INTRODUCTION: Compounds having poorly aqueous solubility are increasingly posing challenge in the development of new drug coming directly from synthesis or from high throughput screening have a very poor solubility [1]. It is well known that drug efficacy can be severely limited by poor aqueous solubility, leading to low dissolution rate and thus result in low absorption in gastrointestinal tract after oral administration hence compromising oral bioavailability. The ability to increase aqueous solubility is thus a valuable aid to increase the efficacy for certain drugs [2]. The biopharmaceutical classification system divides drugs into four classes depending on in vitro solubility and in vivo permeability data. Four classes of compounds can be distinguished: BCS Class I (high solubility, high permeability), BCS Class II (low solubility, high permeability), BCS Class III (high solubility, low permeability) and BCS Class IV (low solubility, low permeability). In the selection process, new chemical compounds with low aqueous solubility and low permeability are preferably filtered out since they might pose problems during pharmaceutical development. It is obvious that for class II drugs the low ability to dissolve is a more important limitation to their overall rate and extent of absorption than their ability to permeate through the intestinal epithelia. Poorly water-soluble drugs are expected to have dissolution-limited absorption. Increasing the drug solubility may substantially contribute to improved drug absorption, and consequently, drug bioavailability. There are several pharmaceutical strategies available to improve the aqueous solubility of poorly soluble drugs: solid dispersion, solubilization using surfactants, the use of cosolvents, and reduction of particle size, hydrotrophy and the use of aqueous soluble derivative or salts [3,4]. Solid dispersion techniques have been used to enhance the dissolution and oral bioavailability of many poorly soluble drugs [5]. A solid dispersion is the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method [6]. The term solid dispersion refers to a 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 drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [7]. To overcome the solubility problem discussed above, many authors formulated solid dispersions using number of various polymers and methods. In spite of tremendous research activity on solid dispersions since 1961, their commercial application is limited. Only a few products have been marketed so far. One aspect of solid dispersion technology on which most workers in the field would agree is that the number of marketed products arising from this approach has been disappointing. Indeed, the sheer simplicity of the manufacturing method, the fact that in general only the drug and carrier are required and the frequently reported improvements in both the dissolution rate and bioavailability would lead one to expect that the transfer to the market place would be rapid and widespread. This has not been the case, despite approximately 500 papers having been published on the subject. While this is to a large extent associated with manufacturing and stability considerations, it is also arguable that a primary reason is poor predictability of solid dispersion behaviour due to the lack of a basic understanding of their properties.
THE MECHANISM BY WHICH SOLUBILITY AND DISSOLUTION RATE ENHANCEMENT OCCURS IN SOLID DISPERSION

Numbers of theories have been proposed yet, but the mechanism by which the dissolution rate is improved is not fully understood, because there are comparatively few papers available which elucidate the mechanism (or mechanisms) involved in solid dispersion. The currently accepted range of possible mechanisms of enhanced dissolution effectively includes the following:

**By particle size reduction and reduced agglomeration:**
When eutectic mixture consist of poorly soluble drug & highly soluble carrier is exposed to water or gastro-intestinal fluid, soluble carrier dissolves leaving the drug in very fine crystalline state that will rapidly go in to solution. Due to increased surface area of insoluble compound, an enhanced dissolution rate & hence increased oral absorption is obtained as can be derived from the Noyes-Whitney equation (Figure 1) [7]. Simple eutectic mixture can be obtained from the rapid solidification of the fused liquid of two components that show complete liquid miscibility and negligible solid-solid solubility. Upon cooling, the molten mixture forms a microfine dispersion of the two components with a concomitant decrease in the melting points of the two components [8]. Several solid dispersions were described using poorly water soluble drugs, such as sulfathiazole, paracetamol and chloramphenicol using urea as high water soluble carrier. These solid dispersions produced faster release and higher bioavailability than conventional formulations of the same drugs. The small particle sizes of the drug were the main reasons for the observed improvements in bioavailability [9,10]. Similarly, the solid solution of poorly soluble drugs in rapidly dissolving carrier achieves a faster dissolution rate than eutectic mixture, because the drug particle size is reduced to its absolute minimum as it is molecularly dispersed in the carrier in a solid solution (Figure 2) [7]. Levy and Kaning developed solid dispersion systems, containing mannitol as carrier, by preparing solid solutions through molecular dispersions instead of using eutectic mixtures [7,11,12]. The observed improvements were attributed to faster carrier dissolution, releasing microcrystals or particles of drug [13]. Examples include digitoxin, hydrocortisone acetate and prednisolone dispersions in polyethylene glycol 6000 (PEG 6000) [6].

