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Solid Dispersion: Recapitulation

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ABSTRACT

The approach to improve dissolution rate of hydrophobic drug and enhance the bioavailability, solid dispersion is one of the promising approaches in which dispersion of one or more drug substances (API) in a hydrophilic carrier at solid state is used. Among all newly discovered chemical entities about 40% drugs are lipophilic and hence fail to reach the market due to poor water solubility. The review highlights the timeline of solid dispersion approach and summarizes the development over the years and its potentiality in the future.

INTRODUCTION

Oral drug delivery is very popular due to its ease of administration, high patient compliance, cost effectiveness, reduced sterility constraints, and flexibility of dosage form design. When a drug is administered orally, it has to cross certain barriers (varies from drug to drug) within the biological system including dissolution in gastrointestinal fluids, permeation across the gut membrane, and first pass metabolism to finally reach its site of action via systemic circulation. Every barrier presents a potential bottleneck, of which dissolution in gastric fluid is of importance. For most drugs the prime requirement is to enable systemic circulation for determining the bioavailability of drugs. The biggest challenge in pharmaceutical development is the poor aqueous solubility and dissolution rate of drug and is becoming more common among new drug candidates over the past two decades due to the use of high throughput and combinatorial screening tools during the drug discovery and selection phase.

Taking into consideration the conceivable rate-constraining steps, Amidon *et al.* (1995) classified active pharmaceutical ingredients (APIs) into 4 groups on the basis of their solubility and permeability known as the Biopharmaceutical Classification System (BCS) as shown in Figure no i. BCS involves mathematical analysis to experimentally determined solubility and permeability of drugs underspecified conditions. According to the US Food and Drug Administration, a drug is considered to be highly soluble when its highest clinical dose strength is soluble in less than 250 mL of aqueous media over a pH range of 1-7.5 at 37.5°C, and it is considered to be highly permeable if the absorption of an orally administered dose in humans is more than 90% when determined in comparison to an intravenous (IV) reference dose. A biowaiver (permission to skip *in vivo* bioequivalence studies) may be applied for certain drugs that pass specific *in-vitro* solubility and permeability requirements.

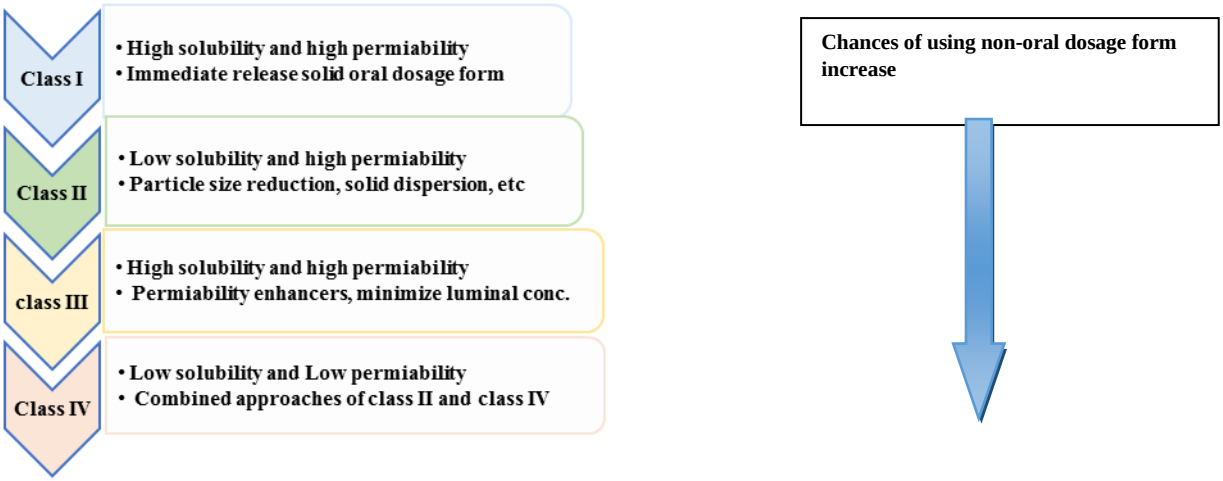

Figure No. i: Biopharmaceutical classification system for different classes of drugs

Model list of Essential Medicines of the World Health Organization (WHO) has assigned BCS classification on the basis of data available in the public domain. Out of 130 orally administered drugs on the WHO list, 61 could be classified with certainty[12].

Table No. 1: BCS classification based on WHO

Class	Category	Percentage
Class I	Highly soluble highly permeable	84%
Class II	Poorly soluble highly permeable	17%
Class III	Highly soluble poorly permeable	39%
Class IV	Poorly soluble poorly permeable	10%

SOLUBILITY

The solubility of substance is the amount that has passed into solution when equilibrium is attained between the solution and excess, *i.e.*, undissolved substance, at a given temperature and pressure. When the aqueous solubility of a drug is less than 100µg/ml, Poor dissolution: Intrinsic dissolution rate <0.1mg/cm^2/min, High molecular weight: (>500), self-association and aggregation and high crystal energy (melting point more than 200°C is said to be poorly soluble).

Table No. 2: Solubility terms

Description Forms range solubility assigned (mg/ml)	Parts of solvent required	One part of solute	Solubility (mg/ml)
Very soluble (VS)<1	<1	>1000	1000
Freely soluble(FS)	1 to 10	100 to 1000	100
Soluble	10 to 30	33 to 100	33
Sparingly Soluble (SPS)	30 to 100	10 to 33	10
Slightly soluble(SS)	100 to 1000	1 to 10	1
Very slightly soluble(VSS)	1000 to 10000	0.1 to 1	0.1
Practically insoluble (PI)	>10000	<0.1	0.01

TECHNIQUES/APPROACHES FOR SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUG:[11]

The techniques/approaches that have commonly been used to overcome drawbacks associated with poorly water-soluble drugs are as follows:

CHEMICAL MODIFICATIONS

- Salt Formation
- Co-crystallization
- Co-solvency
- Hydrotropic
- Solubilizing agent
- Nanotechnology

PHYSICAL MODIFICATIONS

- Particle size reduction
- Modification of the crystal habit

- Complexation
- Solubilization by surfactants
- Drug dispersion in carriers i.e., Solid dispersions

OTHERS:

- Supercritical fluid method
- Spray freezing into liquid and Lyophilization
- Evaporative precipitation into aqueous solution
- Hot melt extrusion
- Electrostatic spinning method
- Direct capsule filling
- Polymeric Alteration
- High- Pressure Homogenization
- Inclusion Complexes

SOLID DISPERSION

The term 'solid-in-solid solutions' was first used by Levy (1963) and Kanig (1964) who indicated that many drugs could form 'solid-solid solutions' with mannitol[10]. Sekiguchi and obi1 were the first to report an improved dissolution of the drug from sulfamethoxazole-urea solid dispersion[14].

