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DISSOLUTION RATE ENHANCEMENT BY SOLID DISPERSION: A REVIEW

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ABSTRACT :

The endless challenge in the pharmaceutical industry is related to the maximum poor solubility of drugs. Several techniques have been developed to solve this problem, but none of them seem promising. Solid dispersion is a soluble technique primarily aimed at drug and polymer systems where the dispersion and stabilization of drugs is key to formulation development. Therefore, this technique is known as a very useful tool for improving the solubility properties of weak drugs in water, and much knowledge of solid dispersion has been accumulated in recent years, but its commercial application is limited. This Review summarizes our current understanding of the various methods of making solid dispersions by highlighting the fundamental aspects of this important technology. Therefore, in order to overcome such problems and increase the solubility, it is desirable to develop a solid dispersion having carriers having good solubility in water. Therefore, solid dispersion methods are an effective method for developing drug solvents that show poor solubility in water. This study shows the various aspects of solids dispersion type, rationality, benefits, limitations, and production methods for the commercialization of limited solids dispersion.

Keywords: Solid dispersions, hydrophilic, carrier, solubility, polymer, bioavailability.

INTRODUCTION :

With modern medical defects techniques, with progress in mixed chemistry and high productivity, fill the drug development pipelines with a large solution chemical institution (NCS). It is estimated that during the years, about 40% to 70% of the NCS is soluble in water, a large number of scientists participate in the invention of NCEN and the conversion rate is weak. Usually, drugs with the absorption of a solution in poor water from limited solubility and drug by absorbing weak membrane permeability, the limited blogging. Therefore, two drug research areas focus on improving oral environmental areas for active means include the promotion of solubility and melting water-soluble drugs and promote poor permeability drugs.[1,3]

The most important features, improvement of the account when increasing the level of the surface by reducing the size of the steel composite particles and / or improving the properties of surface hydration, to reduce the thickness of the boundary class, for the thickness of the boundary class, improves the boundary class, for the following and finally, but finally, but finally, but finally, At least, physiological disorders appeared to improve the melting of the drug. It is difficult to mention these options, change the changes in hydrodynamics in vivo and maintain the sink conditions on the permeability of mucous mucus in the boat, as well as the formation and size

of lumen fluids. Although some research efforts aimed at improving permeability with separate separate assistance, the results are not particularly encouraged. To overcome these issues, the best option for solving the solubility problem is to promote the solubility and the speed of solving the poor drugs that are constant in dispersion. So solid is one of the best techniques. To melt, male and more oral energy for poor water. Two pharmaceutical research areas focus on improving the active environmental environment, including solubility and melting rate in water and improve the permeability of other permeability. This narrative assessment focuses on the use of solid dispersion and improve water-soluble solutions in water and mouth more.[5,7,8]

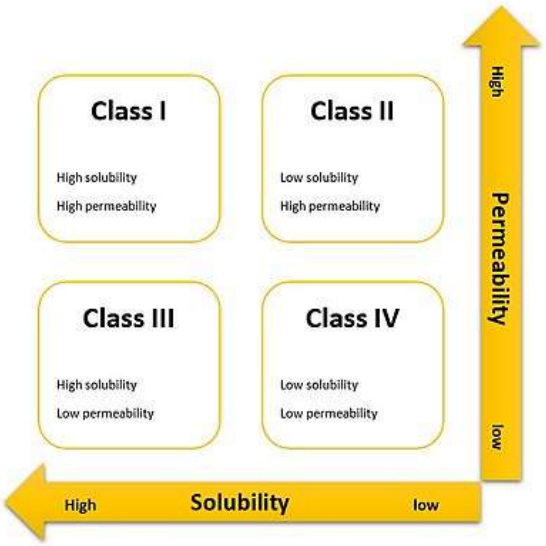

Fig No. 1: BCS Classification

TYPE OF SOLID DISPERSION: [3,11]

1) Eutectics
2) Amorphous solid solutions
3) Solid solution
    a) Continuous solid solution
    b) Discontinuous solid solution
    c) Substitutional solid solution
    d) Interstitial solid solution
4) Glass solution and suspension

