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Solid dispersion a new horizen in novel drug delivery system

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ABSTRACT

The enhancement of dissolution rate and oral bioavailability is one of the greatest challenges in the development of poorly water soluble drugs. So, solid dispersion is an efficient tool for increasing the oral bioavailability and dissolution rate of a range of hydrophobic drugs. Solid dispersion is used to produce a homogeneous distribution of a small amount of drug in solid state. This article reviews the various preparation techniques of solid dispersion and compiles some of the recent technologies. This article summarize some of the practical aspects for the preparation of solid dispersion like selection of carrier ,method of physicochemical characterization, their advantages, limitations and applications along with an insight into the molecular arrangement of drug in solid dispersion. Solid dispersion technique is widely used to study various approaches and applications of drug properties and polymers used in pharmaceutical research. Hence, solid dispersion is a very useful method for pharmaceutical point of view because of its capability to solve the solubility problems by using solid dispersion method.

Keywords: solid dispersion, hydrophilic matrix, bioavailability, solubility, dissolution, fusion, solvent evaporation, spray drying.

INTRODUCTION

DEFINITION OF SOLID DISPERSION:

The term solid dispersion refers to a group of solid products consisting of a hydrophilic matrix and a hydrophobic drug, frequently prepared by fusion solvent method. The matrix can be amorphous or crystalline in nature [8]. This method makes modified form of drug which is more soluble in water then the parent compound. Many solid dispersion techniques have been provided in pharmaceutical literature to enhance the dissolution behavior of poorly soluble drugs [11-15]. Various methods such as solubilization of drug in solvent, complexation with cyclodextrin, salt formation and particle size reduction are used to enhance the dissolution properties of poorly water soluble drugs. Plasdone_S630, Polyvinyl pyrrolidone, Polyethylene glycols are most commonly used hydrophilic carriers for solid dispersion [9]. Numerous surfactants like Tween -80, Pluronic –F68 and sodium lauryl sulphate are used in this technique[7] Chiou and Riegelman suggested, a water soluble polymer, Polyethylene glycol as a universal carrier for increasing the absorption of water insoluble drugs[8].The solubility of some drugs is increasing by using solid dispersion technique which is enlisted below such as:Mifepristone, Dyhydroartemisinin, Piroxicam, Furosemide and others.

Table 1: Various methods to increase the solubility of drugs: [10, 37, 28]

Physical Modification		
a.Particle size reduction 1 Micronization 2 Nanosuspension • Homogenization • Wet milling 3 Sonocrystallization 4 Supercritical fluid process 5 Spray drying	b.Modification of crystal habit 1. Polymorphs 2. Pseudo Polymorph c.Drug dispersion in carriers 1. Eutectic mixtures • Hot plate method • Solvent evaporation • Hot-melt extrusion • Melting-solvent method	d.Complexation 1.Use of complexing agents • Inorganic Coordination • Chelates • Metal-olefin • Inclusion • Molecular complexes e.Solubilization by surfactants 1 Microemulsions 2 Self microemulsifying drug delivery system.
Chemical Modification a. Soluble prodrugs b. Salt formation		
Other Techniques a. Co-crystallisation b. Cosolvency c. Hydrotrophy d. Solubilizing agents e.Nanotechnology Approaches.		

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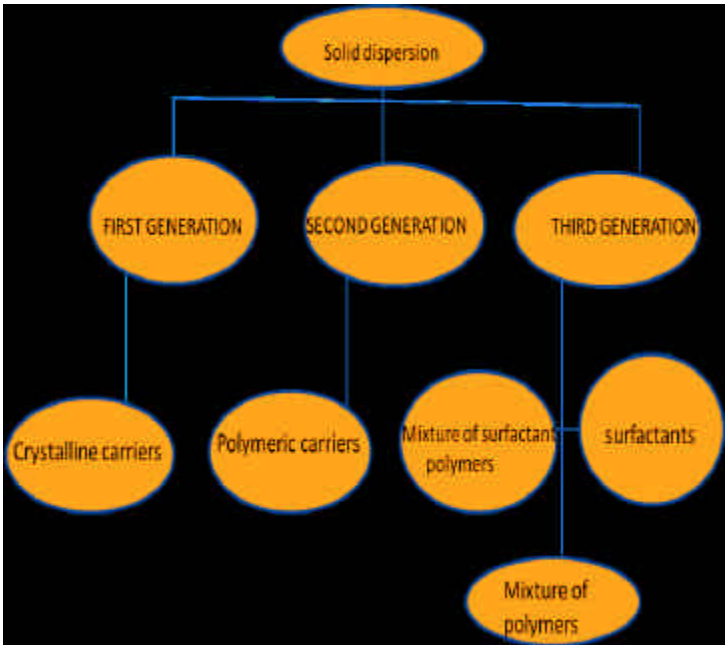