Solid dispersion is one of the approaches employed to improve dissolution of poorly soluble drugs whose absorption is dissolution rate limited.

DEFINITION[5]

SD refers to the group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug; the matrix can be either crystalline or

amorphous. The solid dispersion was first introduced to overcome the low bioavailability of lipophilic drugs by forming a eutectic mixture of drugs with water soluble carriers.

Chiou and Riegelman defined the term solid dispersion as "A dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures."[38]

The promising results of solid dispersion in solubility and dissolution rate enhancement of poorly soluble drugs can be attributed due to:

• Amorphous structure was replaced by crystalline structure to improve local solubility and wettability of the poorly soluble drug in the solid dispersion matrix.

• The ability of carrier functional groups to form interactions with the drug to increase the glass transition temperature (Tg) of the solid dispersion mixture

• Inhibited drug precipitation from supersaturated solution to resulting metastable drug polymorphous[6]

COMPONENTS OF SOLID DISPERSIONS

The main components of the solid dispersions are:

1. Hydrophobic drug is the active ingredient which has limited solubility in the aqueous phase.

2. Hydrophilic matrix consists of carrier which plays prominent role in enhancing the solubility of the hydrophobic drug.

IDEAL REQUIREMENTS OF CARRIERS

The ideal characteristics of carrier which are used in solid dispersions are:

· It should be non-toxic and inert in nature.

· It should show good water solubility (To improve wettability and dissolution).

· The glass transition temperature (Tg) of the carrier should be high. (To produce amorphous structure).

· The melting point of the carrier should be low. (To obtain stable formulations)

· The solubility profile of the carrier should be similar with the profile of drug.

CARRIERS USED IN SOLID DISPERSION

Table no 3. List of solid dispersion carriers

CATEGORY	EXAMPLE OF CARRIERS
Polymers	Polyvinylpyrrolidone (PVP), Polyvinylalcohol (PVA), Polyethyleneglycols (PEG), Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC)
Surfactants	Tweens, Spans, Polyoxyethylene stearates, Caprolactone, Ethylene oxide, Renex, Texofor
Dendrimers	Starburst, polyamidoamine (PAMAM)
Polyglycolized Glycerides Acid	Gelucire 44/14, Gelucire 50/13, Gelucire 62/05
Cyclodextrins	β-Cyclodextrins, Hydroxypropyl- β- cyclodextrins
Acids	Succinic acids, Citric acids, Phosphoric acid
Sugar	Dextrose, Sorbitol, Mannitol, Lactose, Sucrose, Galactose, Maltose
Miscellaneous	Hydroxyalkylxanthines, Urea, Urethans, Microcrystalline cellulose, Dicalcium phosphate, Silica gel, Sodium chloride, Skimmed milk

CLASSIFICATION OF SD

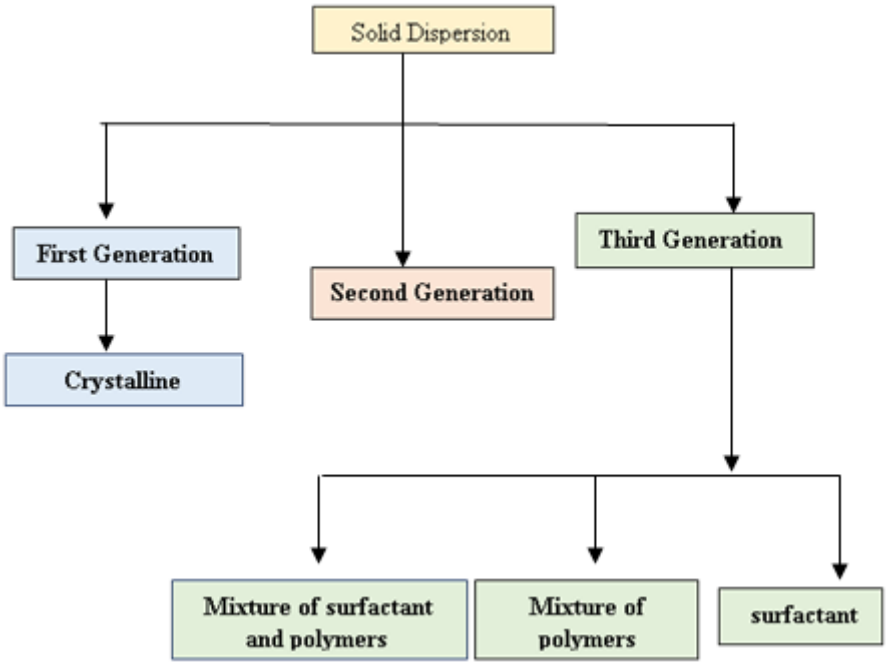

Figure No. ii: Classification of solid solution

First generation solid dispersions[7]

In first generation solid dispersion, formulation of eutectic mixtures or molecular dispersion improved the rate of drug release which in turn increases the bioavailability of poorly water-soluble drugs. Example Crystalline carriers: Urea, Sugars and Organic acids.

Second generation solid dispersion[2]

In second generation we use amorphous state of carrier which improves drug release; likes fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates. Natural product-based polymers are mainly composed by cellulose derivatives, such as hydroxypropyl methylcellulose (HPMC), ethylcellulose or hydroxypropyl cellulose or starch derivates, like cyclodextrins.

Third generation solid dispersion[7]

In third generation we use polymers (carrier) which have surface activity and self-emulsifying property. The surfactants decrease the re-crystallisation of drug and which help

to improve the solubility of drug. Example: Surface active self-emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/14.