1. **Eutectics Mixtures:** A simple eutectic mixture consists of two compounds that are perfectly miscible in the liquid state, but very limited in the solid state. This material is made by rapid freezing of a two-component melt that can be mixed completely in liquid form, but has little solid solution.
2. **Amorphous Precipitation:** This is similar to simple eutectic mixtures but only difference is that drug is precipitated out in an amorphous form.
3. **Solid solutions :** Solid solutions are similar to liquid solutions and consist of only one phase, regardless of the number of components. In the case of solid solutions, the particle size of the drug has been reduced to an absolute minimum. The molecular dimensions 7 and the rate of dissolution are determined by the rate of dissolution of the carrier. Classification according to miscibility (continuous solids versus discontinuous solids) or secondly, depending on the distribution of the solvent molecules in the solution (alternative, intermediate or amorphous).
    i. **Continuous Solid Solutions:** In a continuous solid solution, the components are miscible in all proportions. In theory, this means that the bond strength between the two components is stronger than the bond strength between the molecules of each component individually. Solids of this type have never been reported in the pharmaceutical world.
    ii. **Discontinuous Solid Solutions:** In the case of discontinuous mixed crystals (Figure 2), the solubility of each component in the other component is limited. For practical reasons, Goldberg et al.[11,12]

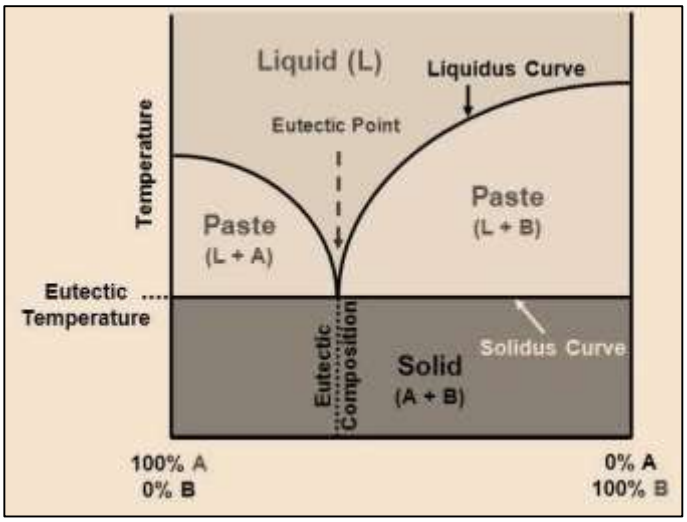

Figure 2: Phase diagram for a discontinuous solid Solution

iii. **Substitutional Solid Solutions:** An exchange is only possible if the size of the dissolved molecules is less than 15% or more than the size of the solvent molecules. Classical solids have a crystal structure (Figure 3) in which dissolved molecules either replace solvent molecules in the crystal lattice or are proportional to the intrinsic elements between solvent molecules.

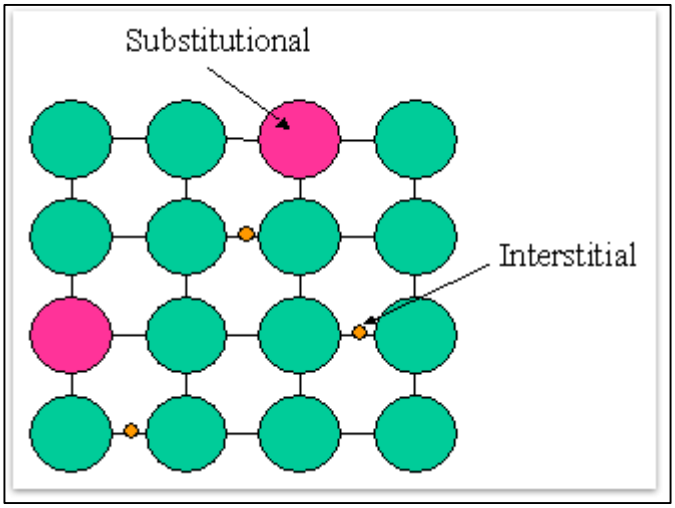

Figure 3: Substitutional crystalline solid solution.

iv. **Interstitial Solid Solutions:** In interstitial solids (Figure 3), dissolved molecules occupy the spaces between solvent molecules in the crystal lattice. The diameter of the dissolved molecule should be less than 0.59 times the molecular diameter of the solvent.