Fig 1: Classification Of Solid Dispersion:

1] First generation solid dispersion:
It was given by obi and sekiguchi in 1961 eutectic mixture improves the rate of drug release which will increase the bioavailability of poorly water soluble drugs [12]. Levy and kaning developed solid dispersion technique, containing mannitol as a carrier. They will form the crystalline solid dispersion.

2] Second generation solid dispersion:
It was examined that solid dispersion with drugs having crystalline state is not effective because they are thermodynamically stable. So, second generation of solid dispersion have amorphous carriers instead of crystalline [21].

3] Third generation solid dispersion:
Third generation solid dispersion contains surfactants as carriers or a mixture of amorphous polymers. It will increase the bioavailability of poorly water soluble drugs and reduce recrystallization. Surfactants are used to stabilize the formulation, thus potentiate their solubility and reduce drug recrystallization. In these, dissolution profile can be increased by using carriers.

SELECTION OF CARRIERS USED IN SOLID DISPERSION:
The selections of carrier have a profound effect on dissolution characteristics of a drug [24]. So, a water soluble carrier leads to faster release of drug from the matrix and a water insoluble carrier leads to slower release of drug from the matrix [4].
It should fulfill the following criteria for improving the dissolution characteristics of a drug:
1] It does not form a strongly bonded complex with the drug [23, 25].
2] It should be chemically compatible with the drug.
3] It should be soluble in a number of solvents.
4] It should be pharmacologically inert.
5] It should be nontoxic.
6] It should be able to increase the aqueous solubility of drug.

First generation carriers:
These include - Sugars, organic acid, and urea [6].

Second generation carriers:
These includes – Starch derivatives like cyclodextrins, Cellulose derivatives like ethylcellulose,hydroxypropylcellulose,hydroxypropylmethylcellulose and fully synthetic polymers like polyethylene glycols,povidone, polymethacrylates[26].

Third generation carriers:
These includes-Tween 80, poloxamer 408, Gelucire 44/14[27].

CLASSIFICATION OF CARRIERS: [1,27,6]
1] Polymers- These include polyvinylalchol, polyvinylpolypyrrolidone, polypyrrolidone, polyethylene glycols, hydroxypropylcellulose, hydroxypropylmethylcellulose, methacrylic copolymers S100 sodium salts etc.
2] Cyclodextrins- These includes
Beta-cyclodextrins, hydroxypropyl-beta-cyclodextrins.
3] Carbohydrates- These includes
Lactose,sorbitol,mannitol,glucose,maltose,soluble starch,cyclylodextrins ,galactose,xylitol,galactomannan etc.
4] Surfactants- These includes
Tweens, spans, polyoxyethylene stearates, poly (caprolactone)-b-poly (ethylene oxide) etc.
5] Superdisintegrants- These includes
Sodium starch glycolate, croscarmellose sodium, cross-linked polyvinyl pyrrolidone, cross-linked algin, gellen gum, xanthan gum, calcium silicate etc [6].
6] Dendrimers-These includes
Citric acid, succinic acid, phosphoric acid, starburst, polyamidoamine etc.
7] Hydrotropes- These includes
Sodium acetate, sodium citrate, sodium-o-hydroxyl benzoate, sodium-p-hydroxyl benzoate etc.
8] Polyglycolized glycerides acids: These includes
Gelucire44/14, gelucire 50/13, gelucire62/05 etc.
9] Miscellaneous: This includes Dicalcium phosphate, silica gel [27], sodium chloride, skimmed milk, microcrystalline cellulose etc.