MECHANISM OF DRUG RELEASE FROM SOLID DISPERSIONS[9-12]

The suggested mechanisms behind increase in dissolution rate may include:

1) Reduced particle size or reduced agglomeration

2) Increased solubility or dissolution rate of the drug

3) Transferring the drug from crystalline to amorphous state/formation of high energy state

4) Wetting

5) Drug release from the solid dispersion was observed by two mechanism:

A) Carrier-controlled Release B) Drug-controlled Release

6) Partial transformation of crystalline drug to the amorphous state or altering the crystalline morphology as follows:

- Formation of solid solution

- Formation of complexes

- Mixing of the drug with hydrophilic excipients

- Reduction of aggregation and agglomeration

- Improved wetting of the drug and solubilization of drug by the carrier at the diffusion layer

ADVANTAGES OF SD[14-15]

The increase in dissolution rate for solid dispersion can be attributed to a number of factors. These include the following:

1. **Particles with reduced particle size:** In solid dispersion particle size is reduced resulting in a high surface area, an increase in dissolution rate and consequently bioavailability may be improved.

2. **Particles with improved wettability:** The solid dispersion improves the wettability and solubility. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.

3. **Particles with higher porosity:** Particles in solid dispersions possess higher degree of porosity, thus hastening the drug release. The increase in porosity also depends on the carrier properties.

4. **Drugs in amorphous state:** The enhancement of drug release can be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process.

5. Cost effective

6. Increase the solubility without using physiological inert carrier.

7. A fixed dose combination comprising of soluble and the insoluble drug is feasible.

8. In solid dispersions drugs are available in supersaturated solutions which are considered to be metastable polymorphic form. Thus, the drugs in amorphous form increase the solubility of the particles.

9. Rapid dissolution rates result in an increase in the rate and extent of the absorption of the drug and reduction in presystemic; both can lead to lower doses of the drug.

10. No special technique required, ease of processing SD and less time consuming.

DISADVANTAGES[14]

1. The major disadvantages of solid dispersion are accounted to the instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate with aging.

2. Moisture and temperature have significant effect on deterioration as compared to physical mixtures. Some solid dispersion is prone to tackiness making handling difficult.

3. Two fixed dose combination is a must for formulation.

4. In drug-drug solid dispersion one of the drugs must be highly soluble.

5. Poor scale-up for the purpose of manufacturing.

6. The polymers used in solid dispersion absorb moisture causing phase-separation, crystal growth and conversion into crystalline form. Thus, resulting in decrease solubility and dissolution rate.

7. A tedious method of preparation.

8. It causes reproducibility of physicochemical characteristics.

LIMITATIONS[14-16]

1. Formulations formulated using high loads of carriers.

2. Reproducibility of physicochemical properties of the drug cannot be regained.

3. Physical and chemical instability observed due to the modification of basic structure of drug.

4. Handling of the solid dispersions may be difficult due to its tackiness.

APPLICATIONS[16]

1. To obtain a homogeneous distribution of a small amount of drug in solid state.

2. Stabilization of unstable drug.

3. To dispense liquid or gaseous compounds in a solid dosage.

4. To formulate a fast release primary dose in a sustained released dosage form.

5. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.

6. To reduce pre systemic inactivation of drugs like morphine and progesterone. Polymorphs in a given system can be converted into isomorphism, solid solution, eutectic or molecular compounds.

7. To increase the solubility of poorly soluble drugs thereby increasing the dissolution rate, absorption and bioavailability.

8. To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerisation, photo oxidation and other decomposition procedures.

9. To reduce side effect of certain drugs.

10. Masking of unpleasant taste and smell of drugs.

11. Improvement of drug release from ointment, creams and gels.

12. To avoid undesirable incompatibilities.

13. To obtain a homogeneous distribution of a small amount of drug in solid state.

14. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.

15. To formulate a fast release primary dose in a sustained released dosage form.

16. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.

17. To reduce pre systemic inactivation of drugs like morphine and progesterone.

TYPES OF SD

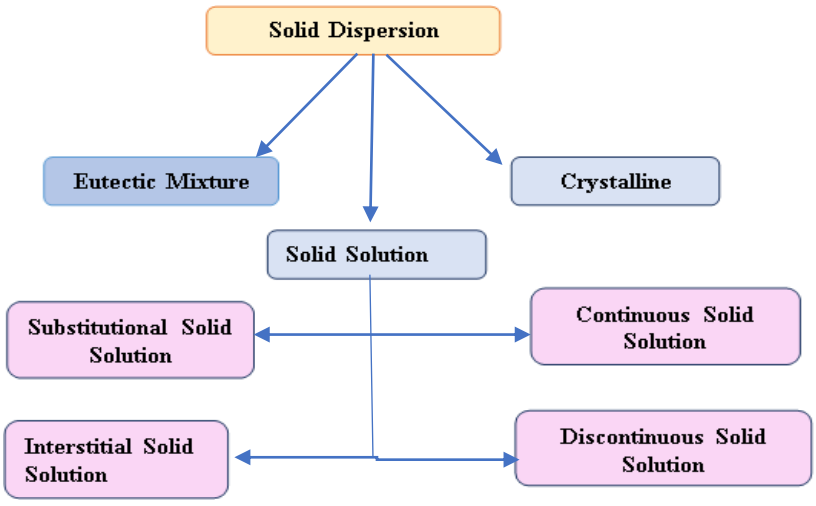

Figure No. iii: Types of solid solution

Eutectic mixture[8]

A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state but only to a very limited extent in the solid state. It is prepared by rapid solidification of fused melt of two components that shows complete liquid miscibility but negligible solid-solid solution. The X-ray diffraction pattern of a eutectic mixture constitutes an additive composite of two components. Example, Chloramphenicol - urea; Paracetamol - urea; Griseofulvin and Tolbutamide with PEG 2000. When a composition E with a mixture of A and B is cooled, at first A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out, while after that when composition E is further cooled one component start crystallize out before the others[13], as shown in Fig. iv.