4. **Glass Solution and Suspensions:** Glass solutions are a homogeneous glass system in which a solute is dissolved in a glass container. Glass suspensions are mixtures in which deposited particles are suspended in a glass solvent. The energy of the tissue in solution and glass suspension is much lower.[15,16]

Methods of preparation of Solid Dispersion: Melting and solvent evaporation methods are the two major processes of preparing solid dispersions.

1. **Melting method:** In this method, the drug is dissolved in a suitable liquid solvent. The solution is then taken up directly in a melt of polyethylene glycol, which is obtained at a temperature below 70 ° C. without removing the liquid solvent. It has been shown that 5-10% (w / w) of the liquid composition can be incorporated into 6000 polyethylene glycol without significant loss of its solid properties. . - Wear the solution and immediately heat it to dissolve. The finished solid mass is ground and sifted. Fittingly, he made several changes by pouring a homogeneous melt in a thin layer onto a stainless steel plate and cooling it on the other side of the plate with a flow of air or water. In addition, supersaturation of a solute or drug in a system can be achieved by rapidly quenching the solute at a high temperature. Under these conditions, a temporary freezing process traps the soluble molecule in the solvent matrix. The quenching

process gives a much finer dispersion than crystals when used for eutectic mixtures. This process is also known as the fusion process. However, many substances, both drugs and carriers, can decompose or evaporate during the process due to high temperatures. One way to overcome these problems is to heat the mixture in a closed container or to melt it in vacuo or in the presence of an inert gas such as nitrogen to prevent oxidative decomposition of the drug or carrier.[17]

2. **Melt agglomeration method:** When it comes to the foreground, you can prepare hard tricks in a simple high Hyderson. It consists of a moleline career in heat in heat, the heat consists of the heat, the carrier and on the transition of the neck. To create a difficulty of the party's sharing, it is to keep these technical breeds, that is, to organize the techniques, which is part of. In addition, the strong-tacky point you have been prepared for your molecular point you can be easier, and because more of the heat is easier, and for more it. Particular type of productivity and particles of production and particles of shadows are important pieces in preparation. With the melting, the procedure can also cause pharmaceutical distribution in the next. The most important parts of the component of the component, while progress is completely completely completely, part of a melted bowl.
3. **Solvent evaporation method:** The solvent evaporation process involves dissolving the drug and carrier in a volatile solvent, which then evaporates. With this method, thermal decomposition of drugs or carriers can be prevented because small amounts of organic solvents evaporate. Basic process involved. To make a solid dispersion of this type, dissolve the drug and polymer carrier in a common solvent such as ethanol, chloroform, ethanol mixture and dichloromethane. The resulting films are usually crushed and ground.
4. **Kneading method:** A mixture of accurately weighed drug and carrier is wetted with solvent and kneaded thoroughly for some time in a glass mortar. The paste formed is dried and sieved. Ex. furosemide and crospovidone solid dispersion was prepared by this method [14]
5. **Co-Grinding method:** Accurately weighed pure drug powder and the carrier are physically mixed for some time using a blender at a specified speed. The mixture is then charged into the chamber of a vibration ball mill. A certain number of steel balls are added. The powder mixture is ground. Then the sample is collected and kept at room temperature in a screw capped glass vial until use. Ex. chlordiazepoxide and mannitol solid dispersion was prepared by this method.
6. **Co-precipitation method (co-evaporates):** Accurately weighed carrier is dissolved in water and drug in organic solvent. After complete dissolution, the aqueous solution of carrier is then poured into the organic solution of the drug. The solvents are then heated and evaporated. The dispersion is pulverized with pestle and mortar, sieved and dried. [15]
7. **Co-precipitation with supercritical fluid:** Conventional methods for the preparation of solid dispersions include either the fusion or solvent processes, with supercritical fluid processing (SCP) emerging as an alternative solvent- evaporation method for formulating co precipitates of smaller particle size, lower residual organic solvent and better flowability. A supercritical fluid exists as a single fluid phase above its critical temperature and pressure. Carbon dioxide is currently the most commonly used supercritical fluid because of its low critical temperature of carbon dioxide makes it attractive for processing heat labile pharmaceuticals. In the context of manufacturability, rate of cooling and solvent removal is stringently controlled, resulting in acceptable batch to batch variation. A precipitation vessel with a nominal capacity of 50ml was loaded with a 7ml solution of pure drug or drug: polymer (carbamazepine: polyethylene glycol) in acetone. The supercritical carbon dioxide was added from the bottom of the chamber and when the liquid phase expanded, the formed particles were retained in the vessel by a suitable filter. During the co-precipitate formation, the pressure was fixed at 70 bar and the temperature at 40^0C.[18]
8. **Spray drying method:** Accurately weighed amount of drug with lipid carrier are dissolved in methanol to obtain a clear solution. This solution is then spray dried using a laboratory scale dryer. The sample is stored over silica gel in a vacuum desiccators.
9. **Gel entrapment technique:** Carrier for example hydroxyl propyl methyl cellulose is dissolved in organic solvent (dichloromethane) to form a clear and transparent gel. Then drug for example carbamazepine is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by glass mortar and sieved.[19,20]