Table 2: CLASSIFICATION OF CARRIERS IN TABULAR FORM: [8, 14, 6, 27]

S.NO.	CATEGORY	POLYMER
1	Cyclodextrins	ß-Cyclodextrins, Hydroxypropyl- ß- cyclodextrins etc
2	Carbohydrates	Lactose,Soluble starch,Sorbitol,Mannitol,Galactose etc.
3	Surfactants	Poloxamers,Polyglycolized glyceride etc.
4	Super disintegrants	Sodium starch glycolate,CMC,PVP,Gellan gum etc.
5	Polymer	PVP, Polyvinylalcohol, PEG, HPMC etc.
6	Polyglycolized Glycerides	Gelucire 44/14, Gelucire 50/13, Gelucire 62/05
7	Dendrimers	Citric acid, Succinic acid, Phosphoric acid Starburst
8	Hydrotropes	Urea, Nicotinamide, Sodium benzoate etc.

SIGNIFICANT PROPERTIES OF SOLID DISPERSION:
There are various properties of solid dispersion which are described below: [11, 6]
1] Reduced drug particle size- This will increase dissolution rate and hence improves bioavailability of poorly water soluble drugs.
2] Improved wettability-Urea improved drug wettability. It will leads to enhancement of drug solubility. Carriers such as cholic acid and bile salts can improve the wettability properties of drug [12].
3] Drugs in amorphous state- Since during the dissolution process no energy is required to break up the crystal lattice so the enhancement of drug release can usually be achieved.
4] Higher porosity of drug particles- It will depends upon the properties of used carriers such as solid dispersion contains reticular polymers results in higher dissolution rate and hence higher bioavailability [28].
5] Approaches for avoiding drug recrystillization- It is the major disadvantage of solid dispersion since amorphous drug particles are thermodynamically instable and have capacity to change to a more stable state. By increasing Tg of miscible mixture, many polymers are used to improve the physical stability of amorphous drugs.

TYPES OF SOLID DISPERSION: [29, 22, 11, 40]
1] Simple eutectic mixtures
2] Solid solutions
A] According to their miscibility:
1] Continuous solid solution
2] Discontinuous solid solution
B] According to the way in which the solvate molecules are distributed in the solvendum:
1] Glass solution
2] Amorphous solid solution
3] Substitutional crystalline solid solution
4] Interstitial crystalline solid solution
5] Amorphous precipitation in crystalline matrix

1] Simple eutectic mixture:
Solid eutectic mixtures are prepared by rapid cooling of a co –melt of two compounds to obtain a physical mixture. When a mixture consists of slightly soluble drug and a highly soluble carrier in an aqueous medium, the carrier will dissolve rapidly results in releasing very fine crystals of drug [22].

2] Solid solution:
It consists of one phase instead of number of components. In these drug particle size reduced to its molecular dimension. In these dissolution rate is determined the dissolution of carrier.

A] According to their miscibility:

1] Continuous solid solution-
In the continuous solid solution, the components are miscible in all proportions. This type of solid solution has not been reported in the pharmaceutical world till date. Theoretically it means that the bonding strength between two components is stronger than the bonding strength between molecules of the individual component.

2] Discontinuous solid solution-
In the case of discontinuous solid solution, the solubility of each of the components in the other component is limited [11]. It has been suggested by Goldberg et al.that the term solid solution should only be applied of the two components exceed 5%.Below a certain temperature, the solubility of two components goes on decreasing[20]. Whether or not a given solid solution can be utilized as a dosage form will depend not only on the solubility of two components but also depends upon the dose of drug component.

B] According to the way in which solvate molecules are distributed in the solvendum:

1] Glass solution-
Chiou and Riegelman first introduced the concept of formation of glass solution for increasing the drug dissolution and absorption. It is a hom23ogeneous glassy system in which solute dissolves. The glass can be used to describe either a pure chemical or a mixture of chemicals in a vitreous state. The vitreous state is obtained by abrupt quenching of the melt. It is characterized by brittleness and transparency. It is a modification of dosage form for improves drug absorption and dissolution.

2] Amorphous solid solution-
In these molecules are molecularly dispersed within the amorphous solvent.Chiou and Riegelman were the first o report that amorphous solid solution improves the drug dissolution properties.
Other carriers used are sucrose, dextrose and galactose.Moreever organic polymers like polyethylene glycol, polyvinylpyrrolidone and various cellulose derivatives are used for this purpose [11]. The solute molecules are used to plasticize the polymers, leads to reduce its glass transition temperature.

3] Subsitutional crystalline solid solution:
Substitution is possible only if size of solute molecules differ by less than 15%. A Substitutional crystalline solid solution is a type of solid solution which has a crystalline structure and solute molecules substitutes for solvent molecules. Solid solutions of p-dibromobenzene and p-chlorobromobenzene represent substitutional crystalline solid solutions.