![Phase diagram for a eutectic system](image-url)
Formation of amorphous structure replacing crystalline structure:
Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. From a thermodynamic point of view, amorphous solids, compared with corresponding crystalline solids, demonstrate excess in properties meaning they have higher free energy, entropy and specific volume. Amorphous solids exhibit higher transient solubility, dissolution rate, vapor pressure and molecular mobility. Normally, in order to dissolve a crystalline drug, energy is required to break up the crystalline lattice. This required energy is often considered as a barrier for the drug dissolution. In solid molecular dispersions, long-range crystalline structure is absent and the drug is dissolved or molecularly dispersed in a polymeric carrier. Here, the drug exists in an amorphous state which exhibits a higher kinetic solubility (up to a few orders of magnitude) and dissolution rate than that of the crystalline drug [7,14,15]. Solid molecular dispersion of diclofenac sodium, naproxen and piroxicam using Poly (2-hydroxyethylmethacrylate) (PHEMA) hydrogel as carrier were prepared by solvent method in which conversion of crystalline drug into amorphous form take place having higher aqueous solubility [16].

By improving local solubility and wettability of the poorly soluble drug in the solid dispersion matrix:
The enhancement in solubility and dissolution rate of poorly soluble drugs is also related to the ability of matrix carrier to improve the local solubility and wettability of the drug. Goldberg et al. reported the effect of hydrophilic carrier urea on the solubility of chloramphenicol in his experiments where the physical mixture of chloramphenicol and urea was melted, well mixed and solidified for subsequent solubility and dissolution rate studies. It was observed that as the urea concentration increased from 0% (w/v) to slightly above 60% (w/v), the solubility of chloramphenicol in the presence of urea increased by greater than sevenfold. In addition, Verheyen et al. reported the observed solvent effect of PEG 6000 on the solubility of diazepam and temazepam as they showed 3.5 fold and 2.5 fold increases in solubility, respectively, in the presence of 15% (w/w) PEG 6000 at 30°C. Moreover, Verheyen et al. suggested that the mechanism of improved solubility and dissolution rate of diazepam and temazepam in PEG 6000 matrix also involves enhanced wettability of the drug in a polymer-rich microenvironment as the polymer dissolves [6,7,17,18].

Interactions of the drug with Carrier functional groups:
In addition to the ability of carrier matrix to improve the local solubility and wettability of the drug, they also contribute to enhance aqueous solubility and dissolution rate of the drug through specific interactions with the drug [19,20].

a) The intermolecular hydrogen bonding:
Konno and Taylor reported that hydrogen bonding interactions existed in felodipine solid dispersions with polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and hydroxypropyl methylcellulose (HPMC) where all polymers were able to maintain the amorphous state.
of the drug even at low excipient concentrations [19]. Tantishaiyakul et al.’s studies, the intermolecular hydrogen bonding between piroxicam and PVP in their solid dispersions was also confirmed by FTIR. Solid dispersions of piroxicam were prepared using polyvinylpyrrolidone K-30 by solvent method. The dissolution of drug in solid dispersion was dependent on drug to PVP ratio. The drug: PVP in 1:4 ratio, solid dispersion gave highest dissolution rate of about a 38-fold higher than that of pure drug [20].

b) By elevating the Tg of the solid dispersion mixtures:
In addition to forming molecular interactions with the drug molecule, polymeric carriers have been shown to retard amorphous drug crystallization by increasing the viscosity and glass transition temperatures (Tg) of the polymer-drug mixtures. Glass transition temperature is the temperature below which the amorphous mixture exists in a glassy state where coordinated molecular motion becomes very slow and restricted [21] (Figure 3). Figure 3 shows relationship between temperature (T) and volume (V) or enthalpy (H) for liquid, glassy and crystalline state of a material. It is desirable to elevate the Tg of the solid dispersion mixture in order to restrict the mobility of drug molecules in the carrier matrix and to prevent subsequent recrystallization. In principle, such stability can be maintained by storage at a temperature well below Tg. The stabilizing effect of polymeric carriers in solid dispersions has been discussed by Van den Mooter et al. and Yoshioka et al. in their studies where increasing the content of PVP was shown to increase the Tgs of the solid dispersions of ketoconazole and indomethacin, respectively [22,23].

