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Solid Dispersion: An approach to enhance Bioavailability

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ABSTRACT: Improving oral bioavailability of drugs given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. Different approaches are being used to improve the solubility of poorly water soluble drugs; one of such approaches is using solid dispersion techniques. Solid dispersion techniques have attracted significant interest for improving the dissolution rate of highly lipophilic drugs thereby improving their bioavailability either by reducing drug particle size, improving wettability or forming amorphous particles. This present article reports different types of solid dispersion, various preparation techniques, advantages of solid dispersion over other techniques, applications of solid dispersion, marketed formulations, patents and future prospects. Some of the practical aspects to be considered for the preparation of solid dispersions, such as selection of suitable drug candidate, selection of carrier and methods of physicochemical characterization, mechanism of drug release have also been discussed.

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INTRODUCTION:

The solubility behavior of drugs remains one of the most challenging phases in formulation development. The drugs having very low solubility in biological fluids can lead to poor bioavailability after oral administration. Solid dispersion is one of the techniques used to improve solubility and hence bioavailability of poorly water soluble drugs. In 1961, Sekiguchi and Obi first put forward the utilization of solid dispersions to increase the dissolution and oral absorption of poorly water soluble drugs. They proposed the formation of a eutectic mixture of a poorly water-soluble drug with a physiologically inert, easily soluble carrier. In 1971 Chiou and Riegelman defined solid dispersion as the

dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method [1]. The solid dispersions may also be called solid-state dispersions, as first used by Mayersohn and Gibaldi [2]. This review article focuses on the progress in methods of manufacturing, promising drugs that can be incorporated into solid dispersion techniques, marketed formulations, and development of patents, aging of solid dispersions and its future prospective.

Classification of solid dispersions:

Solid dispersions are classified into four different generations. Brief information about each generation is discussed below [3].

First generation:

The first generation solid dispersions includes eutectic mixtures of sulphathiazole [4], fused conglomerates of chloramphenicol and urea [5], as prepared by Levy [6] and Kanig [7] using mannitol as carrier and using chloramphenicol-urea system [8]. All these solid dispersions were prepared using crystalline carriers like urea and sugars. But they have the disadvantage of forming crystalline solid dispersions, which are more thermodynamically stable and cannot release the drug as quickly as amorphous ones [9].

Second generation:

Amorphous carriers are used which are usually polymers. They may be synthetic polymers such as poly vinyl pyrrolidone, polyethylene glycols, ethyl cellulose polymethacrylates, natural product based polymers such as hydroxypropyl methylcellulose and hydroxypropyl cellulose or starch derivatives like cyclodextrins. In second generation solid dispersions drugs are molecularly dispersed in an irregular form within an amorphous carrier which is usually polymers [10]. The most common solid dispersions do not use crystalline carriers but amorphous one. According to molecular interaction of drug and carriers amorphous solid dispersions can be of three types that are solid solutions [11-13], solid suspensions [14-15] or a mixture of both [16].

Third generation:

In this case surfactant carriers or mixtures of amorphous polymers are used as carriers. If the carriers have surface active or self-emulsifying properties and surfactants as carriers which shows improved dissolution rate of poorly soluble drugs ultimately shows increase in bioavailability of such drugs. The drawback of solid dispersion like precipitation and recrystallization was avoided due to incorporation of surface active carriers or self-emulsifying carriers. Examples of carriers in third generation solid dispersions include inulin [11], inutec SP1 [13], compritol 888 ATO [17], gelucire 44/14 [18-20], poloxamer 188 [21-22], poloxamer 407 [23-24], PEG and polysorbate 80 mixture [25], HPMC-poloxomer and HPMC-polyoxyethylene hydrogenated castor oil [26] polyethylene glycol-HPMC [27,28].

Fourth generation:

The objective of this generation is to prepare the solid dispersion having controlled release of poor water-soluble drugs with a short biological half-life. It has two targets that are enhancement in solubility and prolonged release in a controlled manner. In controlled release solid dispersions, drugs can be released by two mechanisms such as diffusion and erosion. Drug release retarded polymer in controlled release solid dispersions include ethyl cellulose (EC), HPC, polyethylene oxide (PEO) and Eudragit RS RL [29]. The features of different generations of solid dispersions are illustrated in (Fig 1).