4] Interstitial crystalline solid solution:
In these the guest molecules occupies the interstitial space in the Host lattice or the solute molecules occupies the interstitial space in the solvent lattice. In these, the diameter of solute molecules should be less than 0.59 of solvent molecules. Therefore, solute molecules volume should be less than 20% then the solvent. In the case of interstitial solid solution, the crucial criteria for classifying a solid solution are its relative molecular size. Solid solutions of Digitoxin, Prednisolone acetate, Hydrocortisone, Methyltestosterone are examples of interstitial crystalline solid solution [40].

5] Amorphous precipitation In Crystalline Matrix:
In Amorphous precipitation in crystalline matrix, drug is precipitated out in an amorphous form. It is similar to simple eutectic mixture.

Table 3: TABULAR REPRESENTATAION OF TYPES OF SOLID DISPERSION:

S.No	Eutectics	C	C	Solid dispersion	Reference
1	Amorphous precipitation in crystallian matrix	C	A	Rarely encountered	4,5
2	Continous solid solution	C	M	Miscible at all preparation	1
3	Discontinous Solid preparation	C	M	Partially miscible	3
4	Interstitial solid Solution	C	M	Usually limited miscibility	2
5	Glass solution	A	M	Require miscibility or solid solubility	6
6	Glass suspension	A	C	Particle size of dispersed phase dependent upon evaporation rate	7

**A: matrix in the amorphous state, C: matrix in the crystalline state.*
***A: drug dispersed as amorphous clusters in the matrix, C: drug dispersed as crystalline particles in the matrix, M: drug molecularly dispersed throughout the matrix*

MANUFACTURING METHOD USED TO PRODUCE SOLID DISPERSION:
Many techniques have been applied for manufacturing of solid dispersion and deals with mixing of matrix and a drug. During the preparation on a molecular level, matrix and drug are poorly miscible demixing and formation of different phase is observed. The formation of different phase can be controlled by some approaches which can be described as follows [8, 32, 35]:
1] It can be controlled by maintaining the driving force low for phase separation.
2] Rapid cooling procedure minimized the extent of phase separation.
3] Phase separation can also controlled by maintaining a low molecular mobility of matrix and drug.

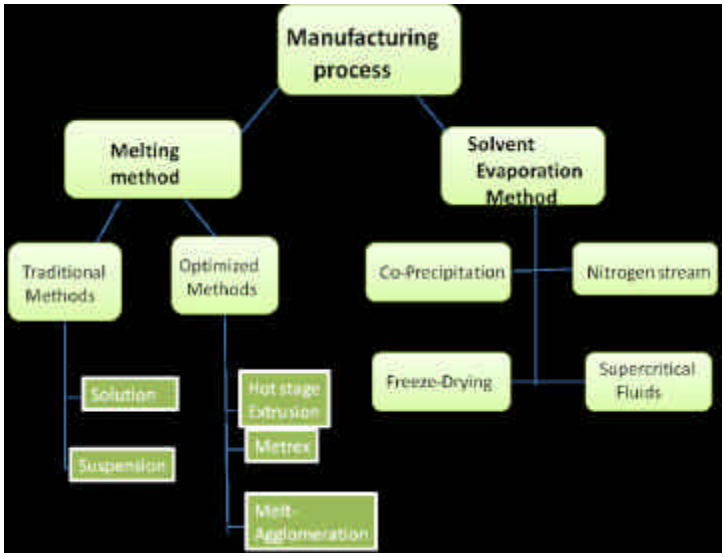

Fig 2: Diagramatic representation is shown as below:

MANUFACTURING PROCESSES USED TO PRODUCED SOLID DISPERSION

COMMONLY USED TECHNIQUES ADOPTED FOR PREPARATION OF SOLID DISPERSION: [30-38]
1] Fusion method (Melting method)

2] Melt-extrusion method
3] Solvent evaporation method
4] Melting solvent method (Melt evaporation)
5] Melt –agglomeration method
6] Solvent method
7] Supercritical fluid method
8] Lyophilization method
9] Extruding method
10] Spray-drying
11] Kneading method
12] Electrospinning
13] Use of adsorbent
14] Crystallizations in aqueous solvent

The Description of these methods in detail described below:

1] Fusion Method (Melting Method):
Melting method was first introduced by Sekiguchi and Obi [35]. When the starting material is crystalline, than fusion method is also referred as melt method. It consists of a physical mixture of drug and water soluble carrier. Then the physical mixture is placed on ice-bath for solidification. Then it is crushed, pulverized and sieved. The first solid dispersion for pharmaceutical use consists of sulfathiazole and urea as a matrix is prepared by fusion method. If high temperature is used then many drugs and carriers may often evaporates or may be decomposed. So, to avoid this problem the physical mixture should be heated in a sealed container or in the presence of an inert gas like Nitrogen. Therefore, use of high temperature is the limitation of this method.

