gaseous substances [[5]].

Selection of carrier

The following qualities are necessary for a carrier to be effective at speeding up medication dissolution:

- ➢ The carrier should have a high rate of dissolution in water, be readily soluble in water, be non-toxic by nature, be pharmacologically inert, and have a low melting point and heat stability.
- ➢ The medication must be soluble in water, chemically compatible, and not form tightly bound complexes with the medication.
- ➢ Economical [[24]].

USE OF POLYMERS IN SOLID DISPERSIONS:

PEG (Polyethylene Glycol): Using ethylene glycol paired with ethylene oxide, these substances can be created. Polyethylene oxide is often used to refer to PEGs with a molecular weight of 300,000 or more [[25]].

Phospholipids: It is possible to increase the complexity of glycerides by adding phosphate groups to the terminal hydroxyl of glycerides. In addition to ethanolamine, serine, and inositol, phosphate, inositol, glycerol esters, and choline are also common phospholipid head groups. Variations in fluidity are observed depending on the temperature at which gel transitions to the liquid crystal. As with triglycerides, glycerol backbones with different head groups and fatty acid substitutions can lead to a wide range of species.

In addition to its chemical function, phospholipid solubility is strongly related to aggregation material identity. Monoacyl phospholipids are frequently more soluble in aqueous solutions and have the propensity to form micelles [[25]].

PVP (Polyvinyl Pyrrolidone): The molecular weight of PVP ranges from 2500 to 3000000.It is soluble in a variety of solvents, including isopropyl alcohol, chloroform, PVP and ethanol, degrades at high temperatures. Because melting occurs at such high temperatures, it is unsuitable for the production of solid dispersions using the melting process [[25]].

Cyclodextrins: In addition to increasing solubility, cyclodextrins also protect chemicals, mask flavors, and make liquids easier to handle because they entrap liquids [[25]].

METHODS

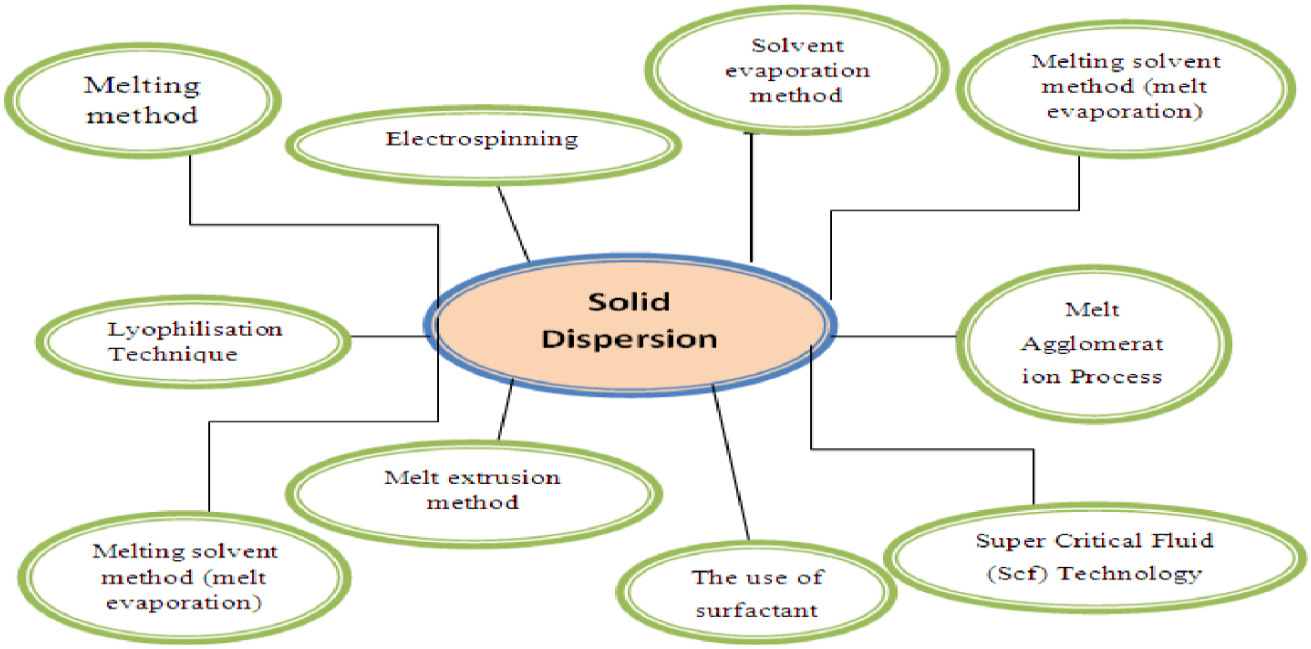

Fig 9: Methods of Solid Dispersion

1) Melting method:
The physical mixing of a medication with a water-soluble carrier before being heated until it melts is known as the "melting and fusing" approach. The liquid is first melted, and then it quickly freezes solid in an ice bath while being vigorously stirred. The final solid mass is then broken up, ground up, and sieved [[26]].