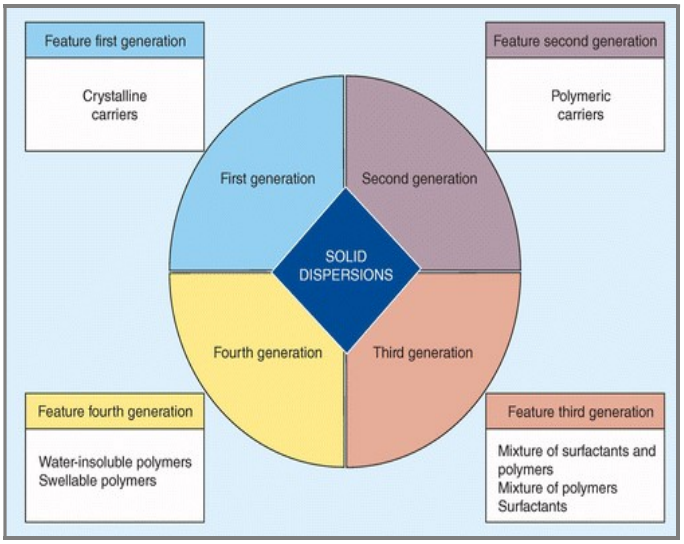

Fig 1. Features of different generations of solid dispersions.

Ideal candidates for solid dispersion:

Ample of research has been reported on solid dispersion technologies involving drugs that are poorly water soluble and highly permeable to biological membranes because dissolution is the rate limiting step to absorption for them. Hence, the hypothesis has been that the rate of absorption *in vivo* will be concurrently accelerated with an increase in the rate of drug dissolution [30]. In the Biopharmaceutical Classification System (BCS) Class II drugs are those with low aqueous solubility and high membrane permeability [31] and therefore, solid

dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. According to the BCS, drug substances are classified into four groups as shown in (Fig 2). Table 1 and 2 represents some BCS Class II drugs on the WHO model list of essential medicines. The most well-known classification system for pharmaceutical compounds considers solubility and permeability in the Biopharmaceutical Classification System. This classification divides compounds into four quadrants. They are as follows.

Fig 2. Biopharmaceutical Classification System (BCS).

Methods of preparation of solid dispersion:

Various preparation methods for solid dispersions have been reported in literature. These methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, de-mixing (partially or complete) and formation of different phases is observed. Various methods for preparation of solid dispersion are specified in Fig 3.

Melting method:

This method was first used to prepare simple eutectic mixtures by Sekiguchi and Obi [34]. Leuner and Dressman [12] used to describe the melting method as the hot melt method. This method consists of melting the drug within the carrier followed by cooling and pulverization of the obtained product. This method does not need any solvent which is the main advantage of this method and the important requirement of this method is carrier and drug miscibility in their molten state to form a homogenous mixture.

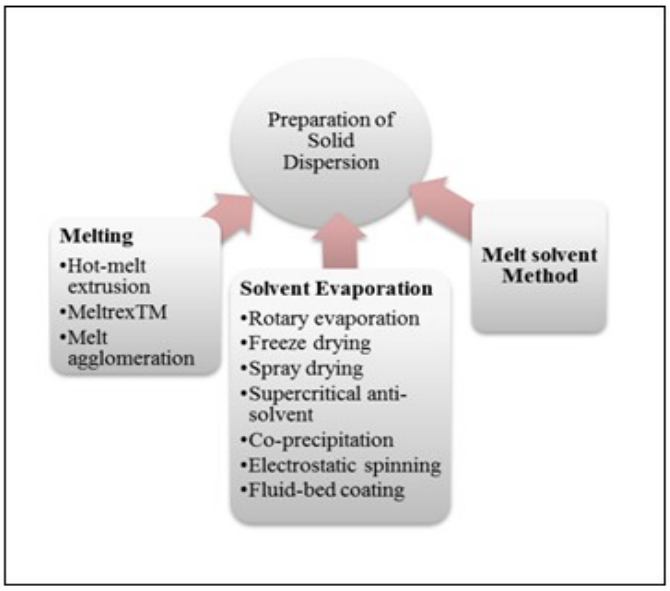

Fig 3. Methods of preparation of solid dispersion [33].

The limitations of this method are as follows;

- Due to the use of high temperatures drug degradation may occur.
- Carrier and drug incomplete miscibility occurs because polymeric carriers show high viscosity in their molten state.
- During cooling the phase separation may occur due to change in drug-carrier miscibility [35-36].

To avoid these limitations several modifications were introduced to the original process; i.e. hot stage extrusion [37,38], Meltrex® [39,40], melt agglomeration [41-43], injection molding [44], hot-spin-melting [45-47].

Solvent evaporation method:

This technique mainly aims at dissolving the drug and carrier simultaneously in a common solvent, followed by removal of solvent through evaporation. Tachibana and Nakumara were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution [48]. The method was then taken up by Mayersohn and Gibaldi [2]. With the discovery of the solvent method, many of the problems associated with the melting method were solved and for many years the solvent method was the method of choice for polymer-based systems. With time, however, the ecological and subsequent economic problems associated with the use of organic polymers began to make solvent based methods more and more problematic.

