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SOLID DISPERSION METHODS AND ITS ADVANTAGES: A REVIEW

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ABSTRACT:

The solubility behaviour of drug is one of the most challenging aspects in formulation development. Thus, a greater understanding of dissolution and absorption behavior of drug with low aqueous solubility is needed to successfully formulate them into more soluble and hence bioavailable drug product. Solid dispersions have piqued the interest of researchers as an effective technique of increasing the dissolution rate and hence bioavailability of a variety of hydrotrophic medicines. The use of water-soluble carriers in solid dispersions of weakly water-soluble medicines reduces the occurrence of these issues and improves dissolution. "One of the most promising ways for increasing solubility is solid dispersion." ("Solid Dispersion: A Novel Approach to Improving the...") A solid dispersion is a type of solid product that consists of at least two separate components, often a hydrophilic matrix and a hydrophobic medication. The matrix might be crystalline or amorphous in nature. According to the biopharmaceutical categorization system, class II medicines have poor solubility and high permeability and are good candidates for improving bioavailability by solid dispersion. This article discusses the many forms of solid dispersion, various solubility enhancement methodologies in solid dispersion, the benefits of solid dispersion over other techniques, and solid dispersion applications ("(PDF) SOLID DISPERSION - A TECHNIQUE FOR SOLUBILITY ENHANCEMENT OF...").

Keywords: Solubility, Dissolution, Solid Dispersion, Hydrophobic, Hydrophilic, Biopharmaceutical Classification, Enhance Dissolution, Amorphous.

INTRODUCTION:

The term solid dispersion refers to the dispersion of one or more active ingredients in the hydrophilic inert carrier matrix at molecular level. There are several problems in the current drug delivery method that led many novel potential therapeutic entities to be abandoned due to poor water solubility, which results in lower bioavailability. However, in this modern era of the Drug Delivery System, there are new technologies that can solve the solubility and permeability issues. Among the various issues that might arise when administering an active substance orally is limited drug absorption, which results in low bioavailability. Various pharmaceutical sectors employ ways to promote medication solubility and dissolution in the body with penetration capacity that might be low or high. Other approaches for improving the dissolving capabilities of weakly water-soluble pharmaceuticals include salt creation, complexation with cyclodextrins, solubilization of medications in solvent(s), and particle size reduction. The BCS classification system refers to the biological classification of medicinal medications based on solubility and permeability. And medications with poor solubility and high permeability are classified as Class II pharmaceuticals, which are excellent for increasing drug solubility and bioavailability.

Table 1: Table of BCS Classification System.

Class	Solubility	Permeability	Examples
Class I	High Solubility	High permeability	Benazepril, Loxoprofen, Sumatriptan etc.
Class II	Low Solubility	High permeability	Valsartan, Nimesulide, Loratadine, Aceclofenac, Glimepiride etc.
Class III	High Solubility	Low permeability	Gabapentin, Topiramate, Atropine etc.
Class IV	Low Solubility	Low permeability	Hydrochlorothiazide, Furosemide, Meloxicam etc.

