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A Review: Solubility Enhancement of Poorly Water Soluble Drug

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ABSTRACT :
The solubility characteristics of pharmaceuticals continue to be one of the most challenging aspects in the development of formulations. With the introduction of combinatorial chemistry and high throughput screening, there has been a significant increase in the number of compounds that exhibit poor water solubility. Approximately 40-45% of newly discovered chemical entities fail to make it to the market due to their inadequate solubility in water. This limitation in solubility impacts the bioavailability of drugs, necessitating the need for solubility enhancement strategies. Among these strategies, solid dispersions have garnered significant attention as an effective approach to improve the dissolution rate and subsequently the bioavailability of drugs. Consequently, the application of this technique has become a crucial tactic for pharmaceutical companies. Nevertheless, a comprehensive understanding of solid dispersions is essential for the successful scale-up of formulations, from laboratory to industrial scale. Several methods are available to address the solubility challenges of new drugs, with solid dispersion emerging as a promising option. Typically, a solid dispersion consists of two main components - the drug itself and a polymer matrix. Therefore, this approach holds great potential for the future commercialization of many poorly water-soluble and water-insoluble drugs in solid dispersion formulations. This article provides an overview of the various preparation techniques, carriers employed, advantages, and limitations of solid dispersions, while also highlighting some of the recent advancements in this field.

Keywords: Bioavailability, Solid Dispersion, Hydrophilic carriers, Polyethyleneglycol.

I. INTRODUCTION

The oral route is the most common andfavored route for drug administration due to its convenience and ease to ingestion. When the drug administered orally in solid dosage form like tablet, capsule; firstly it undergo dissolution in the GI fluids before absorption. For various poorly soluble drugs bioavailability is an limit by the dissolution rate. In the development of pharmaceutical dosage form, many problems arise due to the poor watersoluble drugs. Therapeutic efficacy of a drug depends upon the solubility can be the defined as a qualitatively as well as quantitatively. Quantitatively solubility can be known as the solute concentration in a saturated solution at a particular temperature. Where as qualitative it can be defined as thespontaneous interaction of two substances to produces a homogenous molecular dispersion.[1,2]

The absorption of drug from soliddosage forms generally occurs by two process as follow:

- In vitro drug dissolution to produce a solution.
- Dissolved drug was transport of the across the gastrointestinal membrane.

In the Biopharmaceutical Classification Systemdrugs are classifying on the basis of aqueous solubility and membrane permeability. Many poor water soluble drugs come to the BCS classes of II and IV.The process of drug absorption from oral route for such types of drugs is occurs via dissolution rate limiting step. So that it's essential to highly dissolution of these drugs. Before studying the many techniques to increase dissolution it is importance to understand the dissolution process. In the dissolution process solid substance(Active Pharmaceutical Ingredients) comes into the solution. The solubility of drug is directly proportional toit's dissolution rate as per Noyes-Whitney equation and hence solubility is an important parameter of a drug for the determination of it's absorption and dissolution rate hence it's bioavailability. Parameter such as particle size, salt form, solubility, wetting, complexation, polymorphism, etc. affect the rate of dissolution and hence can be used to increase solubility of poorly water soluble drug.[3,4]

The aqueous solubility of a drug is a critical factor to evaluate the oral bioavailability of orally administered poorly water soluble drugs. The modification into the dissolution profile of these

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lipophilic drug molecules without change in the molecular structure can be the possible by various technique to the enhancement of aqueous solubility of drug candidates. Some of these techniques include particle size reduction, solid dispersion, crystal modification, lipid based system, pH modification, use of surfactant of delivery in dosage form. To highly solubility used of hydrophobic carbohydrates, surfactant, super disintegrants and polymers, hydroxypropyl methylcellulose, mannitol, etc.[5-7]

Drug compound poorly soluble is an major difficulties in to the drug business, and the lowering particle size is an easy an effective solution. Recently, the more active pharmaceutical ingredients are poor solubility, which in the difficult in drug research and development. These are problems to find produce because scientists do not fully understand the more chemical,physiological, and metabolic processes that occurs between administration and absorption and the impact bioavailability.[8,9]