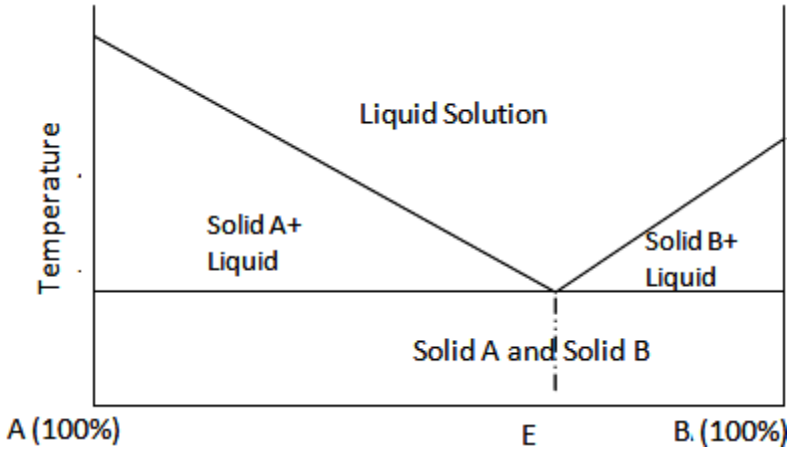

Figure No. iv: Phase Diagram for simple eutectic mixture

Amorphous precipitation in crystalline carrier[8]

In this system usually the high energy state of the drug produces higher dissolution rates than its related crystalline forms of the drug, Fig V. The drug is precipitated out in amorphous forms as compared to eutectic mixture. Sulfathiazole was precipitated in the amorphous form in crystalline urea[6].

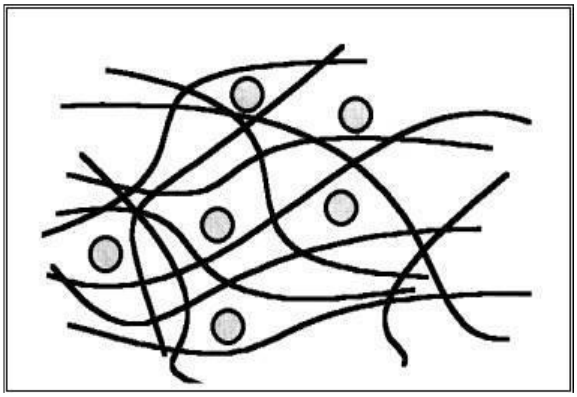

Figure No. v: Amorphous solution

Solid solution[8]

A solid solution, compared to the liquid solution is made up of a solid solute dissolved in a solid solvent. It is often called a mixed crystal because the two components crystallize together in a homogenous one phase system. Solid solution of poorly soluble drug in rapidly soluble carrier achieve a faster dissolution rate than a eutectic mixture because the particle size of drug in solid solution is reduced to a minimum state, in other word dissolution of drug takes place in solid state prior to its exposure to liquid medium, Figure no vi.

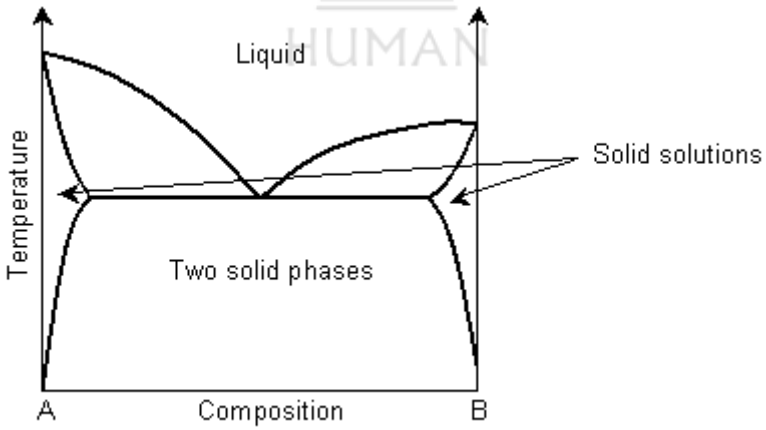

Figure No. vi: Phase diagram for simple solid solution

TYPES OF SOLID SOLUTION

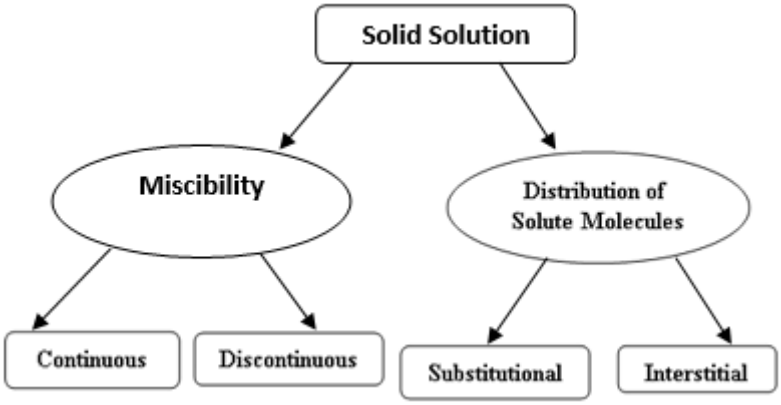

Figure No. vii: Types of solid solution

A] BASED ON MISCIBILITY

1. Continuous solid solution
2. Discontinuous solid solution

B] BASED ON DISTRIBUTION OF SOLUTE MOLECULE

3. Substitutional crystalline solution
4. Interstitial crystalline solid solution

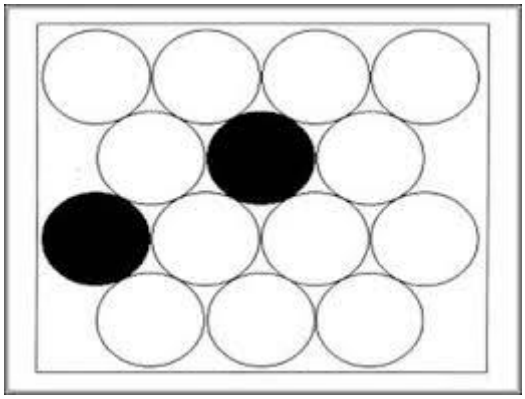

Figure No. viii: Substitutional crystalline solid solution

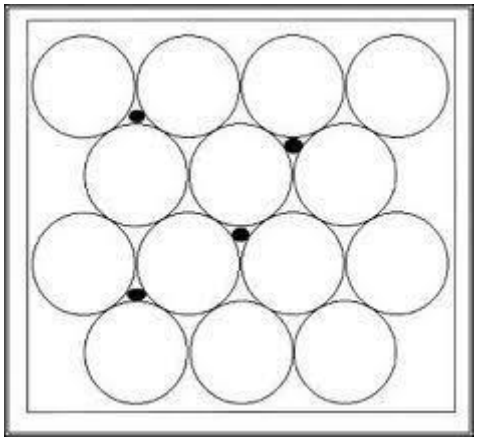

Figure No. ix: Interstitial crystalline solid solution

Glass solutions and glass suspension[5]

A glass solution is a homogenous, glassy system in that a solute diffuse in a glassy solvent. The term glass can be used to describe either a pure chemical or a combination of chemicals in a glassy vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency and brittleness below the glass transition temperature. Lattice energy is much lower in glass solution and suspension.

