An Outline On Improving Solubility And Dissolution Rate In Solid Dispersion Technique.

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Abstract:
To improve dissolution of poorly water-soluble drugs and thus enhancing their bioavailability, the dispersion of one or more active pharmaceutical ingredient in a carrier at solid state is used. This process is known as solid dispersion. It has engrossed significant interest as an efficient means of improving the dissolution rate. Solid dispersions are being employed frequently to improve bioavailability of poorly soluble molecules by enhancing the rate and extent of dissolution in drug product development process. This review discussed the methods for solubility enhancement of poorly soluble drugs and the mechanism by which solubility and dissolution rate enhancement occurs in solid dispersion. The present article also discuss about the manufacturing methods for solubility enhancement, its mechanism and outcome of various low soluble drugs, applications, limitations of the solid dispersions.
***Keywords*: Solid Dispersion, solubility enhancement mechanism, bioavailability.**

INTRODUCTION:

The number of pharmaceutical ingredients (APIs) having low aqueous solubility is currently one of the key issues restricting their biological application. According to estimation, upto 70% of APIs and novel therapeutic entities have poor water solubility, resulting in sluggish absorption and insufficient and unpredictable drug bioavailability [1]. When an active substance is given orally, it must first dissolve in stomach before it can pass through the GI tract's membranes and enter systemic circulation. As a result, a drug with low aqueous solubility will have limited absorption, while a drug with low membrane permeability will have permeation rate limited absorption [2]. As a result, enhancing the bioavailability of active agents by: (i) improving the solubility and dissolution profile of poorly water-soluble medications, and (ii) improving the permeability of drugs. The oral route is the most popular route of administration of the drug due to various reasons like its convenience, good patient acceptance and low medicine production costs [3]. Particle size reduction, salt formation, crystallization, and the use of surfactants and co-solvents are all methods for improving the dissolving capabilities of weakly aqueous-soluble medicines. However, these methods has its own set of constraints, such as the difficulty in forming salts for neutral and weakly acidic/basic medications, and the addition of surfactants/co-solvents leads in liquid formulations with known commercial viability and patient tolerance issues [4]. Furthermore, despite their higher permeability, the majority of potential NCEs are absorbed mostly in the intestine, with absorption dropping substantially after the ileum, showing that absorption is limited [5, 6].

As a result, these medications will have a limited bioavailability if they are not entirely released in this gastrointestinal area. Therefore, improving the water solubility of pharmaceuticals is primary contemporary difficulties facing the pharmaceutical industry [7, 8, 9]. It is feasible to increase bioavailability and prevent side effects by altering the drug release profile of these drugs [10, 11, 12]. Solid dispersions have proven to be most effective ways to enhance the release of low soluble medicines. These are molecular combinations of low aqueous soluble medicines in hydrophilic carriers that have a drug release profile dictated by the polymer characteristics. [13]. Solid dispersion technologies are utilised to improve the solubility properties and, as a result, the bioavailability of low water-soluble compounds. Water insoluble drugs have poor solubility in aqueous gastrointestinal fluids, resulting in insufficient bioavailability. Increased solubility and dissolving rate of the medicine in the gastro-intestinal fluids can improve bioavailability, especially for drugs categorized as Class II by the Biopharmaceutics Classification System. Solid dispersions (SDs) are a well-known approach for improving aqueous solubility and, as a result, oral bioavailability and drug dissolution rate.