The BCS category medicine in class II based on the less solubility and high penetration in the human body. About 70% of BCS II medicines have less solubility and high permeability. Maximum of drugs are presents in second class of drug which is poor soluble drug. BCS class of drug divided into four categories-high solubility and high permeability, high solubility and less permeability, less solubility and less permeability. Solubility of drug can be the increase by the increasing the dissolution rate. Improved into the dissolution rate by increase the surface area through the particle size reduce of poor soluble drugs results into the poor bioavailability.[10]

Solubility characterized effective role into the pharmaceutical dosage form. Solubility may be known as solute dissolve in particular solvent at certain temperature. Other than 90% of drug administered as well as orally drug absorption, bioavailability and pharmacokinetic profile are dependent on the solubility parameter. Good solubility shows the good dissolution and absorption poorly soluble and dissolution profile creates the difficulties in the pharmaceutical industries for development of dosage form. Many solubilization techniques are available for increase solubility as well as permeability like micronization, coacervation, complexation solid dispersion and co-solvent.[11-13]

IMPORTANCE OF SOLUBILITY:[14]

- The oral ingestion is the most convenient and commonly employed route of drug delivery (easy administration, high patient compliance, cost effectiveness, at least sterility containers and flexibility in design of dosage form).
- But, the major challenge with the design of oral dosage form lies with in the poor bioavailability. The cause of low oral bioavailability in poor solubility and low permeability.
- The low aqueous solubility in the major difficulties in encountered is formulation development of new chemical entities as well as generic development.
- The any drug to be absorbed must the present in the form of aqueous solution at the site of absorption. More than 40% of New Chemical Entity (NCE) developed in the pharmaceutical industry are the insoluble in water. for the reason, the difficult of solubility in one of the major challenges of formulation chemists.

APPROACHES:

- **PARTICLE SIZE REDUCTION:**[15-17]

The solubility of drug is often constitutionally related to drug particle size; as a particle become a small, the surface area to volume ratio increase. The larger surface area allow greater interconnection with the solvent which cause an rising in solubility.

Conventional method of particle size reduction, such as comminute and spray drying, rely upon mechanical stress to disarticulate the active compound. Particle size reduction is thus permitting an effective, clone, and economic means of solubility enhancement. However, the mechanical forces constitutional to comminute, such as milling and grinding, often impart notable amount of physical stress upon the drug product which may persuade degradation. The thermal stress which may appear during comminute and spray drying is also a concern when processing heat sensitive or unstable active compound. Using conventional approaches for nearly insoluble drugs may not be able to increase the solubility up to desired level.

Advantages:

- The uniform particle with narrow particle size distribution and high in the surface area.

Limitations:

- High energy steps, causes suspension in drug crystal lattice and in the final product amorphous or disordered region is present.
- Disordered or Amorphous region are the

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thermodynamically unstable and upon storage in the hot and humidity condition they are susceptible to the recrystallization.

- **PH ADJUSTMENT:**[18-21]

A drug that is poor water soluble may potentially dissolve in water if the pH is changed. The buffer capacity and tolerability of the selected pH are important to considered when solubility using this method. Excipients that increase the environmental pH within the dosage form to a range higher than pKa of weekly acidic drugs increase the solubility of that drug, those excipients that function as alkalizing agents may increase the solubility of weekly basic drugs. It can be used on crystalline and lipophilic poorly soluble substances as well.

Advantages:

- Analysis and formulation both are simple.
- Small amount of chemical are used, making it ideal for high-throughput testing.

Limitation:

- Tolerance and toxicity the both local and systemic associate with the non physiological pH and severe Ph.
- The dilute in aqueous fluid with a pH less then compound solubility, there is a change of precipitation. This can create emboli intravenously, and it also cause variability when taken oral.