Table 4: SOME OF THE PREPARATION OF SOLID DISPERSION BY FUSION/ MELTING METHOD:

S.NO.	DRUG	CARRIER	MELTING TEMPERATURE	REFERENCES
1	Aceclofenac	Urea,Mannitol	80-85 degree celsius	14
2	Albendazole	Poloxamer	63 degree celsius	18
3	Atorvastatin	Mannitol	60 degree celsius	15
4	cefdinir	PEG-4000	50-58 degree celsius	17
5	Fenofibrate	Poloxamer-4000	60 degree celsius	20
6	Gliclazide	PEG-4000,6000	----------	19
7	Furosemide	PEG-6000	75 degree celsius	16

2] Melt-extrusion method:
It is same as melting method. In melt –extrusion method, mixing of component is done by twin-screw extruder. In these drug and carriers are melted, homogenized, extruded and then shaped as tablets, granules, pellets, sheets, sticks and powder. Further intermediates can be processed into conventional tablets [32]. Melt-extrusion method offers the advantage to shape the heated drug matrix into Implants, opthalamic inserts and oral dosage form. As compared to fusion method it offers the possibility of continuous production. An important advantage of melt-extrusion method is that drug- carrier mixture is only exposed to a high temperature only for about 1 min [22].

3] Solvent-evaporation method:
In solvent-evaporation method, both drug and the carrier are dissolved in a common solvent with the help of a magnetic stirrer and evaporate the solution under vaccum [35] . Then the produced mass is placed in a dessicator for 1-2 days depends upon the removal rate of solvent for drying purpose. Mixing at molecular level leads to optimal dissolution properties. The solid dispersion prepared by this method was termed as co precipitates by Bates. Gibaldi and Marersohn dissolved polyvinylpyrrolidone and Griseofulvin in chloroform and evaporate the solvent to achieve a solid solution.Simonelli et al use the solid dispersion of sulfathiazole and polyvinylpyrrolidone which is precipitated in sodium chloride by the addition of hydrochloric acid. So, solid dispersion prepared by solvent –evaporation method is termed as co-evaporates instead of co-precipitates.

In solvent-evaporation method, temperature lies in the range of 23-65 degree Celsius. In these methods, solvent can be removed by spray drying or freeze drying [30]. In these, both the drug and the carrier are completely dissolved in the solvent.
The main advantage of solvent-evaporation method is that in these drugs and carriers cannot be thermally decomposed because a very low temperature is used for evaporation of organic solvents. However some disadvantage of this method related to its higher cost of production, difficulty in reproducing crystal form, selection of common volatile organic solvent and difficulty in completely removing organic solvent.

4] Melt –agglomeration method:
In Melt-Agglomeration method is used to prepare solid dispersion in which solid dispersion is prepared in conventional high shear mixtures and binder itself act as a carrier [22]. In this a mixture of drug, carrier and excipient are heated to a temperature above the melting point of the carrier using a high shear mixer. The equipment used for Melt-Agglomeration is Rotary Processor and is used to produce stable solid dispersion.

5] Supercritical fluid method:
In Supercritical Fluid Method, a solvent free solid dispersion dosage form is prepared to increase the solubility of poorly soluble compounds [31]. This method is commonly applied with carbon-di-oxide, which is used as anti-solvent. In these technique drug and carrier are dissolved in a common solvent leads to particle formation vessel through a nozzle using carbon-di-oxide. The use of this method reduces residual solvent content, particle size without any degradation.

The preparation of solid dispersion of carbamazepine in polyethylene glycol-4000 increases the rate and dissolution properties of carbamazepine. Some of the most commonly used Supercritical solvents are nitrous oxide, ethylene, carbon-di-oxide, propylene, propane, ammonia, ethanol and water. The most commonly used Supercritical Fluid is carbon-di-oxide due to its unique properties [38].