Examples of carriers which form glass solutions and suspensions are citric acid, PVP, urea, PEG, sugars such as dextrose, sucrose, and galactose.

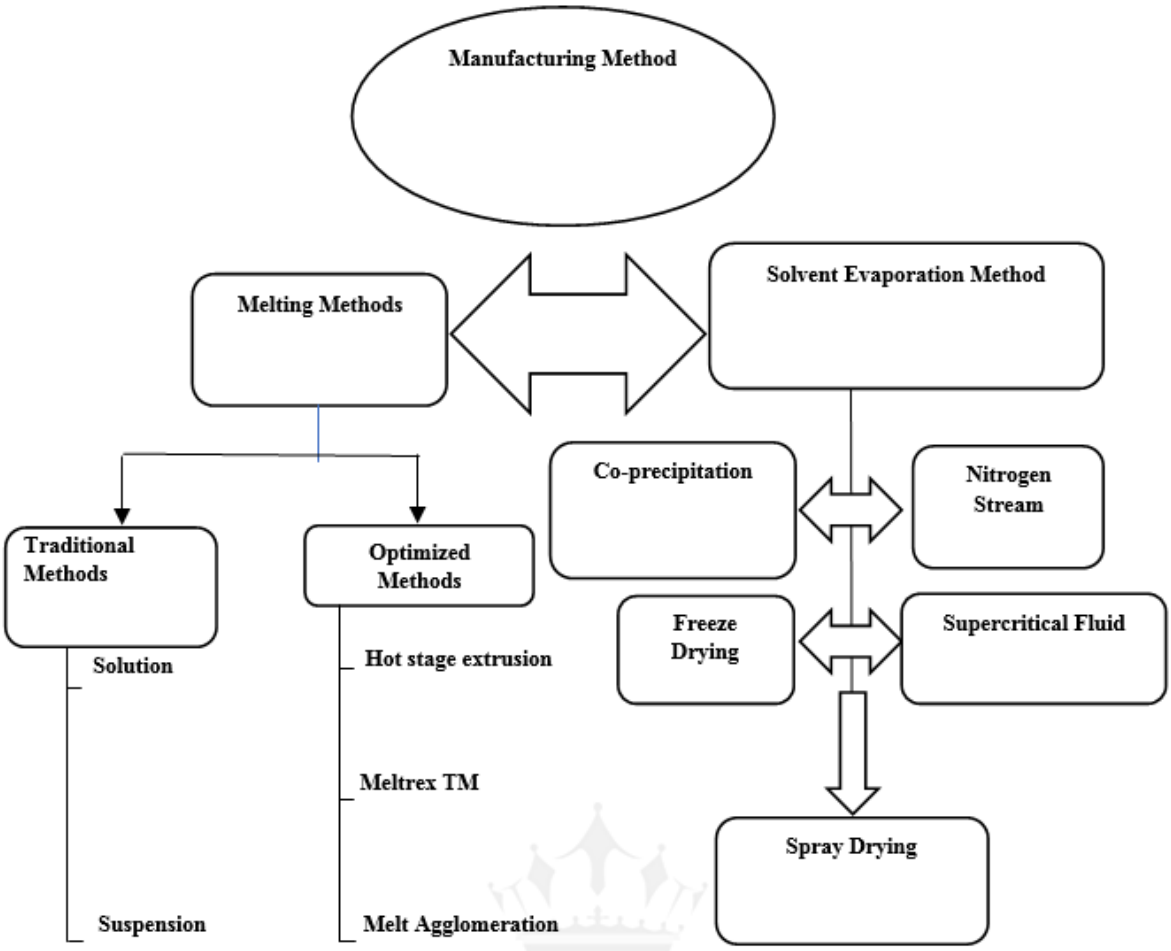

Figure No. x: Methods for preparation of solid dispersion system

METHODS USED FOR PREPARATION OF SOLID DISPERSION

The various methods used for preparation of solid dispersion is depicted in figure no x.

Melting method[2]

Sekiguchi *et al* were the former to use a melting technique containing melting of drug in the carrier followed by cooling and pulverization of the obtained product[37]. Within the melting method, the molecular mobility of carrier is high enough to alter the drug's incorporation[23]. A common adaptation to the melting stage consists of suspending the active drug in a formerly melted carrier, instead of using both drug and carrier in the melted state, therefore, reducing the process temperature. To cool and solidify the melted mixture, several processes were used such as ice bath agitation, stainless steel thin layer spreading followed by a cold draught, solidification on petri dishes at room temperature inside a desiccator, spreading on plates placed over dry ice, immersion in liquid nitrogen or stored in a desiccator[19-32]. After

cooling, the mixture must be pulverized concerning its handling. However, using the high temperatures several drugs are prone to degradation, a limitation of melting method. The immiscibility between drug and carrier that will occur, owing to the high viscosity of a polymeric carrier within the melted state, is another limitation of the technique. To avoid the melting technique limitations, some modifications, like hot-stage extrusion, MeltrexTMor melt agglomeration were introduced[34].