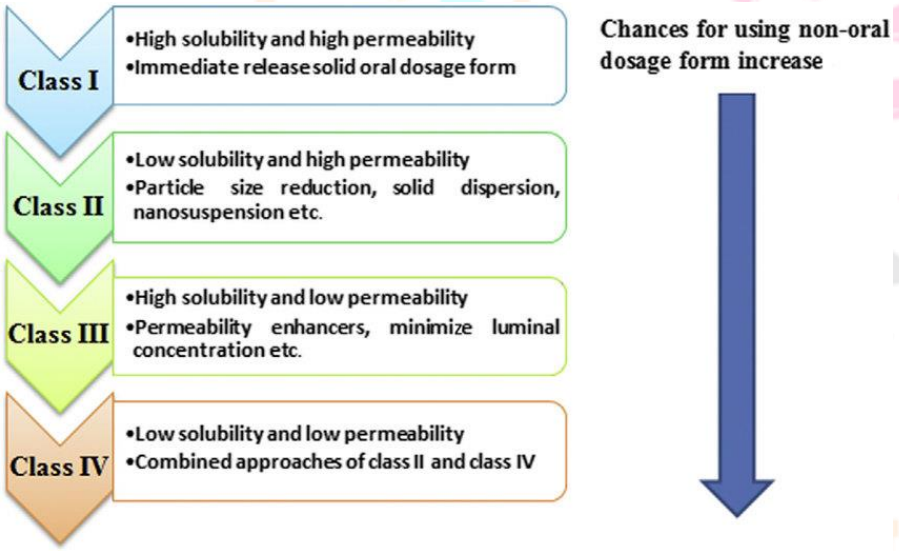

Fig 1: BCS system and formulation approaches for different class of drugs.

ORAL DRUG DELIVERY SYSTEM:

An oral drug delivery system is thus believed to be provide continuous oral release of the drug throughout the course of its gastrointestinal (GI) transit.

The most frequent route of medication delivery is orally. It is the favored method because to benefits such as non-invasiveness, patient compliance, and ease of medication delivery. Several variables influence oral medication absorption, including drug solubility, mucosal permeability, and gastrointestinal tract stability. Efforts to overcome these hurdles have centered on understanding the physicochemical, biochemical, metabolic, and biological limitations that restrict total medication bioavailability. To improve oral medication absorption, many pharmaceutical technologies and drug delivery systems such as nanocarriers, micelles, cyclodextrins, and lipid-based carriers have been investigated.

ADVANTAGES:

1. Convenient and easy administration
2. Quick onset of action
3. Better patient compliance

4. Improved absorption and bioavailability
5. Avoidance of first-pass metabolism
6. Reduced dose frequency
7. Ability to target specific sites in the body
8. Improved stability of labile drugs
9. More cost-effective than other delivery methods
10. Increased patient comfort and reduced pain associated with injections

SOLID DISPERSION:

"The phrase solid dispersion refers to the molecular dispersion of one or more active substances in a hydrophilic inert carrier matrix." ("Solid Dispersion as a Method for Increasing Bioavailability of...") It is cooked in many ways. The procedure is tailored to the interaction between the medicine and the carrier.

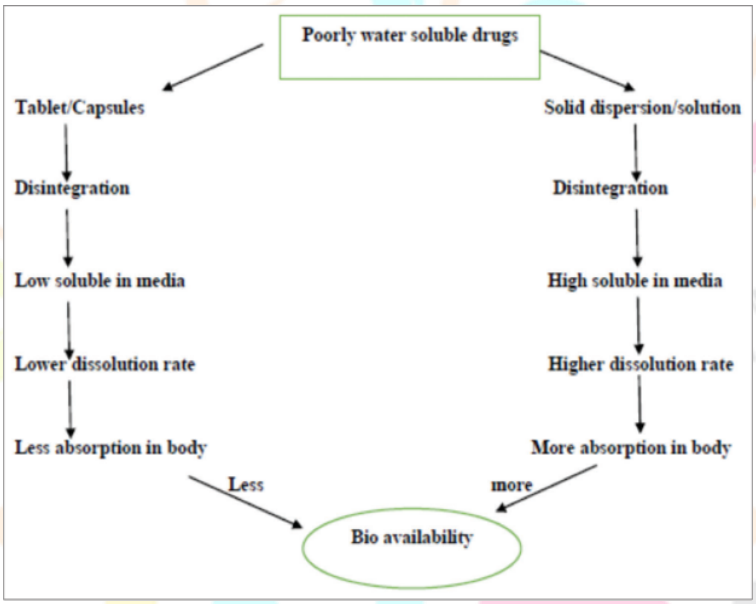

Fig 2: schematic representation enhancement of bioavailability of the poorly water-soluble drugs by solid dispersion.

• **Noyes Whitney Equation:** shows how the dissolution rate of even the most weakly soluble chemicals may be increased to reduce the restrictions of oral bioavailability:

$$dC/dt * h = AD. (Cs - C)$$

Where, dC/dt is the rate of dissolution, A is the surface area available for dissolution,
D is the diffusion coefficient of the compound, Cs is the solubility of the compound in the dissolution medium,
C is the concentration of drug in the medium at time t, h is the thickness of the diffusion boundary layer next to the surface of the dissolving compound.