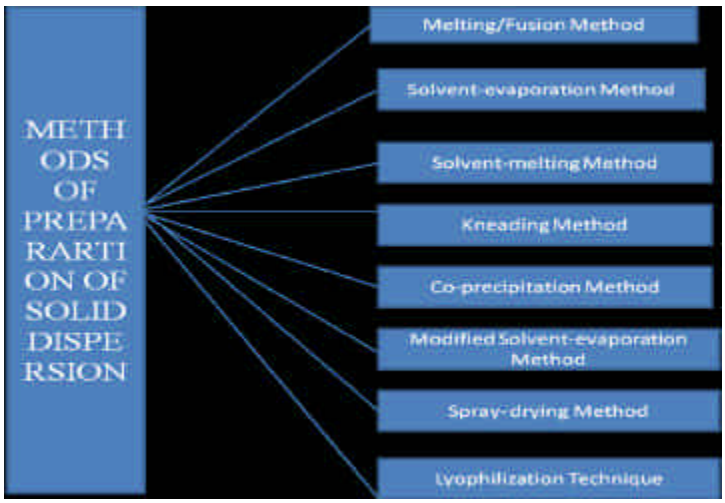

Fig 3: Methods of preparation of solid dispersion: [10,65]

ALTERNATIVE STRATEGIES:

1] Spray-drying:

It is one of the most widely used techniques in the preparation of solid dispersion. In these method drug and carrier are dissolved or suspended and the solvent is removed by spraying it into a stream of heated air[39].Van Drooge prepared a solution of Diazepam and povidone and then sprayed into liquid nitrogen and then lyophilized. It is 40-50 times less expensive then freeze –drying ,so it is cost-effective and simple.

2] Co-precipitation:

This technique is widely used for improving the dissolution characteristics of poorly water soluble drugs. In this method, drug and carrier are mixed in an organic solvent [8]. On precipitation, drug and carrier are separated and separation is mainly depends upon solubility properties of drug and the carrier.

In this method, required quantity of drug and carrier were added in a solvent to obtain a clear solution. The solution was dried at room temperature and then placed in incubator for 12 hours [40]. At last, it was passed through a sieve.

3] Dropping method:

This method was first developed by Bulau and Ulrich in 1977. It facilitates the crystallization of different chemicals and formation of round particles from melted solid dispersion.

It is used for laboratory scale preparation as follows: Solid dispersion of melted drug-carrier is dropped on to a cooling plate for solidification into round particles [33]. Factors such as size of pipette and viscosity of melt determine the size and shape of particles. It is very important to adjust the temperature, when the melt is dropped on to the plate for solidification into spherical particles as viscosity is highly temperature dependent.

4] Electrostatic spinning method:

In these technology, solid dispersion technique is used in combination with Nanotechnology [35].In these method, a liquid stream of drug/polymer solution is exposed to a potential of 5-30KV.In these method, fibres of submicron diameter are formed and the formed fibers are collected on the screen after evaporation of the solvent.

The advantage of these technique is that the process is simple and cheap, has potential for the preparation of nanofibres and is utilized for the preparation of solid dispersion in future[36].The disadvantage of this method is that it is less economical for all drugs and carriers.

5] Physical mixture method:

In this method, the required amount of drug and carrier are mixed in a glass-mortar by triturating. Then the obtained physical mixture is passed through sieve no.44 and sample was stored in a dessicator for further use [3].

6] Freeze-drying:

In freeze drying technique drug and carrier are dissolved in a common solvent, which is immersed in liquid nitrogen. Then this solution is lyophilized [19]. Freeze-drying is most suitable technique for incorporating drug substance in stabilizing matrices. In this method, during the formation of solid dispersion, drug is exposed to minimal thermal stress and phase separation risk is reduced.

ADVANTAGES OF SOLID DISPERSION:

There are many advantages of solid dispersion technique which are enlisted below:

1] Solid dispersion technique is useful to enhance solubility and bioavailability of poorly water soluble drugs [41].

2] It is easier to produce and is more applicable [43].

3] It leads to increase in extent and rate absorption of a drug, hence rapid dissolution rate occurs.

4] Transformation of liquid form of drug into solid form [45].

5] Control of various parameters like molecular weight, composition, particle porosity and wettability can enhance the bioavailability of poorly water soluble drugs.