Hot-stage extrusion[2]

Hot-stage extrusion consists of the extrusion of drug and carrier at high RPM and at melting temperature for a short period of time. The final product is collected after cooling at room temperature and milled. A reduction in processing temperature can be achieved by the association of hot-stage extrusion by using carbon dioxide as a plasticizer[25-33], that broadens the application of hot-stage extrusion to thermally labile compounds. Solid dispersions of para-aminosalicylic acid/ethylcellulose, itraconazole/ PVP[25] and itraconazole/ethylcellulose were successfully prepared by this approach. Thus, solid dispersions of itraconazole/Inutec SP1 formulated by hot-stage extrusion presented itraconazole in a fully glassy state, whereas it was partly in glassy in solid dispersions prepared by spray drying[26].

MeltrexTM[2]

The crucial parts in the MeltrexTM technology is that the use of a special twin screw extruder and therefore the presence of two different hoppers in which the temperature can vary over a broad temperature range. This method permits a reduced duration of the drug within the extruder, allowing a continuous mass flow and avoiding thermal stress to the drug and excipients. Additionally, it is possible that the application of this process to protect drugs susceptible to oxidation and hydrolysis by complete elimination of oxygen and moisture from the mixture.

Melt agglomeration

Melt agglomeration process allows the preparation of solid dispersions in conventional high shear mixers. It is prepared by adding the molten carrier containing the drug to the heated excipients, by adding the melted carrier to a heated mixture of drug and excipients, or by heating a mixture of the drug, carrier and excipients to a temperature in or above the melting

range of the carrier. It can also be used to produce stable solid dispersions by melt agglomeration method in a rotary processor[22].

Solvent evaporation method

The solvent evaporation technique consists of the solubilization of the drug and carrier in a volatile solvent which is later evaporated. The thermal decomposition of drugs or carriers will be prevented, since organic solvent evaporation takes at low temperature.

The method comprises of dissolving the drug and the polymers in a common solvent, such as ethanol, chloroform, or a mixture of ethanol and dichloromethane. Normally, the ensuing (resulting) films are powdered and processes. Difference in solvent evaporation processes are associated with the solvent evaporation procedure, which typically include vacuum drying, heating of the mixture on a hot plate, decrease the rate of evaporation of the solvent at low temperature, the application of a rotary evaporator, a stream of nitrogen, spray-drying, freeze-drying and the use of supercritical fluids (SCF).

Spray-drying

Spray-drying is one of the most commonly used solvent evaporation technique for the production of solid dispersions. It consists of dissolving or suspending the drug and carrier and spraying it into a stream of high temperature airflow to remove the solvent prepared an alternate to solid dispersion by spraying a povidone and diazepam solution into liquid nitrogen, formed suspension that was then freeze dried[23].

Freeze-drying

The basic freeze-drying method consists of dissolving the drug and carrier in a typically common solvent, which is inserted in liquid nitrogen till it is absolutely frozen. The frozen solution is then freeze dried[23].

Supercritical fluid

In the supercritical fluid process, the drug and carrier are in the fluid phase above their critical temperature and critical pressure. A very fine dispersion of the hydrophobic drug in the hydrophilic polymeris obtained. Carbon dioxide (CO_2) is the most ordinarily used supercritical fluid because it is chemically inert, non-toxic and non-flammable. The method

consists of dissolving the drug and the carrier in the same solvent which is introduced into a particle formation vessel through a nozzle and simultaneously carbon dioxide is also mixed. Once the solution is sprayed, the solvent is gradually extracted by the supercritical fluids (SCF), which results in the precipitation of solid dispersion particles on the walls and bottom of the vessel. The application of process using supercritical fluids SCF decreases particle size, residual solvent content, without any degradation, and sometimes results in high yield.

Co-precipitation method

Another common method is the co-precipitation method, in which a non-solvent is added drop by drop to the drug and carrier solution, with constant stirring. Within the course of the non-solvent addition, the drug and carrier are co-precipitated to make microparticles. At the end, the resulted microparticle suspension is filtered and dried.

Spin-coated films

Spin-coated films a newer approach to prepare solid dispersions by the solvent evaporation technique that consists of dissolving the drug and carrier in a common solvent that is dropped onto a clean substrate which is extremely spinned. Solvent is evaporated while spinning. This method is applicable for moisture sensitive drugs since it is performed under dry conditions.

The solvent evaporation technique suffers disadvantages, to name a few, the use of organic solvents, difficulty in completely removing the solvent, and high preparation price. Moreover, slight alterations in the conditions used for solvent evaporation could result insignificant changes in product performance.

CHARACTERIZATION OF SOLID DISPERSION [39]