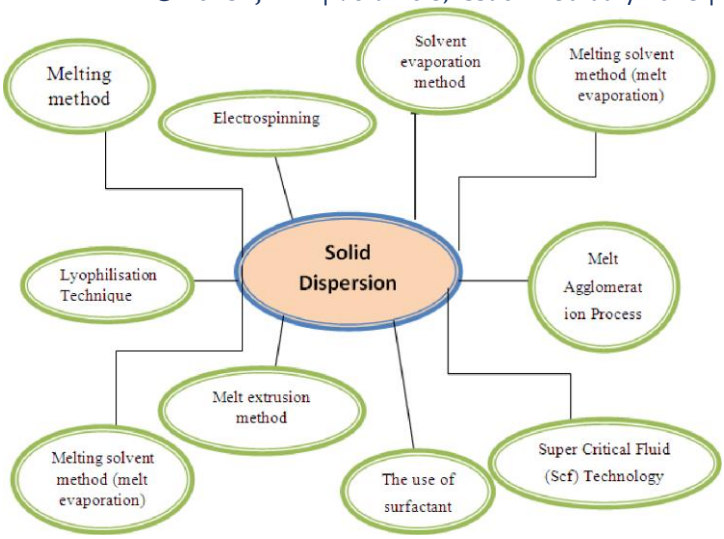

Fig 3: Flow chart of various solid dispersion methods.

TYPES OF SOLID DISPERSION:

1. Amorphous solid solutions
2. Eutectic mixtures
3. Solid solutions
   a. Continuous solid solutions
   b. Discontinuous solid solutions
   c. Substitutional solid solutions
   d. Interstitial solid solutions
4. Glass solution and suspension

1. Amorphous solid solution

Similar to eutectic mixtures only difference in structure is drug precipitated out in solid amorphous form.

2. Eutectic mixtures

Eutectic mixtures are made up of two chemicals that are entirely miscible in liquid but only to a very limited amount in solid. ("Eutectic mixes as a method of improving solubility and dissolution...") "It is made by rapidly solidifying a fused melt of two components that are completely liquid miscible but have little solid-solid solution." ("authorSTREAM |SOLUBILIZATION TECHNIQUES")

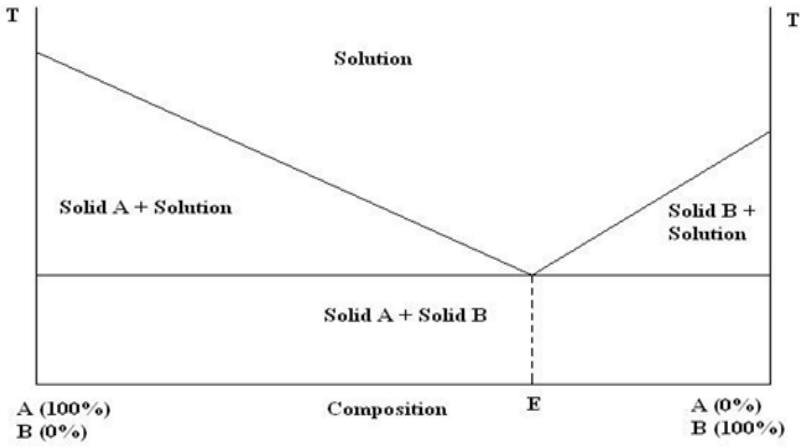

Fig 4: Illustration of eutectic mixtures.

3. Solid solution

"Regardless of the number of components, solid solutions are comparable to liquid solutions in that they consist of only one phase." ("Improving drug solubility for oral administration with solid dispersions"). The particle size in this medicine has been reduced to its absolute minimum, namely the dimensions,

and the dissolving rate is determined by the carrier's dissolution rate. They are classified according to their miscibility or, alternatively, according to how the solvent molecules are dispersed in the solvent.

a. **Continuous solid dispersion**

The components are miscible in all proportions. Theoretically, this means that bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components.