- **USE OF SURFACTANT:**[22,23]

Permeability and dissolution rate can be enlarged be surfactant. Absorption rate also be enlarge due to increasing of particle size. Mechanism include firstly permeability and then penetration of solvent in the particles of drug. Solubility of much poorly water soluble anti-microbial drugs can be increasing use of surfactant. Three types of surfactant;cationic,anionic and non-ionic. Anionic and cationic select over the non-ionic surfactant. It act as good solubility agent.

Advantages:

- Reduces IFT :- the enhance aquifer remediation of the petroleum hydrocarbon contamination in the soil and bedrock aquifer.

Limitations:

- Expensive :- the absorption into the rock surface, formulation of the micelle at the highest concentration.

- **CO-SOLVENCY:**[24-26]

The solubility of poorly water soluble drug can be increased by mixed with a certain amount of water miscible solvent in which the drug is freely soluble. This process is also called as co-solvency and the solvent that are used in amalgamation are known co-solvent. The co-solvent system reduce the interfacial tension during the aqueous solution and hydrophobic solute. It is also called as solvent blending. The addition of organic co-solvent into the water there is a dramatic change in the solubility of drugs.

Advantages:

- Has large soluble capacity of poorly soluble drugs.

Limitation:

- Toxicity and tolerability related with the level of solvent administration to be considered.
- The drugs are exceedingly insoluble in water and do not quickly re-dissolve after precipitation from the co-solvent mixture may have a potential risk for embolism and local adverse effect at the site of injection.

- **SOLID DISPERSION:**[27-31]

Solid dispersion method is the most essential for improve the solubility of poorly water soluble drugs and also improving bioavailability by the physical modification. They are classify into six types; eutectic mixture, solid solution, glass suspension, amorphous precipitates, complex and combination. solid dispersion increase the solubility and dissolution rate by reduce the porosity. Solid dispersion prepared by the solvent evaporation, co grinding, hot melt extrusion and supercritical method and etc. Select the polymer is the essential step in creating solid dispersion. Select the polymer based on various consideration, The glass transition temperature, hydroscopic, solubilization, and the solid capacity of solutions.

Advantages:

- ✓ Improve bioavailability in water of a poorly water soluble drug in a pharmaceutical.
- ✓ Increase absorption rate of drug.
- ✓ Avoid degradation or decomposition of drugs.
- ✓ To improve porosity of drug.
- ✓ To prepared rapid disintegration oral tablets.

Limitations:

- Instability of solid dispersion.

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- **CHARACTERIZATION:**[32,33]

Solid dispersion can be study by the more process; FTIR spectroscopy-ray diffraction., Electron microscopy, Dissolution rate, Differential scanning colorimetric (DSC), Differential thermal analysis (DTA), Phase solubility study, Production yield, Drug content, Powder X-ray diffraction, etc.

- **Importance of solid dispersion:**[34,35]

1. To increase the solubility of poorly soluble drugs they are increase the dissolution rate, absorption and bioavailability.
2. To stabilize on stable drugs against hydrolysis, oxidation, recrimination, isomerization, photo-oxidation and the other decomposition procedures.
3. Improvement of the drug release from ointment, creams, and gels.
4. To obtain a homogeneous distribution of the small amount of drug in the solid state.
5. To dispense liquid (up to 10%) or gaseous compound in the solid dosage.

II. CONCLUSION:

The enhancement of solubility of drugs that are poorly soluble in water remains a highly challenging aspect in the field of drug development. The process of solubilizing a drug is crucial in determining the rate at which it is absorbed orally, and subsequently impacts the drug's absorption in vivo. The solubility problem encountered with many drugs adversely affects their bioavailability, thus necessitating the enhancement of solubility. Solid dispersions have emerged as a highly appealing method to improve the poor water solubility of drugs. The utilization of various solubility enhancers such as water-soluble carriers, co-solvents, surfactants, and super disintegrants through the solid dispersion approach (fusion method and solvent evaporation method) aids in the enhancement of solubility. These methods significantly contribute to the improvement of bioavailability and bioequivalence.

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