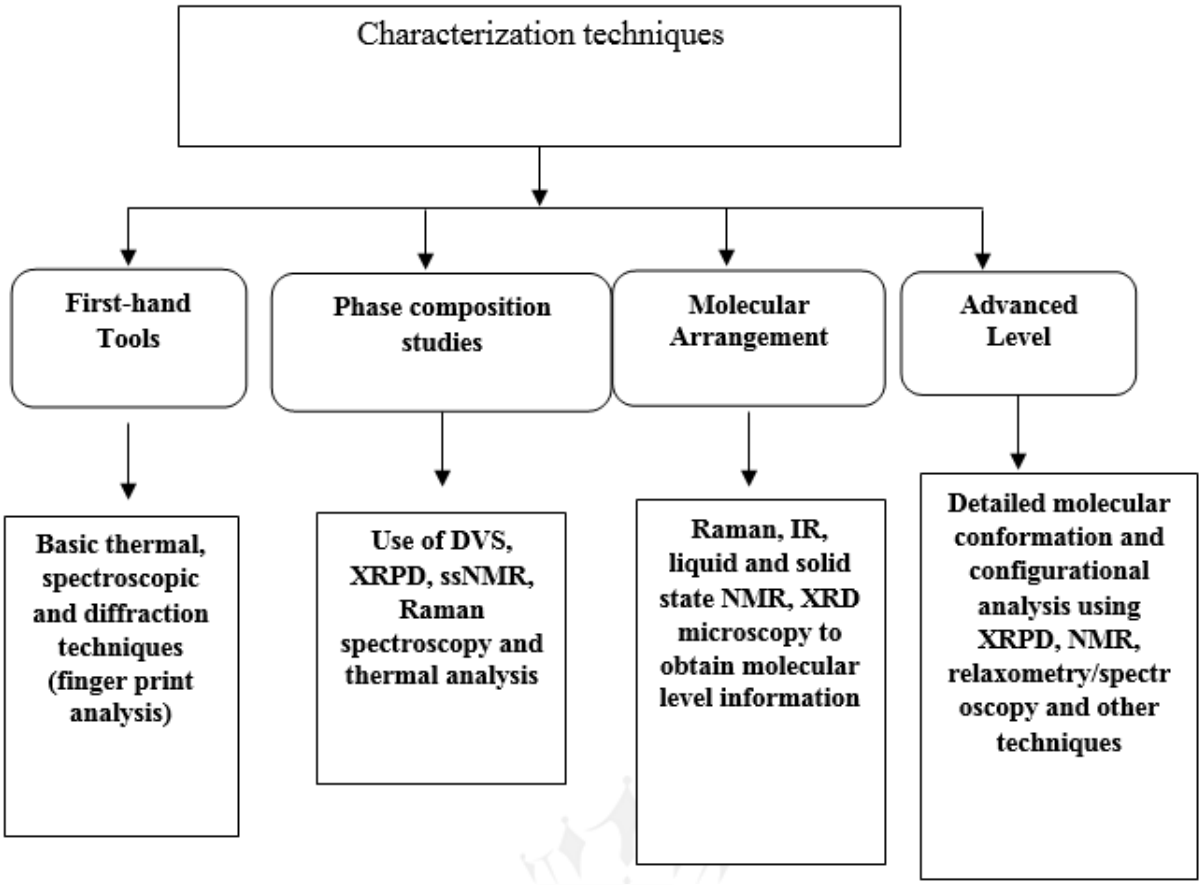

Figure No. xi: Characterization of SD

DETECTION OF CRYSTALLINITY IN SOLID DISPERSION [39]

The amount of amorphous material is unable to measure directly but sometimes derived from the amount of crystalline material in the sample. The various techniques for measuring the crystallinity are as follows:

Powder x-ray diffraction

It can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material. Recent advances in X-ray powder diffraction (XRPD) instrumentation and software can provide useful information under non ambient conditions, such as XRPD equipped with variable temperature (VT) or humidity control which can provide an insight into molecular behaviour of amorphous drugs in solid dispersion under stressed conditions. Semi-quantitative is the recently developed X-ray equipment.

Infrared spectroscopy

It can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Crystallinities of under 5-10% cannot generally be detected.[carriers used] FTIR is useful to detect accurate crystallinities ranging from 1 to 99% in pure material.IR spectroscopy is helpful in determining the solid state of the drug (such as molecular dispersion, amorphous, crystalline or a combination) in the carrier regardless of the state of the carrier[18].

Water vapour sorption

It can be used to differentiate between amorphous and crystalline material when the hygroscopicity is different. This method necessitates accurate data on the hygroscopicity of both completely crystalline and completely amorphous sample.

Isothermal microcalorimetry

It measures the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg).

Dissolution calorimetry

It measures the energy of dissolution, which is dependent on the crystallinity of the sample. Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.

Microscopic techniques

Those measure mechanical properties that are different for amorphous and crystalline material can be indicative for degree of crystallinity. Density measurements and Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity and viscosity and thus affected by the degree of crystallinity.

THERMAL ANALYSIS TECHNIQUES [39]

DSC and thermogravimetric analysis are widely used thermal analysis methods.

Thermo-microscopic methods

This is a visual method of analysis using a polarized microscope with a hot stage to determine the thaw and melting points of solids. The technique has been used to support DTA or DSC measurement. It gives information about the phase diagram of binary systems.

Differential scanning calorimetry (DSC)

In DSC, both the sample and reference materials are subjected to linear heating, but both are maintained at the same temperature. The change in temperature is not recorded, but the heat flow into the system is recorded which is required to maintain isothermal conditions. The method is useful to study the behaviour of crystallization and melting and deriving phase diagrams of solid dispersions. An insight into processes occurring at a molecular level in the solid dispersion such as glass transition, crystallization, polymorphic transition, molecular mobility, structural relaxation, and miscibility between drug and polymer can be obtained using DSC[4].

Differential thermal analysis (DTA)

This is an effective thermal method for studying the phase equilibria of pure substance or solid mixture. Differential heat changes that accompany physical and chemical changes are recorded as a function of temperature as the substance is heated at uniform rate. In addition to thawing and melting, polymorphic transition, evaporation, sublimation, desolvation and other types of changes such as decomposition of the sample can be detected. The method has been used routinely to identify different types of solid dispersion.

DETECTION OF MOLECULAR STRUCTURE IN AMORPHOUS SOLID DISPERSION[39]

The properties of solid dispersion are highly affected by the uniformity of the distribution of the drug in the matrix.

Confocal Raman spectroscopy

It is used to measure the homogeneity of the solid mixture drug and polymer. It was described that a standard deviation in drug content smaller than 10% was indicative of

homogeneous distribution. Because of the pixel size of 2 μm, uncertainty remains about the presence of nano-sized amorphous drug particles.

Temperature modulated differential scanning calorimetry (TMDSC)

It can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. Furthermore, the value of the Tg is a function of the composition of the homogeneously mixed solid dispersion. The sensitivity of TMDSC is higher than conventional DSC. Therefore, this technique can be used to assess the amount of molecularly dispersed drug, and from that the fraction of drug that is dispersed as separate molecules is calculated.

STABILIZATION[3]

The stabilization of amorphous solids is multi-faceted, including:

(i) Labile biomolecules stabilization (e.g., proteins and peptides) through additives,

(ii) Prevent crystallization of excipients,

(iii)Specification of storage temperatures to retain shelf life, and

(iv)Prevent chemical degradation and microbial growth (use of anti-oxidant, pH buffer, preservatives, etc).

Labile biomolecules stabilization

Freezing and drying are essential steps in the preparation of protein and peptide formulations and in the preservation of organisms. Co-processing with certain excipients (carbohydrates and derivatives such as sucrose, trehalose, mannitol, sorbitol, etc.). The mechanism of stabilization is not firmly established but it may be accounted to both vitrification and direct interactions.