6] It is easier to produce rapid disintegration oral tablets by solid dispersion.

7] It is used to mask the bitter taste of drug.

8] It is used to improve porosity of drug [42].

DISADVANTAGE OF SOLID DISPERSION:

The disadvantages of solid dispersion are enlisted below:

1] It leads to the poor scale-up for the purpose of manufacturing [41].

2] The polymers used in solid dispersion can absorb moisture and cause phase-separation, crystal growth and convert amorphous form into crystalline form. Thus result in decrease solubility and dissolution rate.

3] It is laborious method of preparation.

4] It causes reproducibility of physicochemical characteristics [44].

CHARACTERIZATION OF SOLID DISPERSION:

1] X-ray diffraction:

Long range order materials are detected by powder x-ray diffraction method [48]. Sharper diffraction peaks shows more crystalline materials. Semiquanitative is recently developed X-Ray equipment [57].

2] Infrared spectroscopy:

Regardless of the state of carrier it helps in determining the solid state of drug in the carrier [46]. In these, by matching the peaks of spectra interaction between drug and polymers can also be determined. Crystallinities in range of 5-10% cannot be determined by IR Spectroscopic method.

3] Differential scanning calorimetry:

It is mostly used technique to determine the amount of crystalline materials [50, 49]. In these, presence of polymer may affect the melting behavior of drug (for ex. Melting point Depression).It also reflects changes in physical state of solid dispersion during heating.

4] Dissolution testing:

Dissolution rate-limited absorption drugs must have intrinsic dissolution rate of < o.1mg/cm2/min [54]. By comparing the dissolution profile of drug, physical mixture of drug, carrier and solid dispersion reflects the mechanism of improved release of drug in formulation [47].

5] Particle size:

Microscopic surface morphology of drug and carrier is determined by Scanning Electron Microscopic Polarization Method. This method also determines the polymorphism of drug. In the carrier matrix the fine dispersion of drug particles can be visualized [58].

6] Detection of molecular structure in amorphous solid dispersion:

The properties of solid dispersion are highly dependent upon the uniformity of distribution of drug in the matrix [50, 52]. There are some studies which focus on the discrimination between amorphous versus molecular distribution:

A] IR and FTIR can determine the interaction between drug and matrix [53, 56].

B] Solid mixture of Ibuprofen in PVP is determined by Confocal Raman Spectroscopy.

C] Degree of mixing of incorporated drug can be determined by Temperature Modulated Differential Scanning Calorimetry [55].

7] Melting enthalpy for calculation of entropy change.

8] Differential Thermo Analysis Method and Hot Stage Microscopy [51].

Table 5: Various characterization methods to assess solid dispersion: [12, 58]

S.NO	Characterization	Methods	Significance
1	Drug-carrier miscibility	Diffrential scanning microscopy	To find out the complex formation between drug and carrier
2	Drug-carrier interaction	FTIR	To find out the solid state interaction between drug and carrier
3	Surface properties	Dynamic vapou sorption	To study the morphology and degree of crystallinity
4	Amorphous content	Optical microscopy	To find out the amorphous transition
5	Stability	Dynamic vapour sorption	To find out the degree of recrystallization
6	Dissolution rate	Dissolution studies	To find out the rate and extent of drug release

EVALUATION OF SOLID DISPERSION:

1] Microscopy:
A] Scanning Electron Microscopy: It is very useful in determining the particle size and morphology of drug particles [27].
B] Optical Microscopy: Stage Micrometer and Calibrated Ocular Micrometer are used in Optical Microscopy and is used for particle size analysis of powder [59] E. Various number of particles are measured and their mean diameter can be calculated.

2] Drug carrier compatibility [24]:
This is used determining the formation of inclusion complexes. Various methods used for this purpose are:
A] Solid State NMR Studies
B] Raman Spectroscopy
C] Differential Scanning Calorimetric Analysis
D] FTIR Spectroscopy

3] Drug-carrier miscibility:
It is used to find out the complexation between drug and carrier. Hot Stage Microscopy, DSC, NMR and PXRD are used to carry out this study.

4] Phase-solubility studies:
In phase –solubility studies an excess amount of drug is added to the specific carrier containing. Increasing concentration [59]. It is shaken at 37 degree Celsius for 48 hours in thermostatically controlled water –bath. Then the solution is filtered through a cellulose nitrate membrane filter. The filtrate is diluted and analyzed spectrophotometrically [27].