Table 1. Some BCS class II drugs on the WHO model list of essential medicines [32].

Drug	Used as
Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: Drugs with reliable solubility and permeability	
Carbamazepin	Antiepileptic
Dapsone	Antirheumatic/leprosy
Griseofulvin	Antifungal
Ibuprofen	Pain relief
Nifedipine	Calcium channel blocker
Nitrofurantoin	Antibacterial
Phenytoin	Antiepileptic
Sulfamethoxazole	Antibiotic
Trimethoprim	Antibiotic
Valproic acid	Antiepileptic
Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: Drugs for which complete solubility and/or permeability data are lacking	
Iopanoic acid	Contrast medium
Nalidixic acid	Antibacterial agent
Nevirapine	Antiviral
Praziquantel	Anthelmintic
Rifampicin	Antituberculotic

Table 2. Some BCS class II drugs on the WHO model list of essential medicines [32].

Drug	Used as
Classification of orally administered drugs on the WHO model list of Essential Medicines according to the BCS: drugs with inconclusive data	
Albendazole	Antiparasitic
Amitriptyline	Antidepressive
Artemether + Lumefantrine	Antimalarial agents
Chlorpromazine	Antidepressive
Ciprofloxacin	Antibiotic
Clofazimine	Antibacterial agent
Diloxanide	Antiprotozoal agent
Efavirenz	Antiviral
Folic acid	Vitamin
Glibenclamide	Antidiabetic
Haloperidol	Neuroleptic
Ivermectin	Anthelmintic
Lopinavir	Antiviral
Mebendazole	Anthelmintic
Mefloquine	Antimalarial
Niclosamide	Anthelmentic
Pyrantel	Anthelmintic
Pyrimethamine	Toxoplasmose
Retinol	Vitamin
Spironolactone	Diuretic
Sulfadiazine	Antibacterial agent
Sulfasalazine	Colitis ulcerosa
Triclabendazole	Anthelmintic
Verapamil hydrochloride	Calcium channel blocker
Warfarin Sodium	Anticoagulant

For these reasons, hot melt extrusion is the current method of choice for the manufacture of solid dispersions [12]. Identification of a common solvent for both carrier and drug can be problematic and a complete solvent removal from the product can be a lengthy process. The solvent can be removed by various processes including heating of the mixture, vacuum drying, slow evaporation of the solvent at low temperature, the rotary evaporators, freeze drying and spray drying. Many drugs and polymers which could not be utilized for the melting method due to their high melting points could be used for solvent evaporation method.

Melting solvent method:

The melting solvent method is a combination of the two methods like melting and solvent evaporation method. It is carried out by dissolving the drug in a suitable solvent and then mixing of the resultant solution with the molten carrier followed by cooling into solidification. The advantage of this method is that it requires lower temperatures with lesser risk of decomposition of thermo labile drugs [49].

Spray drying process:

Spray drying is the process where a solution of drug substance and carrier is evaporated by spraying the solution as fine droplets into a chamber under controlled conditions of heat, humidity and air flow. The medium of drying is mainly associated with hot air and the product is thus separated after completion of drying. In this type of preparation, the carrier and the drug are suspended or dissolved in a common solvent. It is a fast and quick method because of the large surface area of the droplets, the solvent quickly evaporates and solid dispersion is formed fast. Spray drying is a faster, time-saving technique for obtaining even the smallest quantities of sample in powder form. For particle formation and drying Spray drying is the most widely used industrial process. Spray drying is a suitable method for continuous production of dry solids in powder, granulate or agglomerate particle form of liquid feed stock [50-53].

Hot extrusion method:

It is defined as the process of formation of a new material under controlled conditions such as temperature, mixing, feed-rate and pressure by forcing it through an orifice or die. It is different from simple extrusion; in this process polymer, drug and excipients blends are mixed in the molten state, solvents not for granulation. The molten polymer is used as the thermal binder. The process has been implemented for the preparation of solid dispersion in a single step. In earlier periods HME is used to prepare solid dispersion to enhance solubility of poorly water soluble drugs. But nowadays, its value in developing controlled release dosage forms has gained more attraction. The key advantages of hot-melt extrusion technique include lower temperature and shorter residence time of the drug carrier mixture. Basically, the physical mixture of drug substance along with other ingredients is fed into the heated barrel of the extruder at a controlled rate. As the physical mixture is supplied through heated screws, it is converted into a fluid like state, thus allowing an intimate and homogeneous mixing by the high shear of extruder screws. The die helps in shaping the melt in the required form such as pellets, granules, tablets, sticks, sheets or powder [54,55].