Table 1: Examples of different polymer used in solid dispersion.

Drug	Polymer	Preparation method
Terbinafine HCl	Polyethylene glycol 6000	Melting method
Carbamazepine	Soluplus, Eudragit EPO, HPMC 100, Kollidon VA64 and Affinisol HPMC HME 4000	Hot melt extrusion method
Curcumin	Hydroxy Propyl Methyl Cellulose Acetate Succinate (HPMCAS), Carboxy Methyl Cellulose Acetate Butyrate (CMCAB) and Cellulose Acetate Adipate propionate (CAAdp)	Spray drying technique
Azilsartan Medoxomil	Affinisol 716G (HPMCAS)	Solvent evaporation method
Felodipine	Soluplus	Solvent evaporation method
Simvastatin	Sodium Starch Glycolate (SSG) and Croscarmellose Sodium (CCS)	Coevaporation
Eplerenone	Soluplus	Lyophilization technique
Telmisartan	Poloxamer 407, PEG 6000	Solvent evaporation Method
Piroxicam	skimmed milk	Solvent evaporation technique
Carbamazepine	HPMC (Methocel® E3 LV and Methocel® E5 LV)	Hot melt extrusion

CHARACTERIZATION OF SOLID DISPERSION: [21,22]

a) **Detection Of Crystallinity In Solid Dispersions:** Many different molecular structures of the drug are found in solid dispersions in the matrix. Several attempts have been made to confirm the molecular arrangement in solid dispersion. However, most of the efforts have been made to distinguish between amorphous and crystalline materials. There are several techniques for doing this that indicate the amount of crystalline material in the dispersion. The amount of amorphous material is never measured directly, but is usually determined from the amount of crystalline material in the sample. It should be noted that evaluation of crystallization as a method of quantifying an amorphous drug does not indicate whether the drug is in the form of amorphous drug particles or in the form of molecularly dispersed particles.

b) **Techniques for Degree Of Crystallinity:** A wide variety of materials can be qualitatively detected with powder X-ray diffraction. Sharper diffraction peaks indicate the presence of more crystalline material. Newly built X-ray machines are semi-quantitative. Infrared (IR) spectroscopy can be used to detect differences in the energy distribution of drug-matrix interactions. Sharp vibration bands indicate crystallization. Fourier Infrared Spectroscopy (FTIR) was used to accurately detect 1 to 99% crystals in a pure material. But qualitative proof was only possible in solid dispersion. Water vapor adsorption can be used to distinguish between amorphous and crystalline materials at different humidity levels, and this method requires accurate data on the moisture content of fully crystallized and fully amorphous samples. An accurate isothermal measurement measures the crystallization energy of an amorphous substance that is heated above the glass transition temperature (Tg). However, this technique has some limitations. First, this technique can only be used if physical stability occurs only during the crystallization of the measurement. Second, it must be assumed that all amorphous materials will crystallize. Third, in a binary mixture of two amorphous compounds, it is difficult to distinguish between the crystallization energies of the drug and the matrix. The melting calorimeter measures the solubility energy, which depends on the crystallization of the sample. The dissolution of crystalline material is usually endothermic while the dissolution of amorphous material is exothermic. Macroscopic techniques for measuring the various mechanical properties of amorphous and crystalline materials can indicate the degree of crystallization. Density measurement and dynamic mechanical analysis (DMA) determine the modulus of elasticity and viscosity and are thus influenced by the degree of crystallization. However, these techniques also require knowledge of how these properties are added to closely related binary solids. The most common method