Vitrification

Vitrification-based stabilization refers to the immobilization and isolation of labile substances on rigid glasses of inert stabilizer molecules. Vitrification is may reduce the potential for protein aggregation and diffusion of small molecules required to initiate hydrolysis, oxidation, etc. The vitrification process is insufficient for stabilizing labile substances and

specific interactions are required. In vitrification-based stabilization strategies, *T*g provides a concrete guide to the selection of stabilizers and storage temperatures. By eliminating plasticizers (e.g., water) and introducing antiplasticizers one can increase *Tg* and reduce structural mobility. A more sophisticated analysis takes into account of both *T* and fragility, using the ‘‘zero-mobility’’ temperature *Tg* as the parameter for ranking the relative stability of potential formulations.

Direct or specific interactions

Along with vitrification, direct drug-excipient interactions are also important for stabilization. The selective hydrogen bonding between stabilizing excipients and the drug molecules is an example of such interactions. The conformational change of proteins during freeze-drying is generally harmful and should be avoided as long as the conformational change is irreversible. In the crystallization of carbohydrates and other small organic molecules, conformational changes upon solidification are common, but often reversible upon dissolution. In such cases, conformational changes on freezing and drying would not lead to structural damage.

Protection against crystallization of stabilizing excipients

For an excipient to act as a stabilizer it must be mixed homogeneously with the drug to be stabilized. However, certain excipients (e.g., mannitol) have strong tendency to crystallize and phase separation accompanied by loss of stabilizing power. Despite potential crystallization problems, excipients have strong tendency to crystallize and can sometimes make suitable stabilizers. For example, the excipient mannitol possesses crystallization tendency which is supplemented by a superior chemical stability against oxidation and hydrolysis in comparison to disaccharides. The excipient mannitol is stable at low or high pH whereas disaccharides undergoes hydrolysis. Amorphous sucrose can undergo acid-catalyzed inversion even at very low levels of residual water. In some cases, the ‘‘flaw’’ of mannitol as a poor glass former can be remedied by proteins and peptides themselves, which effectively inhibit crystallization.

The T or T 250 K rule

Molecular mobility that allows physical aging and crystallization of glasses below *T* implies that *T* is unsatisfactory as an indicator for the temperature below which molecular motions ‘‘cease’’ for practical purposes. If structural relaxation follows, then the parameter *T*

represents the temperature at which the relaxation time t goes to infinity (‘‘zero’’ mobility). It has been proposed that *T*, be used as a practical guide for selecting storage temperatures. For many fragile glasses, *T* is approximately 50 K below *T*. The *T* 250 K rule is an important reminder of the finite structural mobility below *T*. This rule, of course, is dependent on several conditions: fragile systems, behavior, and a-relaxation process. With strong materials, *T* will lie significantly below *T* –50 K. For materials, the *T* parameter becomes irrelevant. Finally, even though it is plausible that structural changes required for crystallization and chemical degradation correlate with the cooperative a-process, it has been suggested that the b-process also may regulate the crystallization process.

Trehalose

Trehalose has achieved a special status among stabilizing excipients specially sucrose. Trehalose commonly exists as a dihydrate and has anhydrous polymorphs, whereas sucrose exists as anhydrate (with some hygroscopicity) and is not polymorphic in nature. Trehalose has higher *T*g and is more fragile, both in the dry state and in aqueous solutions, than sucrose. Trehalose have a greater ‘‘destructuring effect on the water structure thus, preventing ice formation, than sucrose and maltose. Such differences have been made trehalose more effective stabilizer: higher *T*g provides rigidity to the matrix, fragility and polymorphism make the matrix more ‘‘adaptable’’ to guest molecules, high *T*g and high fragility lead to high T_0 (temperature of ‘‘zero’’ mobility), the ‘‘destructuring’’ effect makes trehalose an effective anti-freezing agent, and the ability of forming a hydrate ‘‘sequesters’’ moisture otherwise available for chemical degradation.

Patents issued

Table no. 4 Some of the Recent Patents on Solid Dispersion

Sr. No	Method	Polymer	Drug	Patent No.
1	Spray drying, solvent evaporation	copovidone, SPAN®20 (sorbitan laurate), ethyl cellulose, HPMC, PEG or SOLUPLUS®	RUFINAMIDE	US 10,206,874B2 (2019)
2	Spray drying	Polyvinyl pyrrolidone	ROTIGOTINE	US 10 , 130 , 589 B2
3	Hot melt extrusion techniques	Gelucires such as GelucireR44/14, GelucireR50/13 and GelucireR 48/16	TELMISARTAN (TEL)	US 2017/01 19671 A1
4	Spray-drying	polyvinyl acetate, polyalkene, poloxomer	ITRACONAZOLE	US 9,492,446 B2(2016
5	Spray drying lyophilizaion, hot melt extrusion	Soluplus(R), copovidone	HCV NS5A INHIBITOR	US 2015/006.4252 A1
6	Hot melt extrusion techniques.	Polyethylene glycol	VINORELBINE (VINCA ALKALOID)	US 9,061,015 B2(2015
7	Spray drying	HPMC, Copovidone	LEDIPASVIR	US2014/0212487

MARKETED PREPARATION OF SOLID DISPERSION

Table no. 5 Preparations available as solid dispersion in market

Drugs	Carriers	Marketed products	Company, Country
Duloxetine	HPMC AS	Cymbalta	Lilly, USA
Etravirine	HPMC	Intelence®	Tibotec, Yardley, PA
Ibuprofen	Various	Ibuprofen®	Soliqs, Germany
Griseofulvin	PEG	Gris-PEG®	Novartis, Switzweland
Fenofibrate	PEG	Fenoglide®	LifeCycle Pharma, Denmark
Rosuvastatin	HPMC	Crestor®	AstraZeneca
Verapamil	Various	Isoptin SRE-240®	Soliqs, Germany

CONCLUSION

Recently developed drug molecules are mostly poorly soluble in nature which leads to a decrease in oral bioavailability as dissolution step is the rate-limiting step. Hence enhancement of solubility and bioavailability is the major challenge in the pharmaceutical development. There are many approaches to overcome the issue, of which solid dispersion is a promising approach because of its flexibility and ease of preparation.

The solid dispersion technique enables the researchers to choose from wide a variety of excipients and cost-effective techniques is an add-on. The review is an attempt to put forth the use of solid dispersion technique for better management of poorly soluble drugs and extensive compilation for the researchers keen in working in the field of solid dispersion.

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