Supercritical fluid technology:

In the supercritical fluid antisolvent techniques, carbon dioxide is used as antisolvent for the solute but as a solvent with respect to the organic solvent. Supercritical fluid technology is important because it operates at high temperature and pressure. Above critical temperature and pressure supercritical fluid exists as a single phase. The most commonly used SCF is CO_2 due to its low temperature (31.3 $^{\circ}$C) and low pressure (73.8 bar). In this process a mixture of drug and polymer is sprayed with the help of an atomizer into a chamber filled with supercritical fluids. The extraction and expansion of organic solvent into the compressed gas results in lowering the solvent power of organic solvent for polymers as well as drugs, thus leading to their precipitation. Use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient. In addition the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature. Moreover, supercritical fluids are used to lower the temperature of the melt dispersion process by reducing the melting temperature of dispersed active agents. The reason for this depression is the solubility of the lighter component (dense gas) in the forming phase (heavier component) [56,57].

Lyophilization (freeze drying):

It involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilization has been thought of as a molecular mixing technique where the drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. An important advantage of freeze drying is that the drug is exposed to a minimal thermal stress condition during the formation of the SDs.

However, the most important advantage is that the risk of phase separation is minimized as soon as the solution is vitrified [58].

Electrospinning:

This method includes the introduction of a liquid into an electric field whereas the liquid is used to develop fibers. After withdrawal from the liquid, the fibers harden, which may include mere cooling, chemical hardening or evaporation of solvent, and then hardened fibers may be collected upon a suitably charged surface. Tubular products comprising polyurethane fibers can be prepared by this electrostatic spinning method. One example of such a type of tubular product is a vascular prosthesis, basically a synthetic blood vessel [58].

Characterization and evaluation of Solid Dispersion:

There are so many methods available for contributing information regarding characterization of and evaluation of solid dispersion systems. Some of them are depicted in Table 3 and 4 along with their significance [56-60].

Advantages of Solid Dispersion:

***Particles with reduced particle size*:**

Molecular dispersions, as solid dispersions, represent the last stage of particle size reduction and thus the drug possesses a molecular dispersion in the dissolution medium after the dissolution of its carrier.

***Particles with improved wettability*:**

A strong contribution to the enrichment of drug solubility is related to the drug wettability improvement verified in solid dispersions. Carriers with surface activity, such as bile salts and cholic acid, when used, can potentially amplify the wettability properties of drugs.

Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects. Recently, the inclusion of surfactants in the third generation solid dispersions reinforced the importance of this property [59].

***Particles with higher porosity*:**

Particles with solid dispersions have been observed to have a higher degree of porosity. The increased porosity of solid dispersion particles also accelerates the drug release profile. The increase in porosity also depends on the carrier properties, for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate [60].

***Drugs in amorphous state*:**

Poorly water soluble crystalline drugs, in their amorphous state tend to have a higher solubility. However, the enhancement of drug release can usually be obtained using the drug moiety in its amorphous state, as no energy is required to break up the crystal lattice in the interim of dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions [61].

Disadvantages of Solid Dispersion:

- Carriers with high melting points cannot be used.
- Thermal degradation or instability may result at the melting point.
- Decomposition may take place, often dependent upon composition, fusion time and rate of cooling.
- Sublimation or evaporation and polymeric transformation of the dispersion component may take place.
- Solidified melt may be tacky and unhandable [61-62].

Selection of Carriers in Solid Dispersion:

In order to prepare efficacious and stable solid dispersion, the choice of carrier is of great significance. In a solid dispersion, an ideal carrier is required to perform multiple functions. The properties of the carrier have been the major influence on dissolution characteristics of dispersed drug molecules. A carrier should have the following suitable characteristics to enhance the solubility as well as dissolution rate of a drug [63].

Table 3. Different techniques used for characterization of solid dispersion [57-59].