d) By formation of Metastable drug polymorphous with higher solubility and dissolution rate:
In cases where polymeric carriers fail to generate complete amorphous state of the drug, they may still be able to improve the solubility and dissolution rate of the drug by forming metastable crystalline polymorphs of the drug substance which exhibits higher solubility than that of the crystalline drug alone. For example, Martínez-Ohárriz et al. has reported that the resulting crystalline polymorphic form of Diflunisal in its solid dispersions with PEG 4000 is determined by the preparation method, drug loading level and the type of solvent used. Specifically, the presence of polymorphs 1, 3, and 4 were observed in the solid dispersion products [26].

Complex formation:
In this solid dispersion, a drug forms a complex with an inert soluble carrier in solid state. The availability of the drug depends on the solubility and stability constant of the compound or complex and the absorption rate of the drug. It is suggested that the dissolution rate and oral absorption can be enhanced by formation of water soluble complex with high dissolution constant. For example, Carbamazepine/PEG 4000 and PEG 6000 solid dispersions were prepared by the fusion method involving heating a physical mixture of carbamazepine and either PEG 4000 or PEG 6000 in to the liquid state. Dissolution studies suggested that the enhancement in dissolution of solid dispersion may be ascribed to complex formation between carbamazepine and PEG 6000 [27]. One of the most frequently used complex carriers are within the class of Cyclodextrins. Cyclodextrins (CD) are cyclic oligomers typically composed of 6–8 glucose units. CDs represent a class of solubilizing agents that form non-covalent, dynamic complexes with lipophilic molecules by inclusion. The inclusion complex modifies temporarily the physical
properties of the substance. Governed by the equilibrium constant between the free drug, free CDs and the drug-CD complex, the drug will be released constantly and rapidly on dilution. CDs have been demonstrated to improve the stability of substances like proteins or peptides. The CDs that are approved for pharmaceutical products can be classified into three major types differing only in their molecular weight and respective central cavity diameter. Alpha-cyclodextrin (α-CD) has a molecular weight of 972 and a central cavity diameter of around 5Å, these increases to MW 1135 and 6.2Å for β-CD and MW 1297 and 8Å for γ-CD, respectively [28].

Swelling and capillary action of carrier: Dissolution of poorly water soluble drugs can be markedly improved by use of superdisintegrants like sodium starch glycolate, croscarmellose sodium, crospovidone, crosslinked polyvinylpyrrolidone, and crosslinked alginic acid etc [29]. Sodium starch glycolate swells 7- to 12-fold in less than 30 sec. uniformly in all three dimensions while croscarmellose swells 4- to 8-fold in less than 10 sec. in two dimensions leaving fibre length similar. This indicates that rate, force, and extent of swelling have an important role in disintegrants that work by swelling. Cross-linked PVP swells little (due to absence of cationogenic groups in the molecule) but returns to its original boundaries quickly after compression. Wicking or capillary action also is postulated to be a major factor in the ability of crosslinked PVP to work as superdisintegrant [30]. Gellan gum and xanthan gum also have extensive swelling properties for faster disintegration. Calcium silicate is a highly porous superdisintegrant which acts by wicking action. Cross-linked alginic acid is a hydrophilic colloidal substance with high sorption capacity and acts by swelling or wicking action [29].

Surface activity and micellar solubilization: Various surfactants like Polyglycolized glyceride (Labrasol), Tweens, Spans, Polyoxyethylene stearates and synthetic block copolymers like Poly (propylene oxide)-poly (ethylene oxide) – poly (propylene oxide), an example of poloxamers based micelles, Poly (beta-benzyl-Laspartate) -b- poly (ethylene oxide), Poly (caprolactone) –b- poly (ethylene oxide) etc are used as carrier for dissolution enhancement. Improvement of drug solubility by using the amphiphilic surfactants is due to lowering surface tension between drug and solvent, improvement of wetting characteristics and micellar solubilization of the drugs. Micelles are supramolecular self assemblies of macromolecules where unimers are held by non-covalent interactions. The core of the micelles solubilizes drugs whereas the corona/shell allows for their suspension in aqueous media [31]. Solid dispersions of albendazole using poloxamer 407 as surfactant were prepared and results revealed a requirement of 0.75% as minimum concentration of poloxamer for solubility enhancement due to surface active property and critical micellar concentration. The albendazole-poloxamer melt (1:5 ratios) showed 16.1 fold dissolution rate and 9.4 fold in dissolution efficiency as compared to that of pure drug due to solubilization effect in the diffusion layer [32].