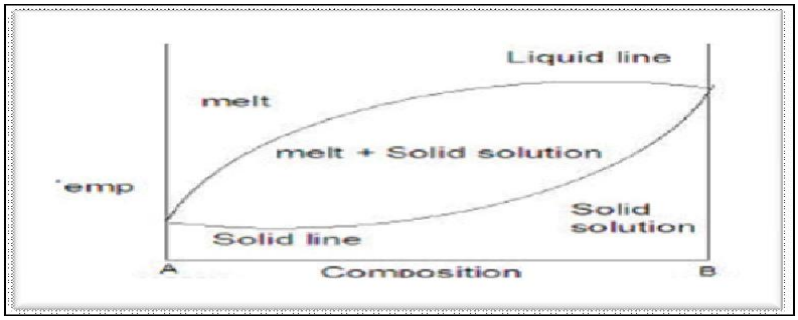

Fig 5: Represents continuous solid dispersion.

b. **Discontinuous solid dispersion**

In this scenario, the solubility of one component in the other component is restricted. Because of particle considerations, Goldberg et al. propose that the term solid solution be used only when the mutual solubility of the two components surpasses 5%.

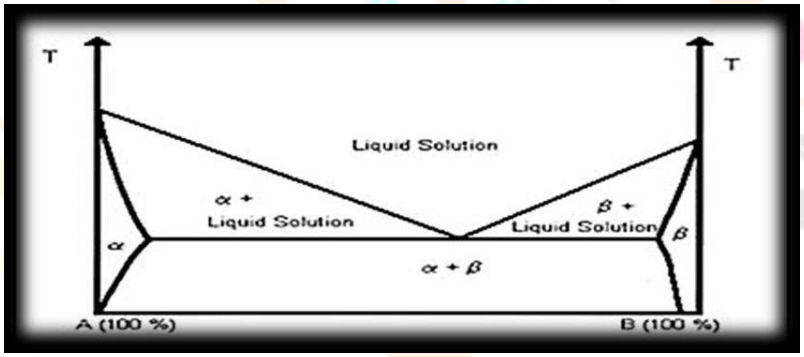

Fig 6: Showing discontinuous solid dispersion.

c. **Substitutional solid dispersions**

This is only conceivable if the size of the solute molecules differs from the size of the solvent molecules by less than 15%. Classical solid solutions have crystalline structure, with solute molecules either substituting for solvent molecules in the crystal lattice or fitting into the interstices between the solvent molecules.

d. **Interstitial solid solutions**

The dissolved molecules in interstitial solid solutions fill the interstitial gaps between the solvent molecules in the crystal lattice. The diameter of the solute molecule should be less than 0.59 times that of the solvent molecule.

4. **Glass solution and suspensions**

Glass solutions are glassy systems in which the solute dissolves in the glass carrier. Glass suspensions are composed of anticipated particles suspended in a glass solvent. Glass solution and suspension have substantially lower lattice energy.

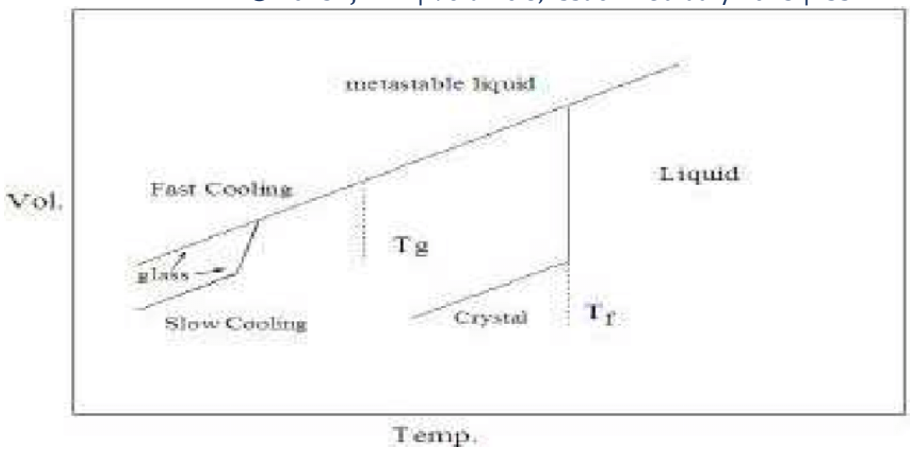

Fig 7: Observation on glass solution and suspension.