Sl. No.	Characterization	Methods	Significance
1	Drug-carrier Miscibility	Powder X-ray diffraction, Hot stage microscopy, DSC (conventional modulated), NMR 1H Spin lattice relaxation time.	To find out the complex formation between drug and carrier
2	Drug-carrier interactions	FT-IR spectroscopy, Raman spectroscopy, Solid state NMR studies.	To find out the integration between drug and carrier and formation of inclusion complex
3	Physical structure	SEM Surface area analysis	To find out the particle size and shape
4	Surface properties	Dynamic vapor sorption, Atomic force microscopy, Raman microscopy	To study the morphology and degree of crystallinity
5	Amorphous content	Polarised light optical microscopy, Powder X-ray diffraction, DSC (MTDSC), Hot stage microscopy, Humidity stage microscopy ITC	To find out the amorphous from drug
6	Stability	DSC (Tg, Temperature recrystallization), Humidity studies, Isothermal Calorimetry, Saturated solubility studies, Dynamic vapor sorption	To find out the degree of crystallinity
7	Dissolution enhancement	Dissolution, Dynamic solubility, Intrinsic dissolution, Dissolution in bio-relevant media	To find out the rate and extent of dissolution

Table 4. Different evaluation parameters of solid dispersion [56-58].

Sl. No.	Methods	Significance
1	*In vitro* dissolution studies	Dissolution is carrying out to decide the rate and dissolution extent in USP- type II paddle apparatus at 37 ± 0.2^0C. Aliquots of 5 ml from the dissolution medium are withdrawn at a different time interval which is filtered through filter paper and analyzed for medicament contents by measuring the absorbance at fixed wavelength using UV spectrophotometer and replenished by an equal volume of fresh dissolution medium.
2	*In vivo* bioavailability enhancement study	The *in vivo* study of the selected optimized formulation shall be performed on one animal from reported animals like Wister rats, Sprague- dawley rats and albino rats. The *in vivo* study will help to determine the enhancement of the solubility and bioavailability of selected BCS class II medicament. The bioavailability shall be determined via the pharmacokinetic/ pharmacological method or in-situ animal modeling as deemed appropriate wherever possible, *in vivo* studies may be replaced with an *in vitro* study.
3	*Ex vivo* permeability	The *Ex-vivo* study of the selected optimized formulation shall be performed on one animal from reported animals like Wister rats, Sprague-Dawley rats and albino rats. The *in vivo* study will help to determine the improvement of the solubility and bioavailability of selected BCS class II medicament. *Ex vivo* environments allocate experimentation on an organism's cells or tissues under more controlled circumstances that is possible *in vivo* experimentation work (in alive creature), at the expense of varying the "natural" environment.

Some of the carriers used in solid dispersions for enhancing dissolution rate of drugs are given in Table 5.

- It should have high water solubility, improves wettability and enhances dissolution.
- It should be nontoxic and pharmacologically inert.
- It should have a high glass transition point (Tg) and improve stability.
- It should be heat stable with a low melting point for the melt method.
- It must be soluble in a variety of solvents for evaporation in the solvent method.
- It must be able to increase the aqueous solubility of a drug.
- It should have a good compressibility index and flow index.
- It must be chemically compatible with drugs and should not possess a strong complex with it.
- It must stabilize the supersaturated solution formed after dissolution of solid dispersion in GIT.
- Must have functional groups which are either acceptors or donors for hydrogen bonds, as specific interactions increase the solid solubility of the drug into its carrier.
- Relatively low vapour pressure and should have high molecular weight to fulfill the requirement of the host.

Mechanism of drug release from Solid Dispersion:

Drug release from the solid dispersion was observed by two mechanisms.

***Carrier-controlled release*:**

Corrigan provided a very valuable contribution by not only measuring the dissolution rate of the incorporated drug but also assessing that of the polymer itself, in this case PEG.

He found that the dissolution rate of the drug in the polymer and the polymer alone were in fact equivalent, leading to the suggestion of carrier-controlled dissolution whereby the dissolution rate of the drug is controlled by that of the inert carrier. This finding was supported by the work of Dubois and Ford who noted that the dissolution rates of a range of drugs in a single carrier, prepared under comparable conditions, were identical in most of the cases. In this instance the particles dissolve into the polymer-rich diffusion layer at a sufficiently rapid rate that there is insufficient time for the particles to be released intact into the medium. Consequently, the drug is molecularly dispersed within this concentrated layer [64].

***Drug controlled release*:**

Sjokvist and Nystrom measured the particle size of the griseofulvin particles released from the dispersions and produced strong evidence that dissolution rate enhancement was a direct function of the size of the released particles. In an attempt to reconcile these contradictions Sjokvist-Saers and Craig used a homologous series of drugs (para-aminobenzoates) in PEG 6000 to interrelate the solid state structure, drug solubility and dissolution rate. These noted that there was a linear relationship between the intrinsic dissolution rate of the model drugs in the dispersions and the drug solubility, clearly linking the properties of the drug (and not the polymer) to the dissolution rate; it may be helpful at this stage to refer to such behavior as drug-controlled dissolution as opposed to carrier-controlled dissolution. Here the dissolution into the polymer diffusion layer is comparatively slow and the drug is released as solid particles. Consequently the dissolution will not be associated with the polymer but will instead be dominated by the properties (size, physical form, etc.) of the drug itself. This may still lead to considerable improvements in dissolution compared to conventional dosage forms due to the higher surface area associated with the particles and the possibility of improved wetting and decreased agglomeration [65].