of detecting the amount of crystalline material is differential calorimetry (DSC). With DSC, samples are heated at a constant heating rate and the amount of energy required for this is determined. DSC can be used to detect the temperature at which thermal events occur. Thermal events can include transfer from glass to rubber, recrystallization, melting, or degradation. In addition, the dissolution and recrystallization energies can be measured. Fusion energy can be used to reveal the amount of crystalline material. The recrystallization energy can probably be used to calculate the amount of amorphous material added so that all of the amorphous material becomes crystalline. If amorphous material crystallizes during DSC measurements, information is obtained about the crystallization kinetics and the physical stability of the amorphous sample. To determine the amount of crystalline material, measurements must be made before crystallization of the amorphous material begins. In some cases this can be demonstrated by a high scanning speed.[26]

c) **Detection Of Molecular Structure In Amorphous Solid Dispersions:** The dispersion properties of the solid are strongly influenced by the uniformity of the active ingredient distribution in the matrix. The stability and solubility behavior can for solid dispersions without crystalline active ingredient particles, i. H. solid dispersions of types V and VI or for types II and III, may be different. But not only the knowledge of the physical state (crystalline or amorphous) is important. The distribution of the drug as amorphous or crystalline particles or discrete particles of the drug is also closely related to the properties of the solid dispersion. However, very few studies focus on the distinction between amorphous compact particles versus molecular distributions or homogeneous mixtures.

i. Confocal Raman Spectroscopy was used to measure the homogeneity of the solid mixture of ibuprofen in PVP. It was described that a standard deviation in drug content smaller than 10% was indicative of homogeneous distribution. Because of the pixel size of 2 mcm3, uncertainty remains about the presence of nano-sized amorphous drug particles.

ii. Using IR or FTIR, the extent of interactions between drug and matrix can be measured. The interactions are indicative for the mode of incorporation of the drug, because separately dispersed drug molecules will have more drug-matrix interactions than when the drug is present in amorphous clusters or other multi-molecule arrangements.

iii. Temperature Modulated Differential Scanning Calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated.

USES OF SOLID DIPERSION: [27,28]

- Solid dispersion improves dissolvability in water of a poorly water soluble drug in a pharmaceutical composition.
- The drug is formulated with a water carrier (e.g. polyethylene glycol) as a solid dispersant to increase solubility and solubility in water. A super-disintegrator (e.g. sodium crosscarmellose) is then used in the tablet formulation to achieve rapid disintegration of the tablets produced by the wet granulation process. Therefore, a solid dispersion is used in the manufacture of oral tablets that disintegrate quickly. These fast-disintegrating pills can be used as an alternative to injection therapy, allowing the patient to self-medicate without water.
- As a formulation medium to facilitate clinical safety and initial clinical studies for new chemicals with low water solubility. A compound with very little or no solubility in water can significantly limit the dose or exposure range of a drug that can be achieved in clinical and clinical trials when formulated using conventional methods. In these cases, solid dispersion formulas can be a means of quickly assessing the safety and effectiveness of a drug that would otherwise be difficult to obtain.
- To optimize immunosuppressive therapy for lung transplant recipients, a dry powder formulation consisting of a solid dispersant (e.g. cyclosporin A) is prepared for inhalation. It can prevent many problems.