ADVANTAGES OF SOLID DISPERSION:

1) Reduced particle size
2) Particles with improved wettability
3) Particles with higher porosity
4) Drugs in amorphous state

DISADVANTAGES OF SOLID DISPERSION:

1) The undefined condition of medication may experience crystalline state, in this way poor soundness is the issue of strong scattering.
2) Handling issue show up because of thickness of some strong scatterings.

3) In the presence of moisture and extreme temperatures, powerful scattering may be dissolved, resulting in the formation of valuable stones.

4) Shelf life forecast of indistinct material is troublesome.

5) The hygroscopicity of polymers used in intense scattering preserves moisture, which can result in the transformation of a hazy structure into a crystalline structure.

LIMITATIONS OF SOLID DISPERSION SYSTEMS:

Problems limiting the commercial application of solid dispersion involve

a) Its method of preparation
b) Reproducibility of its physicochemical properties
c) Its formulation into dosage forms
d) The scale up of manufacturing processes
e) The physical and chemical stability of drug and vehicle

METHODS OF PREPARATION OF SOLID DISPERSION:

1. **Melting method:**
Drug and carrier are mixed using mortar and pestle. To accomplish a homogenous dispersion the mixture is heated at or above the melting point of all the components. It is then cooled to get a congealed mass. It is crushed and sieved. "Ex. albendazole and urea solid dispersion was prepared by this method." ("Solid dispersions: A technology for improving bioavailability")

2. **Solvent evaporation method:**
"The solvent evaporation method was widely used to prepare the polymeric nanoparticles." ("Solvent Evaporation - an overview | ScienceDirect Topics") Solvent evaporation involves emulsification of polymer in aqueous phase and dispersion in a volatile solvent like dichloromethane, chloroform,

and ethyl acetate. Then the solvent is evaporated using high temperature, vacuum, or by continuous stirring.

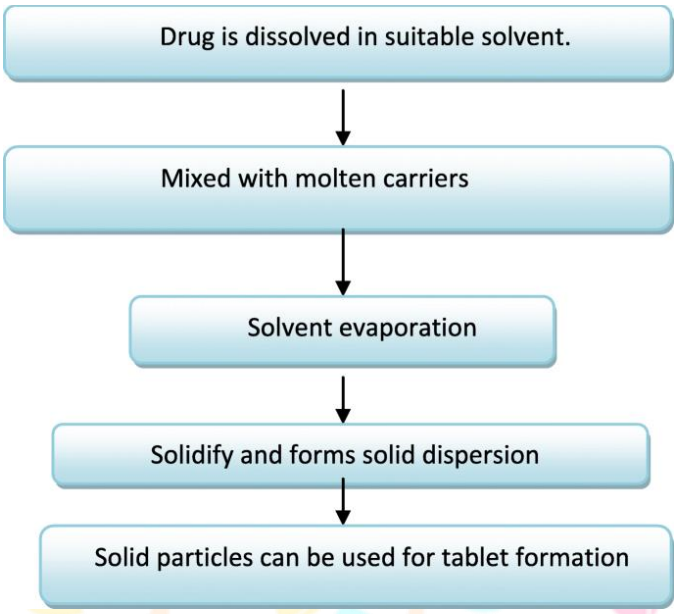

Fig 8: solvent evaporation method process.

3. **Melt evaporation method:**

Both the medication and the carrier are dissolved in an organic solvent in this approach. The solvent is evacuated after complete dissolution. The dry solid mass is pulverized, sieved, then sieved again. ("Solid Dispersion: Methods and Polymers for Improving Solubility...") For example, a solvent evaporation approach was used to create a solid dispersion of furosemide with eudragits.

4. **Melt extrusion method:**

Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w). Melt extrusion technique is used in the preparation of diverse dosage forms in the pharmaceutical industry e.g.- sustained-release pellets.