Pharmaceutical Applications:

The purpose of solid dispersions for increasing drug bioavailability is by no means a new field of pharmaceutical research. It plays an important role in increasing dissolution, absorption and therapeutic efficacy of drugs in future dosage forms. Commercially available solid dispersions are given in Table 6. Some of the important applications are [14, 66,67];

- To enhance the solubility of poorly soluble drugs thereby increasing the dissolution rate, absorption as well as bioavailability.
- To stabilize unstable drugs against hydrolysis, oxidation, isomerization, photo oxidation and other decomposition procedures.
- To reduce side effects of certain drugs.
- Masking of unpleasant taste and smell of some drugs.
- Improvement of drug release from ointment, creams and gels.
- To avoid undesirable incompatibilities.
- To obtain a homogeneous distribution of a small amount of drug in solid state.

Table 5. Carriers used in solid dispersions for enhancing dissolution rate of drug.

Sl. No.	Category	Example of carriers
1	Polymers	Polyvinyl pyrrolidone, Polyvinyl polypyrrolidone, Polyvinyl alcohol, Polyethylene glycols, Hydroxypropyl methylcellulose, Hydroxypropyl cellulose, Poly (2-hydroxyethylmethacrylate), Methacrylic copolymers (Eudragit® S100 sodium salts and Eudragit® L100 sodium salts)
2	Superdisintegrants	Sodium starch glycolate, Croscarmellose sodium, Cross-linked polyvinyl pyrrolidone, Cross-linked alginic acid, Gellan gum, Xanthan gum, Calcium silicate
3	Cyclodextrin	β-Cyclodextrins, Hydroxypropyl-β-cyclodextrins
4	Carbohydrates	Lactose, Soluble starch, Sorbitol, Mannitol, β-(1-4)-2-amino-2-deoxy-D-glucose (Chitosan), Maltose, Galactose, Xylitol, Galactomannan, British gum, Amylodextrin
5	Surfactants	Poloxamers (Lutrol® F 127, Lutrol® F 68), Polyglycolized glyceride (Labrasol), Polyoxyethylene sorbitan monoesters (Tweens), Sorbitan esters (Spans), Polyoxyethylene stearates, Poly (beta-benzyl-L-aspartate) -b- poly (ethylene oxide), Poly (caprolactone) -b- poly (ethylene oxide)
6	Hydrotropes	Urea, Nicotinamide, Sodium benzoate, Sodium salicylate, Sodium acetate, Sodium-o-hydroxy benzoate, Sodium-phydroxy benzoate, Sodium citrate
7	Polyglycolized glycerides	Gelucire 44/14, Gelucire 50/13, Gelucire 62/05
8	Acids	Citric acid, Succinic acid, Phosphoric acid
9	Miscellaneous	Microcrystalline cellulose, Di calcium phosphate, Silica gel, Sodium chloride, Skimmed milk Microcrystalline cellulose, Di calcium phosphate, Silica gel, Sodium chloride, Skimmed milk

Table 6. Commercially available of some solid dispersions [68].

Sl. No.	Commercial products	Dispersant	Manufacturer Company, Country
1	Afeditab (Nifedipine*)	Poloxamer or Polyvinylpyrrolidone (PVP)	Élan Corp, Ireland
2	Cesamet (Nabilone*)	Polyvinylpyrrolidone (PVP)	Valeant Pharmaceuticals, Canada
3	Cesamet (Nabilone*)	Povidone	Lilly, USA
4	Certican (Everolimus*)	Hydroxypropylmethylcellulose (HPMC)	Novartis, Switzerland
5	Fenoglide (Fenofibrate*)	Poltethylene glycol (PEG)	Life Cycle Pharma, Denmark
6	Gris-PEG (Griseofulvin*)	Polyvinylpyrrolidone (PVP)	VIP Pharma, Denmark
7	Gris-PEG (Griseofulvin*)	Polyethylene glycol	Novartis, Switzerland
8	Intelence (Etravirine*)	Hypromellose/ Microcrystalline cellulose	Tibotec, Yardley, PA
9	Isoptin SRE-240 (Verapamil*)	Various	Soliqs, Germany
10	Ibuprofen*	Various	Soliqs, Germany
11	Kaletra (Lopinavir* & Ritonavir*)	Polyvinylpyrolidone(PVP) / Polyvinyl acetate	Abbott Laboratories, USA
12	LCP-Tacro (Tacrolimus*)	HPMC	Life Cycle Pharma, Denmark
13	Rezulin (Troglitazone*)[a]	PVP	Pfizer, USA
14	Sporanox (Itraconazole*)	Hydroxypropylmethyl cellulose (HPMC)	Janssen Pharmaceutica, Belgium
15	Torcetrapib[b]	HPMC acetate succinate	Pfizer, USA