BENEFITS OF SOLID DISPERSION SYSTEM: Solid dispersion systems can provide numerous additional benefits to oral drug therapy beyond improving bioavailability such as:

- Solid dispersion formulations were demonstrated to accelerate the onset of action for drugs such as Nonsteroidal anti inflammatory drugs where immediacy of action is crucial to relieving acute pain and inflammation.
- For anti-cancer drugs in particular, solid dispersion systems were shown to provide bioavailable oral dosage forms which could be substituted for standard injections to improve patient comfort and compliance.
- Solid dispersion systems were also found to reduce food effect on drug absorption, thus increasing the convenience of drug therapy as the need for some drugs to be taken with food was eliminated.
- It was also demonstrated that a solid dispersion- based dosage form allowed for greater drug loading per dose and improved stability over a soft gelatin capsule formulation which thereby improved the convenience of drug therapy by reducing the dosing regime and eliminating the need for refrigerated storage.
- Additionally, the improved absorption efficiency demonstrated for solid dispersion systems allows for a reduction in the content of active agent per dose, thus decreasing the cost associated with these drug therapies.
- Finally it was demonstrated the solid dispersion systems can be produced utilizing functional carriers that offer the added benefit of targeting the release of highly soluble forms of poorly water soluble drugs to an optimum site for absorption.
- These benefits demonstrate the current contributions and future potential of solid dispersion systems toward improving drug therapies for a variety of important medical conditions whose treatment involves poorly water soluble drug.[29]

APPLICATIONS OF SOLID DISPERSIONS :

1. To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailabilty.
2. To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerisation, photo oxidation and other decomposition procedures.
3. To reduce side effect of certain drugs.
4. Masking of unpleasant taste and smell of drugs.
5. Improvement of drug release from ointment, creams and gels.
6. To avoid undesirable incompatibilities.
7. To obtain a homogeneous distribution of a small amount of drug in solid state.
8. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
9. To formulate a fast release primary dose in a sustained released dosage form.
10. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
11. To reduce pre systemic inactivation of drugs like morphine and progesterone. [30]

LIMITATIONS: Solid dispersion is usually prepared with synthetic artificial polymers such as polyvinyl pylveymer polymer, mannitol or polyethylene glycol. These polymers show superior results in promoting drug solutions, but the amount of these polymers is relatively large, about 1: 2 to 1: 8 (drug / polymer). In some comparable experiments, polyvinyl pylvedon and polyethylene glycol for the first time in the media (due to high water melting) puts the drug in offline conditions. Such a situation, although this drug has been controlled or endangered, can not be able to provide moisturizing pharmaceutical molecules. In such cases, there may be quick organs for unpredictable drugs to the most sustainable crystal situation in having a small amount of paintings such as water. [31,32]

The instability of solid dispersion systems results in low melting speed due to the number. for example. Solid dispersion systems can be evaluated with physiotherapy, such as crushing and aging. In melting drugs and polyethylene glycol, solids can be irreplaceable, adhesive, width or glass after cooling. Crushing resulted in the conversion of non-controversial drugs in constant dispersion to crystal formats. Solid diffraction is a high power entry. Separate phase, crystalline growth or unpleasant conversion in crystal form during storage of melting reduction and soluble content and lead to change in oral availability.

RECENT ADVANCEMENT: SE attaches particular importance to the automated emulsification system. Commercial development of solid dispersion actives through advances in filling solid dispersions directly into hard gelatin capsules and the availability of surfactants and emulsifiers themselves. To facilitate manufacture, the manufacturing vector must be able to fill hard gelatin capsules with liquid as it dissolves. The melting point should not exceed 70 ° C (as the maximum acceptable temperature for hard gelatin capsules is 70 ° C). [33]

MARKETED PREPARATIONS OF SOLID DISPERSION:

- ✓ Solid dispersion of VALDECOXIB (NSAID) using PVP by Solvent Evaporation method.
- ✓ Solid dispersion of TERBINAFINE HYDROCHLORIDE (synthetic allyl amine derivative, broad spectrum antifungal activity when used orally/topically) using Polyvinyl Pyrollidone K30 by Solvent Evaporation method .
- ✓ Surface Solid Dispersion Of GLIMEPIRIDE (third generation sulphonylurea, antidiabetic drug which stimulates insulin release) using Crospovidone, Pregelatinised starch, Croscarmellose sodium and Avicel PH 101 by Solvent Evaporation method.

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