5. **Lyophilization technique:**

Heat and mass are transferred to and from the product under preparation during freeze-drying. ("Freeze drying - Principles and Practice for Scaling Up to...") This approach was presented as a substitute for solvent evaporation. Lyophilization is a molecular mixing procedure in which the drug and carrier are co-dissolved in a shared solvent, frozen, then sublimed to produce a lyophilized molecular dispersion.

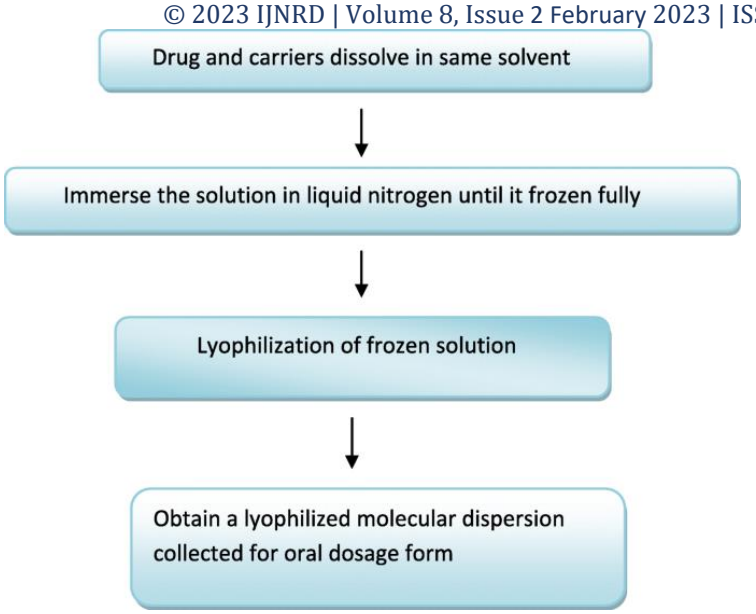

Fig 9: flow chart of lyophilization method process.

6. **Melt agglomeration process:**

This method was used to make Solid Dispersion, in which the binder functions as a carrier. SD(s) is made by either heating the binder, drug, and excipient to temperatures above the binder's melting point or spraying a dispersion of drug in molten binder over the heated excipient with a high shear mixer. "A rotary processor has been proved to be an alternative equipment for melt agglomeration due to easier temperature control and the ability to integrate larger binder content in the agglomerates." ("Solid dispersions: A bioavailability-enhancing technique")

7. **Electrospinning:**

In the polymer sector, electrospinning technology blends solid solution/dispersion technology with nanotechnology. ("Solid Dispersion: A Novel Approach to Improving the...") A liquid stream of a drug/polymer solution is exposed to a potential range of 5 to 30 kV in this technique. Fibers of submicron widths are formed when electrical forces triumph over the surface tension of the drug/polymer solution at the air interface. As the solvent evaporates, the produced fibers can be gathered on a screen to make a nonwoven fabric or on a spinning mandrel to make a yarn. ("Solid Dispersion: Methods and Polymers for Improving Solubility...") Because it is the easiest and cheapest method for producing nanofibers and regulating the release of medicines, this technology has enormous potential for the future manufacture of solid dispersions.

8. **Super critical fluid technology:**

Particle design, nanoparticles, and amorphous dispersions are examples of SCF possibilities. "The primary benefit of employing supercritical fluids is their liquid- and gas-like characteristics, which provide good media for solubilization with a very minimal solvent load." ("Amorphous Solid Dispersion Technologies Overview") Because of the system's design flexibility, SCF may be utilized as a solvent or antisolvent depending on the solubility of the API and the stabilizing polymer. Its applications to ASD research are as numerous as the technique itself, including hot melt extrusion, spray drying, and microprecipitation.

9. **Spray drying method:**

The drug is dissolved in an appropriate solvent, and the necessary amount of carrier is dissolved in water. The solutions are then combined using sonication or another appropriate process to generate a clear solution, which is subsequently spray dried using a spray dryer. Spray-drying is a formulation process in which an excipient combination, often a polymer dispersion containing a medicine, is atomized, sprayed, and dried in a chamber by a hot gas stream.