***=Drug, a=Withdrawn from market, b=Halted in phase III.**

- To dispense liquid (up to 10 %) or gaseous compounds in a solid dosage.
- To formulate a fast release primary dose in a sustained release dosage form.
- To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- To reduce pre-systemic inactivation of drugs like morphine and progesterone.
- Polymorphs in a given system can be converted into amorphous, solid solution, eutectic or molecular addition compounds.

Patents on solid dispersions Technology:

Numerous techniques that have been described in academics and patent literature for numerous products and processes are involved in the solid dispersions technology. The restrictions of conventional techniques of solid dispersions are provoking the researchers to restructure them which results in the number of patents in the area of solid dispersion. Some of the recent patents in the field of solid dispersions as shown in Table 7.

Aging of Solid Dispersions:

The solid dispersion appears to be a potential dosage form modification for increasing dissolution and absorption rates of poorly soluble drugs. Though, the results of aging or storage under various conditions and the effects on the fast-release characteristics and chemical stabilities have not been reported extensively. Hence, this will be an interesting and important research subject for pharmaceutical scientists before the wide and long-range practical applications of this unique approach are feasible. The effects of aging in many non-pharmaceutical systems such as alloys and inorganic compounds have been well studied. Ageing of the solid dispersions has harmful effects on the dissolution of bropirimine whereas such ageing has no effects on the dissolution of the drug from the prepared inclusion complex [90].

Future Prospects of solid dispersions:

Successful development of solid dispersion systems for preclinical or clinical and commercial use has been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. Because of the simplicity of manufacturing and scale up processes, the physicochemical properties and as a result, the bioavailability of solid dispersions is not expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion system to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. One major focus of future research will be the identification of new surface-active and self-emulsifying carriers for solid dispersions.

Only a small number of such carriers are currently available for oral use. Some carriers that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion systems may be the inadequate drug solubility in carriers, so a wider choice of carriers will increase the success of dosage form development. Research should also be aimed at identification of vehicles or excipients that would retard or prevent crystallization of drugs from supersaturated systems. In addition to bioavailability enhancement, much recent research on solid dispersion systems was directed toward the development of extended-release dosage forms. Physical and chemical stability of both the drug and the carrier in a solid dispersion are chief developmental issues, as exemplified by the recent withdrawal of ritonavir capsules from the market, so future research needs to be directed to address various stability issues. Further studies on scale up and validation of the process will also be essential [91].

CONCLUSION:

Therapeutic activity of a drug mainly depends on the bioavailability of the drug and ultimately depends on the solubility. Solid dispersion is one of the most important techniques to increase solubility, dissolution, and bioavailability of drugs. In developing a new solid dispersion system for a given drug, it is important to understand the physicochemical properties of the drug and carrier that best match the properties and find a solid dispersion method.

The preparation method and the amount of the carrier also play a vital role in the enhancement of drug dissolution rate. With future development of this technology, solid dispersions will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs. Various techniques described in this review are successfully used for the preparation of solid dispersions in the bench and lab scale and can be used as industrial scale also.

Table 7. Patents on solid dispersions.