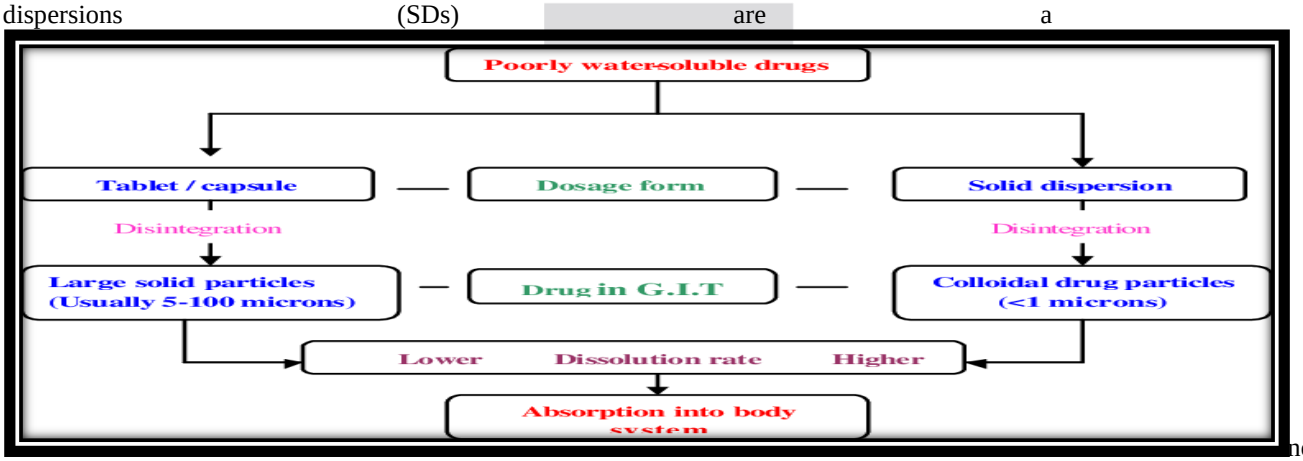

Figure 1: Benefits of a solid dispersion formulation over a conventional tablet or capsule formulation [14].

Applications:

1) The carrier in a solid dispersion plays an important role in enhancing particle wettability. Improved wettability leads to higher solubility, which improves bioavailability [15].
2) Drugs are shown as supersaturated solutions in solid dispersion, which are considered metastable polymorphic forms. Thus, presenting the drug in amorphous form and increases the solubility of the particles [16].
3) Solid dispersions are used for the improvement of the bioavailability of poorly water soluble drugs by enhance the dissolution of the drug [17].
4) Solid dispersions can be formulated as extended release dosage forms.
5) Solid dispersions are better than other particle size reduction methods for improving solubility because other size reduction techniques reduce the size to a limit of about 2-5 microns, which does not result in enough enhancement in drug solubility or drug release in the small intestine, and thus does not improve bioavailability [19].
6) The problems of solid powder such as less size of particles shows poor mechanical properties (include high adhesion and poor flow properties) can be overcome by the use of solid dispersion [19].

Limitations:

1) The polymers employed in solid dispersion can absorb moisture, resulting in phase separation, crystal formation, and the conversion of amorphous to crystalline state [17, 20].
2) Amorphous state of drug undergo crystallization and stability problems.
   Most polymers used in solid dispersions absorb moisture, which can cause phase separation, crystal development, or conversion from amorphous to crystalline state, during storage. As a result, the solubility and rate of dissolution may be reduced [21].
3) In the presence of moisture and high temperatures, solid dispersions may degrade.
4) Difficulty in understanding the physical structure of solid dispersions
5) Difficult to determine the shelf life of Solid dispersion.

Approaches for Solubility Enhancement of Poorly Soluble Drug: The techniques that have commonly been used to overcome drawbacks associated with poorly watersoluble drugs, in general includes [17, 18].

Physical Modifications	*Chemical Modifications*	*Others*
Particle size reduction	Salt Formation	Supercritical fluid method
Modification of the crystal habit.	Co-crystallization	Spray freezing into liquid and lyophillization
Complexation	Co-solvency	Hot melt extrusion
Solubilization by surfactants	Hydrotropic	Electrostatic spinning method

THE MECHANISM BY WHICH SOLUBILITY AND DISSOLUTION RATE ENHANCEMENT OCCURS IN SOLID DISPERSION:

Increased Solubility or Dissolution rate of Drug:

Using a variety of carriers may boost the drug's solubility. As a result, the carrier controls the release of the medication, which is independent of the drug's qualities. Additionally, certain systems exhibit release behaviour that is influenced by drug qualities rather than polymer features. The ability of the matrix carrier to enhance drug's local solubility and wettability is also linked to improved solubility dissolution profile of poorly soluble medicines. In his studies, Goldberg et al. investigated the by melting, fully combining, and hardening the mixture of chloramphenicol and urea for additional solubility and dissolution rate investigations, were able to determine the effect of the hydrophilic carrier urea on the solubility of chloramphenicol [21]. As the urea concentration increased from 0% (w/v) to just over 60% (w/v), the solubility of chloramphenicol in the presence of urea increased by more than seven times [21].