By increasing porosity solid dispersion: Particles in solid dispersions have been found to have a higher degree of porosity. 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. The increased porosity of solid dispersion particles also hastens the drug release profile [33,34].

Combination and miscellaneous mechanisms: Quite often a solid dispersion does not entirely belong to any of previous classes. For example, in solid dispersion system, the drug can exist in amorphous state and the crystalline state in a carrier. Therefore, the observed increased in dissolution and absorption may be due to combination of several mechanisms.

THE STABILITY OF THE SOLID DISPERSIONS ON STORAGE: Numerous studies have observed changes to the dissolution rate on storage. However, again the mechanism responsible is not yet clear. This is arguably a direct result of the poor understanding of the dissolution rate mechanism or mechanisms; it is by definition difficult to understand why a dissolution profile changes with time if the factors determining the initial dissolution behaviour are not known. Clearly, such instability, though not universal, renders the dispersions unsuitable as products when it does occur. Physical instability of solid dispersions such as phase separation and subsequent crystallization may reduce the dissolution rate of the active ingredients. Since many solid dispersions contain amorphous or molecularly dispersed drugs, they are often susceptible to crystallization during storage [35]. Similarly, certain carriers may exist in thermodynamically unstable states in solid dispersions and undergo changes with time [36]. Andronis et al. reported that moisture might facilitate the crystallization of amorphous drugs, and for this reason solid dispersions should be
protected from moisture. Various studies reported reduced dissolution rates of drugs, incorporated into solid dispersions, upon ageing. Solid dispersion systems such as chlorpropamide-urea, indomethacin-polyethylene glycol 6000, and phenylbutazone-polyethylene glycol 6000 showed reduced dissolution rates of active ingredients on storage [35,37].

The dissolution behaviour of solid dispersions must remain unchanged during storage. The best way to guarantee this is by maintaining their physical state and molecular structure. For optimal stability of amorphous solid dispersions, the molecular mobility should be as low as possible. However, solid dispersions, partially or fully amorphous, are thermodynamically unstable. In solid dispersions containing crystalline particles, these particles form nuclei that can be the starting point for further crystallization. It has been shown that such solid dispersions show progressively poorer dissolution behaviour during storage [38,39]. In solid dispersions containing amorphous drug particles, the drug can crystallize, but a nucleation step is required prior to that. In homogeneous solid dispersions, the drug is molecularly dispersed, and crystallization requires another step. Before nucleation can occur, drug molecules have to migrate through the matrix. Therefore, physical degradation is determined by both diffusion and crystallization of drug molecules in the matrix. It should be noted that in this respect it is better to have a crystalline matrix, because diffusion in such a matrix is much slower. Physical changes are depicted in (Figure 4). The physical stability of amorphous solid dispersions should be related not only to crystallization of drug but to any change in molecular structure including the distribution of the drug. Moreover, the physical state of the matrix should be monitored, because changes therein are likely to alter the physical state of the drug and drug release as well.