Sl. No.	Patent No., Year	Summary of Invention/ Method	Medica-ments Used	Carrier Used	Ref.
1	US10265270 B2 (2019)	It relates to a hot-melt extrusion method of solid dispersion of decoquinate medicament. In this hot melt extrusion method, the composition comprises 5-30% of decoquinate, 60-90% of a polymeric carrier and 0-10% of a surfactant	Decoquinate	Polyvinyl capro lactampolyvinyl, Acetatepolyethylene glycol graft copolymer, copovidone, povidone or polyethyleneglycol	69
2	CN108096205 (2018)	It discloses an apixaban tablet. The apixaban tablet is formed through the tableting of apixaban solid dispersion and auxiliary ingredients. The auxiliary ingredients comprise microcrystalline cellulose, polyvinylpolypyrrolidone, superfine silica powder.	Apixaben	Mannitol, micro crystalline	70
3	CN108175751 A (2018)	It includes bufotalin solid dispersion obtained by mixing bufotalin, a hydrophilic carrier and a deposition inhibitor and processing a mixture through solid disperse preparation technology.	Bufogenin	-	71
4	CN108042496 A (2018)	In this, the curcurbitacin B SD consists of cucurbitacin B and a carrier material. The cucurbitacin B solid dispersion is quick in dissolution and high in bioavailability.	Curcurbita-cin B	Hydroxypropyl methyl cellulose, polyethylene glycol caprolactam or polyethylene - polyvinyl acetate - polyethylene glycol	72
5	CN108261401 (2018)	This invention discloses the solid dispersion of antiparasitic medicament along with dispersion carrier, antioxidant and ethanol. The ivermectin tablets prepared by an ivermectin solid disperse system have the advantages of a high dissolution rate and good stability.	Ivermectin	Anhydrous powdered sugar, lactose, sucrose, starch, maltodextrin, and microcrystalline cellulose	73
6	WO2018127088 A1 (2018)	Lurasidone solid dispersion preparation method comprises of melting treatment of a mixture containing lurasidone, a medicinal hot melt carrier, optionally an acidic regulator and plasticizer. Lurasidone is present in a form of free base.	Lurasidone	Povidone, copovidone, polyvinyl caprolactam polyvinyl, cetatepolyethylene glycol.	74
7	CN108186578 A (2018)	Solid dispersion of the medicament is prepared by polymeric carrier by copolymerisation method.	Ritonavir	VA 64	75
8	US20180147154 A1 (2018)	In this solid dispersion comprising of PVP and a noncrystalline form of rotigotine.	Rotigotine	Polyvinylpyrrolidine	76

9	US20170157095 (2017)	In order to resolve the low solubility of by adding a specific carrier and using solid dispersion technology, the dissolution of an active ingredient is effectively increased.	Allisatan isoproxil	Hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, hydroxyl propyl methyl cellulose cellulose acetate succinate	77
10	CN108210472 A (2017)	Invention will increase the *in vivo* bioavailability and dissolution rate of the medicament *via* solid dispersion.	Cilnidipine	Hydroxypropyl cellulose and hydroxy propyl methylcellulose phthalate	78
11	US20170028007 (2017)	The solid dispersion is used for preparing a medicament for treating urinary tract calculi.	Desmodium stracifolium	-	79
12	US20170368031 (2017)	This invention relates to solid dispersion formulations that may be beneficial for the ailment of diseases and disorders caused by the hepatitis C virus ("HCV").	Elbasvir	Hydroxypropyl methylcellulose	80
13	JP2017222728 A (2017)	Fenofibrate solid dispersion is prepared by melting with PVP and then pass through the sieves.	Fenofibrate	PVP	81
14	US10004719 B1 (2017)	A spray-dried SD in which the pharmaceutical compound is dispersed in a polymer matrix formed from the pharmaceutically acceptable polymer.	Heterocyclic compound	Poloxamer 188, PVP K30, PVP VA64, HPC-L, or HPCSSL.	82
15	KR101856911B1 (2017)	It includes the pelruby sustained-release solid dispersion formulation of the propene containing EudragitR RL PO, EudragitR RS PO, and amino Clay (aminoclay) as a pharmaceutical composition to provide.	Pelubiprofen	EudragitR RL PO, EudragitR RS PO, and aminoclay	83
16	US20170273999 (2017)	In this invention method of producing a solid dispersion that can improve the solubility of a hardly soluble polyphenol in water.	Polyphenol	-	84
17	WO2017041679 A1 (2017)	The present invention relates to a process for preparing tadalafil the solid dispersion pharmaceutical excipients.	Tadalafil	Hydroxypropylmethyl cellulose, hydroxy propyl cellulose, povidone, poly ethylene glycol, ethylcellulose, liposomes, methacrylic acid copolymer	85
18	US20160017164 (2016)	It concerns solid dispersion of pigment in the granular form that is suitable for colouring aqueous compositions.	Cold water soluble modified starch	-	86
19	US20160213684 (2016)	The present invention relates to a novel galenic form of a Selective Progesterone Receptor Modulator (SPRM).	Ulipristal acetate	Polyethylene glycols, Nvinyl-2-pyrrolidone polymers, N-vinyl -2-pyrrolidone	87

20	WO2015152544 A1 (2015)	An amorphous solid dispersion comprising a medicament with enhanced solubility, stability, bioavailability.	Taxane	Polyvinylpyrrolidone K-30	88
21	KR101561406 B1 (2015)	Telmisartan medicament is mixed with NaOH and PVP	Telmisartan	Polyethylene glycol almond glycerides, polyethylene glycol Caprylic / capric glycerides	89

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