Sr.No	*Drug*	*Method of preparation*	*Conclusion*	*Reference .*
1.	(Diazepam and temazepam)	Solvent evaporation and fusion method	Diazepam and temazepam's solubility increases by around 3.5 and 2.5 times, respectively.	[22].
2.	Chloramphenicol	Melting method.	In the presence of urea, chloramphenicol's solubility increased by more than seven times.	[22].
3.	Glibencamide	Anti-solvent addition method	For the manufacture of drug ASD, the co-spray drying approach was used, which greatly improved solubility and resulted in the formation of Glibenclamide-rich amorphous droplets.	[23].

Reduced Particle size [24]:

Size reduction has been considered to be result of eutectic or solid solution formation. Additionally, it has been proposed that presenting the particles in the dissolution media as physically distinct entities may lessen aggregation. Many of the carriers employed in solid dispersion may have wetting capability, which can prevent agglomeration and enhance surface area by improving wetting. When a weakly soluble medication and a highly soluble carrier present in a eutectic mixture are exposed to water or digestive fluid, the highly soluble carrier dissolves, leaving the drug in a fine crystalline form that is easily dissolved. As can be determined from the Noyes-Whitney equation, greater surface area of insoluble chemical results in increased dissolution rate and thus increased oral absorption. Several solid dispersions were documented employing urea as a high water soluble carrier for poorly water soluble medicines such as sulfathiazole, paracetamol, and chloramphenicol. Compared to conventional formulations of the same medications, these solid dispersions exhibited faster release and improved bioavailability. The small particle sizes of the drug played important role in enhancing bioavailability [9,10]. Similarly, because the drug particle size is decreased to an absolute minimum as it is molecularly disseminated in the carrier in a solid solution, it dissolves faster than a eutectic mixture.

Formation of amorphous structure replacing crystalline structure:

Sr.No	*Drug and SD Method*	*Mechanism*	*Conclusion*	*Reference*
1.	Ball Milling (Curcumin)	Particle Size Reduction	The amorphous nature and self-formed micelles of Curcumin SD resulted in a significant improvement in pharmacokinetic behaviour, as illustrated by a 19-fold increase in oral bioavailability..	[25]
2.	Nobiletin	Hot melt extrusion	Amorphous solid dispersion had a greater drug concentration and a 7.5-fold faster dissolving rate. In accelerated stability circumstances, Nobiletin permeability was primarily increased and shown to be stable for up to 6 months.	[26]
3.	Licofelone	Cogrinding mixtures	Enhanced dissolution rate and decreased particle agglomeration	[27]

In the amorphous state, poorly water-soluble crystalline medicines have a higher solubility. The amorphous solids free energy is greater, has specific entropy, and specific volume when compared to corresponding crystalline materials from a thermodynamic standpoint. Amorphous pharmaceuticals have a higher energy state, have the lowest stability, and can be considered as cooled

liquids. Because the energy necessary to transfer a molecule from a crystal is larger than that required to transfer a molecule from a non-crystalline (amorphous) solid, non-crystalline (amorphous) solids have greater aqueous solubility than crystalline solids. This necessary energy is viewed as an obstacle to medication breakdown. The amorphous state of novobiocin, has ten times the solubility than that of the crystalline form. Chemicals are dissolved or molecularly dispersed in a polymeric carrier in solid molecular dispersions because they lack long-range crystalline structure. The drug is in an amorphous state, which has a higher kinetic solubility and dissolving rate than the crystalline drug (by several orders of magnitude). [7,14,15]. By solvent technique, solid molecular dispersions of diclofenac sodium, naproxen, and piroxicam were generated utilising Poly (2- hydroxyethylmethacrylate) hydrogel as carrier, resulting in the conversion of crystalline drug into amorphous form with enhanced water solubility(16).

Sr. No	***Drug***	***Method of preparation***	***Conclusion***	***Reference***
1.	(Atorvastatin calcium)	solvent evaporation method	The pharmacokinetic study indicated that the Cmax and AUC 0-8h of solid dispersion were improved nearly 2.87-fold and 1.71-fold.Solubility and dissolution rates were enhanced significantly compared with bulk drug	[28]
2.	Vemurafenib	(Micro-precipitated bulk powder technology)	Better dissolution results and a fivefold increase over HPMCAS-L ASD's crystalline form were revealed.	[26]

Complex formation:

In this solid dispersion, in solid state, a drug and an inert soluble carrier form a complex. The solubility and stability constant of the molecule or complex, as well as the drug's absorption rate, determine the drug's availability. It is proposed that the development of a water-soluble compound with a high dissolution constant can increase the dissolution rate and oral absorption. Carbamazepine/PEG 4000 and PEG 6000 solid dispersions, were made using the fusion method, which entails heating a physical mixture of carbamazepine and either PEG 4000 or PEG 6000 to a liquid state. According to dissolving tests, complex formation between carbamazepine and PEG 6000 may be to account for the improvement in solid dispersion dissolution. (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 are a type of solubilizing agent that, by inclusion, produce non-covalent, dynamic complexes with lipophilic molecules.

Sr.No	***Drug and SD Method***	***Mechanism***	***Conclusion***	***Reference No.***
1.	phenacetin (solvent evaporation)	Mechanical Particle size reduction.	The water-soluble hydroxypropylcellulose swells in water and is trapped in the water-insoluble ethylcellulose so that the release of the drug is slowed.This study shows that it is feasible to control PHE release from MC-CP solid dispersions by controlling the complex formation between MC and CP	[26]
2.	Carvedilol	Complexati on and kneading technique	The complexation constant of the medication and the carriers confirmed the formation of stable complexes. The carvedilol had been transformed to an amorphous state, according to solid state data.	[29]

Swelling and capillary action of carrier [24]:

Superdisintegrants like crospovidone, crosslinked polyvinylpyrrolidone etc can considerably used to improve dissolution rate of poorly water soluble drugs. swells 7- to 12-fold in less than 30 sec. Croscarmellose swells 4- to 8-fold in less than 10 seconds in two dimensions, retaining fibre length equal.This indicates that rate, force, and extent of swelling have an important role in disintegrants that work by swelling.

By improving porosity solid dispersion [24]:

The porosity of particles in solid dispersions has been discovered to be greater. Porosity increases with carrier qualities; eg Solid dispersions with linear polymers produce larger, more porous particles than those with reticular polymers, resulting in a faster dissolving rate.

Interactions of the drug with Carrier functional groups:

In addition to improving the drug's local solubility and wettability, carrier matrix also helps to improve the medication's aqueous solubility and dissolving rate through specific interactions with the drug. [19,20]

a) The intermolecular hydrogen bonding:
b) By elevating the Tg(transition temperature) of the solid dispersion mixtures:
c) Inhibited drug precipitation from supersaturated solution:
d) By formation of Metastable drug polymorphous with improved solubility and dissolution rate:

Sr.No	Drug and SD Method	Mechanism	Conclusion	Reference No.
1.	AZD0837	Hot melt extrusion	The molecule remained amorphous throughout the dissolving process and was kept in a super saturated and stable condition, according to the findings.	[30]
2.	Indomethacin (IND),	Hot melt extrusion	BCS Class II medication that benefits from the addition of a porous carrier to a ternary mixture and exhibits better dissolving capabilities than the drug-polymer binary mixture alone.	[26]

Sr.No	Drug and SD Method	Mechanism	Conclusion	Reference
1.	**Rivaroxaban**	Melt quenching approach	Physical stability of prepared ASDs was aided by intermolecular interactions with moisture.	[31]
2.	**Griseofulvin**	Freeze drying	Because of its high degree of supersaturation and high crystallisation propensity, there was a significant improvement in dissolving and oral absorption.	[32]
3.	**Itraconazole**	Solvent evaporation	In comparison to PVPVA, HPMCAS demonstrated excellent storage stability at RH levels greater than 60%, which can be attributed to its greater glass transition temperature and lower hydrophobicity.	[26]

4.	**Etoposide**	Solvent evaporation	According to experimental studies, the solubility of etoposide above the Critical micellar concentration (CMC) grew linearly, and the ASD permitted super saturation. By boosting P-gp saturation, a high level of super saturation via ASD increased the drug's in-vivo permeability.	[26]
5.	**Curcumin**	Solvent evaporation	Because of the hydrogen bond interaction between the curcumin and the polymer, HPMC E5 has a substantial impact on crystallisation inhibition and enhanced the permeability of the amorphous drug..	[32]

Conclusion:

Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. Various methods have been tried recently to overcome the limitation and make the preparation practically feasible. The problems involved in incorporating into formulation of dosage forms have been gradually resolved with the advent of alternative strategies.

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