2) Solvent evaporation method:

Drug and carrier mixtures are dissolved in a common solvent and evaporated until only free film remains. After drying and sieving the remaining film, it is discarded [[2],[27]].

3) Lyophilization technique:
In this process, heat and mass are moved away from the product. This method was put out as a substitute for the solvent evaporation method. This particular molecular mixing method uses a shared solvent to simultaneously dissolve the carrier and the medication. The molecular dispersion was then frozen and sublimed to produce lyophilization [[2],[26]].

4) Melting solvent method:
In this procedure, a predetermined amount of solvent is added, and the solvent solution is then added to melted polyethylene glycol below 700C. This approach is also employed with high melting point thermolabile drugs. But a small amount of medication and a low therapeutic dosage is needed (below 50mg) [[2],[26]].

5) Melt extrusion method:

For thermolabile drugs, this technique is typically recommended. Twin-screw extrusion is often used to process a mixture of the medication and carrier. The combination is consequently simultaneously melted, homogenised, extruded, and formed into tablets, granules, pellets, sheets, sticks, or powders. The intermediates are then processed one more to produce tablets [[2],[26]].

6) Melt agglomeration method:

This technique uses the binder as a carrier to achieve solid dispersion. Furthermore, solid dispersions are created by either melting the binder, drug, and excipient together (the "melt-in method") or sprinkling a molten drug dispersion over a heated excipient (the "spray-on technique") while employing a high-shear mixer. It is possible to replace melt agglomeration equipment with a rotary processor. For high melt agglomeration, rotary processers are often used. Because a bigger amount of binder may be integrated into the agglomerates and because controlling the temperature is easier [[5],[26]].

7) Spray drying:

In this procedure, the medication and lipid carrier is carefully weighed out and then dissolved in methanol to produce a transparent solution. In a lab size, this solution is sprayed with a drier to create a solid dispersion [[2]].

8) Effervescent method:

To produce effervescence, organic acids like citric or succinic acid interact with sodium bicarbonate. However, when both were combined, the rate at which the poorly soluble medication dissolved and was absorbed increased [[2],[27]].

9) Electrospinning:

Solid filaments are produced by delivering polymeric fluid streams or melts through millimeter-scale nozzles. The primary approach involves creating a powerful electrostatic field around a conductor that is fastened to a reservoir that holds a polymer melt or solution and a conductor collecting screen. When charge species accumulated on the surface of a pendant drop, causing its hemispherical form to be broken and shift into a conical one, the electrostatic field strength rose but did not exceed a threshold point.

The technique is the simplest and least expensive method used for the fabrication of solid dispersion in further. Nanofibers can be made and biomedicine can be released much more effectively using this technology [[5],[26],[12]].

10) SCF Technology:

CO_2 acts as an anti-solvent for the solute in the super-critical fluid anti-solvent approach. Drug particles may be recrystallized at greatly decreased particle sizes after being solubilized in the supercritical fluid. The versatility and accuracy of supercritical fluid technology enable the micronization of medication particles within a constrained particle size range, down to submicron. Today's super-critical fluid techniques are capable of producing nano-particular suspensions of particles in the size of 5-2000 diameter. Spraying the mixture of solute and organic solvent resulted in a continuous supercritical phase [[26]].

Table 1: The Relevance of Various Methods for Characterization of Solid Dispersions [[28]]

CHARACTERISTICS	METHODS USED	SIGNIFICANCE
Evaluation of physical state	Hot stage microscopy, XRD, DSC, humidity stage microscopy.	To determine the physical condition of a sample, as well as the crystallinity and degree of crystallinity of a medication, polymer.
Surface Microscopy	Hot stage microscopy, and SEM, Polarised light optical microscopy.	To investigate crystallinity and Microscopy

Structure elucidation	FTIR spectroscopy, Solid-state NMR spectroscopy.	To research the interactions between a medication and its carrier, such as hydrogen bonds
Drug carrier interactions	NMR Spectroscopy, DSC, FT-IRspectroscopy	To investigate how drugs and polymers interact physically and chemically
Dissolution rate	dynamic solubility, studies Dissolution studies.	To research the amount and speed of medication release
Stability	NMR Spectroscopy, DSC, FT-IRspectroscopy	To Investigate the physiochemical interactions between the polymer and the medication during production and storage.

CONCLUSION

By solid dispersion, a drug's solubility in water and bioavailability can be improved. Therefore, it is necessary to find solutions to various issues with medication stability and flow qualities. Therefore, the least poisonous, biocompatible, and most widely accessible solid dispersion is the ideal choice for increasing the solubility of BCS-II. Using this method poorly water-soluble medicines can be improved in terms of oral bioavailability and release rate. The drug's release pattern might potentially be slowed down or delayed.

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