Table 2: Definition of solubility.

	Part of solvent required for 1 part of solute	Solubility range (mg/ml)	Solubility assigned (mg/ml)
Very soluble	Less than 1	>1000	1000
Freely soluble	From 1 to 10	100-1000	100
Soluble	From 10 to 30	33-100	33
Sparingly soluble	From 30 to 100	10-33	10
Slightly soluble	From 100 to 1000	1-10	1
Very slightly soluble	From 1000 to 10000	0.1-1	0.1
Practically insoluble	Greater than or equal to 10000	<0.1	0.01

SELECTION OF CARRIERS:

The properties of the carrier have a profound influence on the dissolution characteristics of the dispersed drug. To increase a drug's dissolution rate, a carrier must satisfy the following requirements.

Freely water soluble with rapid dissolution properties.

- Nontoxic and pharmacologically inert.
- Heat stable with a low melting point for the melt method.
- Soluble in a variety of solvents.
- Preferably enhancing the aqueous solubility of the drug.
- Chemically compatible with the drug.
- Forming only weakly bounded complex with the drug.

Carriers-

1. **Acids:** Citric acid, tartaric acid, succinic acid, phosphoric acid.

2. **Sugars:** Dextrose, mannitol, sorbitol, sucrose, maltose, galactose, soluble starch, D-glucose, galactose.

3. **Polymeric materials:** polyvinyl pyrrolidone, PEG-4000, PEG-6000, PVP, CMC, hydroxypropyl cellulose, guar gum, xanthan gum, sodium alginate, methyl cellulose, HPMC, Eudragit L-100 sodium salts, Eudragit S100, Eudragit E 100, Eudragit E PO, Eudragit RL PO, Eudragit RL 100, Eudragit RS 100.

4. **Surfactants:** polyoxyethylene stearate, poloxamer, Deoxycholic acid, Tweens and Spans, Docusate sodium, Myrj-52, Pluronic F68, Vitamin E TPGS NF.

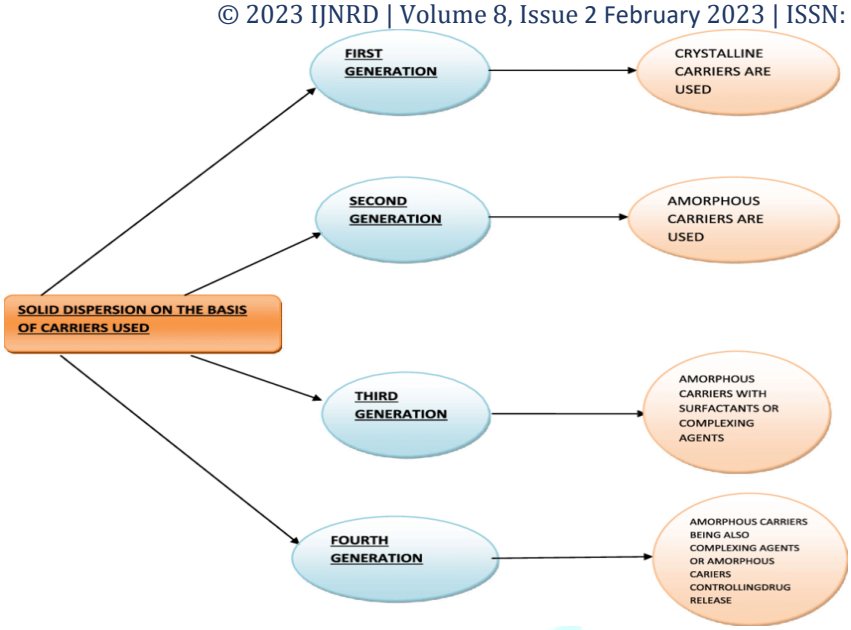

Fig 10: Types of solid dispersion on the basis of carriers used.

CHARACTERIZATION OF SOLID DISPERSION:

Many methods are available that can contribute information about the physical nature of solid dispersion system. A combination of two or more methods is needed to study its complete picture43.