5] Surface properties:
This study includes study of morphology and degree of crystallinity in the solid dispersion. Various methods used are:
A] Atomic Force Microscopy
B] Raman Microscopy
C] Inverse Gas Chromatography
D] Dynamic Vapors Sorption

6] Dissolution studies:
It is used to determine the rate and extent of dissolution [27]. Formulation of solid dispersion is justified by the improved dissolution of drug [59]. The methods used for studying dissolution enhancement are:
A] Intrinsic Dissolution
B] Dynamic Solubility
C] Dissolution
D] Dissolution in bio relevant media

7] Stability studies:
This study is used to determine the stability of solid dispersion on storage for a long period of time [24]. Various methods are used to evaluate the stability studies of solid dispersion are:
A] Isothermal Calorimetry
B] Dynamic Vapor Sorption
C] Saturated Solubility Studies
D] Humidity Studies
E] DSC (Tg, temperature recrystilization)

Table 6: ANALYTICAL METHODS FOR CHARACTERIZATION OF SOLID FORMS: [8, 17]

S.NO.	METHOD	MATERIAL REQUIRED PER SAMPLE
1	Microscopy	1mg
2	Fusion method	1mg
3	Diffrential scanning calorimetry	2-5mg
4	Infra-Red Spectroscopy	2-20mg
5	X-Ray Powder Diffraction	500mg
6	Scanning electron Microscopy	2mg
7	Solubility Analysis	mg to gm

METHODS OF DETERMINATION OF TYPES OF SOLID DISPERSION SYSTEM [60, 61]:
There are many methods available for determination of types of solid dispersion system such as:
1] Infra-Red Spectroscopy
2] Thermal Analysis
3] Microscopic Method
4] X-Ray Diffraction Method
5] Spectroscopic Method
6] Dissolution rate Method
7] Thermodynamic Method [60]
8] Differential Scanning Calorimetry

APPLICATIONS OF SOLID DISPERSION:
Solid dispersion has numerous pharmaceutical applications which are enlisted below such as [60]:
1] Masking of unpleasant smell and taste of bitter drugs [67].
2] To obtained a homogeneous distribution of small amount of drug in solid state.
3] In a sustained release dosage form, a fast release primary dose is formulated [65].
3] To reduce presystemic inactivation of drug such as morphine and progesterone.
4] To dispense liquid or gaseous compound in a solid dosage.
6] By using insoluble carriers, sustained release regimens of soluble drugs are formulated.
7] To stabilize the unstable drug [64, 66].
8] To reduced side effects of some drugs.
9] To avoid undesirable incompatibilities.
10] Improvement of drug release from gels, ointments and creams.
11] In a given system polymorphs can be converted into is eutectic, solid solution, amorphous or molecular addition compounds [62, 63].

CURRENTLY MARKETED SOLID DISPERSION PRODUCTS:
The commercial applications of solid dispersion are limited. Only a few products have been marketed such as: [59, 10]
1] Solufen (Ibuprofen)
2] Gris-PEG (Griseofulvin)
3] Prograf (Tacromilus)
4] Sporanox (Itraconazole)
5] Crestor (Rosuvastatin)
6] Intelence (Etravirine)
7] Cesamet (Nabilone)
8] Ritonavir capsules produced by Norvir, Abott has been temporarily withdrawn from market due to crystallization.

CONCLUSION:
Due to the availability of surface active and self-emulsifying carriers with low melting points, successful development of solid dispersion system for clinical, preclinical and commercial use has been feasible. The popularity of solid dispersion system will grow rapidly due to the simplicity of manufacturing and scale-up processes. Solid dispersion system has an advantage over other commonly used bioavailability enhancement techniques such as micro ionization of drug and soft gelatin encapsulation. Solid dispersion system has been realized an extremely useful tool for improving the dissolution properties of poorly water soluble drugs [1]. Third generation solid dispersions are mainly effective as they use many kinds of surface active agents and act as the plasticizers. Dosage form such as tablets, capsules can be formulated by using solid dispersion technique. Solid dispersion has also been used to produce sustained released microspheres. New optimized techniques are also useful in the industries. Further research is also required for the better implementation of solid dispersion technology for the solubility enhancement of poorly water soluble drugs. Although there are some problems like scale up, there lies a promise that solid dispersion technology will hasten the drug release profile of poorly water soluble drugs.

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