**STRATEGIES TO AVOID DRUG RECRYSTALLIZATION:**

Recrystallization is the major disadvantage of solid dispersions. As amorphous systems, they are thermodynamically unstable and have the tendency to change to a more stable state under recrystallization. Molecular mobility is a key factor governing the stability of amorphous phases, because even at very high viscosity, below the glass transition temperature (Tg), there is enough mobility for an amorphous system to crystallize over pharmaceutically relevant time scales. Furthermore, it was postulated that crystallization above Tg would be governed by the configurational entropy, because this was a measure of the probability of molecules being in the appropriate conformation, and by the mobility, because this was related to the number of collisions per unit time. Several experiments have been conducted to understand the stabilization of solid dispersions. Recent studies observed very small reorientation motions in solid dispersions showing a detailed heterogeneity of solid dispersions and detecting the sub-glass transition beta-relaxation as well as alpha-relaxation, which may lead to nucleation and crystal growth. Molecular mobility of the amorphous system depends; not only on its composition, but also on the manufacturing process as stated by Bhugra et al. Solid dispersions exhibiting high conformational entropy and lower molecular mobility are more physically stable [40]. Polymers improve the physical stability of
amorphous drugs in solid dispersions by increasing the Tg of the miscible mixture, thereby reducing the molecular mobility at regular storage temperatures, or by interacting specifically with functional groups of the drugs. For a polymer to be effective in preventing crystallization, it has to be molecularly miscible with the drug. For complete miscibility, interactions between the two components are required. It is recognized that the majority of drugs contain hydrogen-bonding sites, consequently, several studies have shown the formation of ion-dipole interactions and intermolecular hydrogen bonding between drugs and polymers, and the disruption of the hydrogen bonding pattern characteristic to the drug crystalline structure. These lead to a higher miscibility and physical stability of the solid dispersions [41,42]. Specific drug polymer interactions were observed by Teberekidis et al., showing that interaction energies, electron density, and vibrational data revealed a stronger hydrogen bond of felodipine with PVP than with PEG, which was in agreement with the dissolution rates of the corresponding solid dispersions. Other studies have shown stabilization in systems where hydrogen-bonding interactions are not possible, because of the chemistry of the system. Vippagunta et al. concluded that fenofibrate does not exhibit specific interactions with PEG, independent of the number of hydrogen bonds donating groups presented. The same conclusion was achieved by Weuts et al. in the preparation of solid dispersions of loperamide with PVP K30 and PVP VA64, in which, hydrogen bonds were no absolute condition to avoid crystallization. Konno et al. determined the ability of three different polymers, PVP, HPMC and hydroxypropylmethylcellulose acetate succinate to stabilize amorphous felodipine, against crystallization. The three polymers inhibited crystallization of amorphous felodipine by reducing the nucleation rate. It was speculated that these polymers affect nucleation kinetics by increasing their kinetic barrier to nucleation, proportional to the polymer concentration and independent of the polymer physiochemical properties. The strategies to stabilize the solid dispersions against recrystallization strongly depend on the drug properties and a combination of different approaches appears to be the best strategy to overcome this drawback. Third generation solid dispersions intend to connect several strategies to overcome the drug recrystallization, which has been the major barrier to the solid dispersions marketing success [43].

UNMET NEEDS AND CHALLENGES:
In spite of almost several years of research on solid dispersions, their commercial application is limited. Only a few products have been marketed so far. Amongst these are:

Examples of clinically used Solid dispersions for oral administration:
- Griseofulvin: Gris-PEG®
- Nabilone: Cesamet®
- Nimodipine: Nimotop®
- Nilvadipine: Nivaldi®
- Itraconazole: Sporanox®
- Tacrolimus: Prograf®
- Troylitazone: Rezulin®
- Rosuvastatin calcium: Crestor®
- Liponavir/Ritonavir: Kaletra®
- Etravirine: Intelescence®
- Ritonavir: Norvir®
- Everolimus: Certican®
- Verapamil: Isoptin SR-E

The rare occurrence of solid dispersion based pharmaceutical dosage forms in the clinic are due to problems in scale-up of preparation methods, difficulties in dosage form development and poor and irreproducible physical and chemical stability of drug and matrix. Knowledge about the behaviour of solid dispersions during preparation, storage and dissolution can help to tackle these problems. A thorough understanding of processes that occur place on the molecular level is a prerequisite for rational and more efficient design of solid dispersions. However, development of solid dispersions has often been a trial-and-error approach. Unfortunately, most reports deal with a case, in which the authors used a specific matrix to accelerate the dissolution of a specific drug in-vitro or to show increased bioavailability. The limitations of this technology have been a drawback for the commercialization of solid dispersions. The limitations include:
1. Laborious and expensive methods of preparation,
2. Reproducibility of physiochemical characteristics,
3. Difficulty in incorporating into formulation of dosage forms,
4. Scale-up of manufacturing process, and
5. Stability of the drug and vehicle.

CONCLUSION:
Solid dispersions are one of the most attractive processes to improve drugs poor water solubility. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. In this article more emphasis given to the mechanisms by which solubility & dissolution rate occurs in solid dispersions. The possible mechanisms may be by particle size reduction and reduced agglomeration, amorphous structure replacing crystalline structure, improved local solubility and wettability, interactions of the drug with Carrier functional groups, complexation, Swelling and capillary action
of carrier, solubilization and by increasing porosity solid dispersion etc. similarly particular emphasis given on understanding stability issues.

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