- Physicochemical properties
- Thermal analysis.
- Spectroscopic method.
- X-ray diffraction method.
- Dissolution rate method.
- Microscopic method.
- Thermodynamic method.
- Modulated temperature differential scanning calorimetry
- Environmental scanning electron microscopy
- Dissolution testing

Solvent to be included for the formulation of solid dispersion should have the following criteria:

1. Both drug and carrier must be dissolved.
2. Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.
3. Ethanol can be used as alternative as it is less toxic.
4. Water based systems are preferred.
5. Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration.

The pharmaceutical applications of Solid dispersions technique are:

1. To enhance the absorption of drug.
2. To obtain a homogeneous distribution of a small amount of drug in solid state.
3. To stabilize unstable drugs and protect against decomposition by processes such as hydrolysis, oxidation, racemization, photo oxidation etc.
4. To dispense liquid or gaseous compounds.
5. To formulate a fast release priming dose in a sustained release dosage form.

THERMODYNAMICS OF THE PHYSICAL STABILITY OF AMORPHOUS SOLID DISPERSIONS:

The ideas of liquid systems, where miscibility and solubility are used to explain mixing solutions and dissolving solids into solvents, are where the thermodynamic perspective on the physical stability of ASDs is mostly developed. ASDs may be thermodynamically stable if their drug loading is less than their solid solubility in the polymer, given that ASDs are made by dissolving solvates in solvents. Miscibility, as opposed to solubility, is the notion for characterizing the mixing proportions of two liquids to produce single-phase solutions at a certain temperature and pressure, for example, combining water and phenol. Similarly, amorphous pharmaceuticals and amorphous polymers may be seen of as two liquids, and at certain temperatures and pressures, thermodynamically stable ASDs can develop if the drug to polymer ratio in the system is within the single-phase area, as shown. To date, miscibility and solid solubility have been predicted or calculated using theoretical models and experiments, and the details of these techniques are presented.

MISCIBILITY BETWEEN DRUG AND POLYMER:

When developing ASD formulations, the prediction of drug-polymer miscibility is a valuable method for screening polymeric carriers and determining drug loadings. Solubility parameter approach, molecular modelling, and Tg evaluation of solid dispersions are some of the often-published methods for estimating the miscibility of a medication and a polymer.

SOLUBILITY PARAMETER:

The cohesive energy density required to separate a unit volume of molecules from condensed phase to infinite distance is defined as the square root of the solubility parameter. Based on the notion of likes dissolving likes, medicines and polymers with comparable solubility properties are deemed miscible. The group contribution technique is commonly used to determine the solubility characteristics of compounds with complicated structures and high molecular weight. The compound with a complicated chemical structure may be split into numerous tiny functional groups using this approach, and the solubility parameters of these small groups can be obtained using the evaporation method, allowing the solubility parameter of the entire molecule to be estimated. Chemicals, for example, are simply listed in Fedor's solubility parameter divided into small groups, and the solubility parameter is calculated by

$$\delta = (\Sigma E_{coh} / \Sigma V)^{1/2}$$

where δ represents solubility parameter, Σ Ecoh represents the sum of cohesive energy of each group and Σ V represents the sum of the molar volume of each group.

CONCLUSION:

As the number of poorly soluble drug candidates grows, so does the demand for advancements in drug production technologies. As a result, solid dispersion technology appears to be a potential alternative for enhancing such medications' dissolving properties. Aspects that must be addressed in the coming years include larger-scale manufacturing improvements and better predictions of whether a specific drug/carrier combination will result in a true solid solution or a partially crystalline dispersion, as well as whether the dispersion will remain physically stable during further processing and storage. Last but not least, while this article has focused on the use of solid dispersions to increase release rate and oral bioavailability, by making careful choice of solid dispersions, it is also feasible to postpone or slow down the release pattern of a medicine by manufacturing it as a solid dispersion with careful carrier selection. The availability of a large range of polymers that are either insoluble or swell in aqueous conditions suggests that solid dispersions have enormous promise in the field of controlled release dosage forms.

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