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SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUGS: A REVIEW

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ABSTRACT: Many water insoluble drugs present in class 2 and it is characterized by low solubility and high permeability. Solubility of drug can be enhancing by increasing of dissolution rate. Many solubilization techniques are available for increasing of solubility as well as permeability like micronization, coacervation, complexation, solid dispersion, and cosolvent. Poorly soluble and dissolution profile creates problem in pharmaceutical industry for development of dosage form. Solid dispersions are the most attractive method for improving of bioavailability of poorly water soluble drugs. Reduction of particle size leads to increase in wettability and porosity of drugs. Porosity and wettability improves the solubility and dissolution rate.


INTRODUCTION: Biopharmaceutical Classification System (BCS) based on its solubility and permeability. Bioavailability of drug affected by three major factor like solubility, permeability and dissolution. Bioavailability of drug may be defined as the rate and extent of drug which is present in systemic circulation at particular period of time.

Majority of drugs are present in second class of drug which is poorly soluble drug. BCS class of drug divided in to four categories-high solubility and high permeability, low solubility and high permeability, high solubility and low permeability, low solubility and low permeability. Solubility of drug can be increase by increasing of dissolution rate.

Improvement in dissolution rate by increasing the surface area through particle size reduction of poorly soluble drugs results in poor bioavailability¹. Poorly soluble drug creates the problem in bioavailability. In this case solid dispersion method is widely used. Solid dispersion method is defined as the one or more solid particle dispersed in inert matrix by fusion, Solvent or melting method².

Solubility plays effective role in pharmaceutical dosage form. Solubility may be defined as solute dissolve in particular solvent at certain temperature. More than 90% of drug administered as orally drug absorption, bioavailability and pharmacokinetic profile are dependent on solubility parameter. Good solubility shows the good dissolution and absorption³.

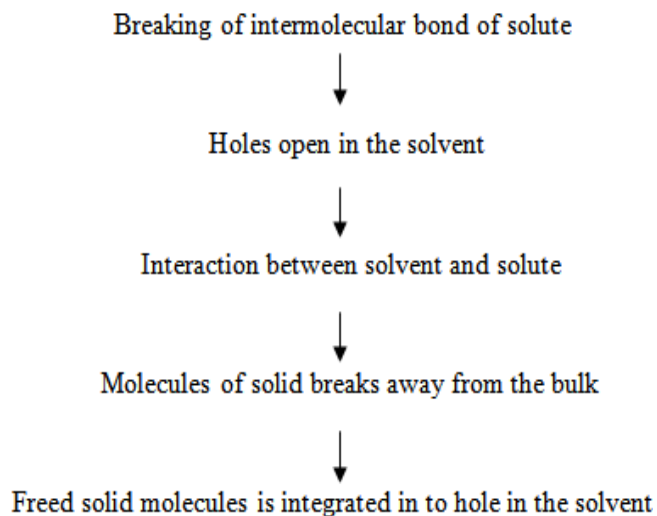
Poorly soluble and dissolution profile creates problem in pharmaceutical industry for development of dosage form. Many solubilization techniques are available for increasing of solubility as well as permeability like micronization, coacervation, complexation solid dispersion and co-solvent.

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Solubility can be also enhanced by alteration in molecular level of physical form of drug⁴. Solid dispersions are the most attractive method for improving of bioavailability of poorly water soluble drugs. Solid dispersions are defined as the dispersion of one or more active substance in matrix at solid state by different method like-fusion or melting solvent method. Solid dispersions are classified in to six category; solid solutions, eutectic mixture, glass suspensions, precipitations, complexes and combinations of above five.

Reduction of particle size due to solid dispersions increases the wettability and porosity of drugs. Porosity and wettability improves the solubility and dissolution rate. Many manufacturing methods are available in literature; fusion method, solvent evaporation method, hot melting extrusion, co-grinding method, supercritical method etc. Aqueous solubility is major problem for achieving of good bioavailability. To overcome this problem many methods has been investigate in drug development research⁵.

PROCESS OF SOLUBILISATION⁶:



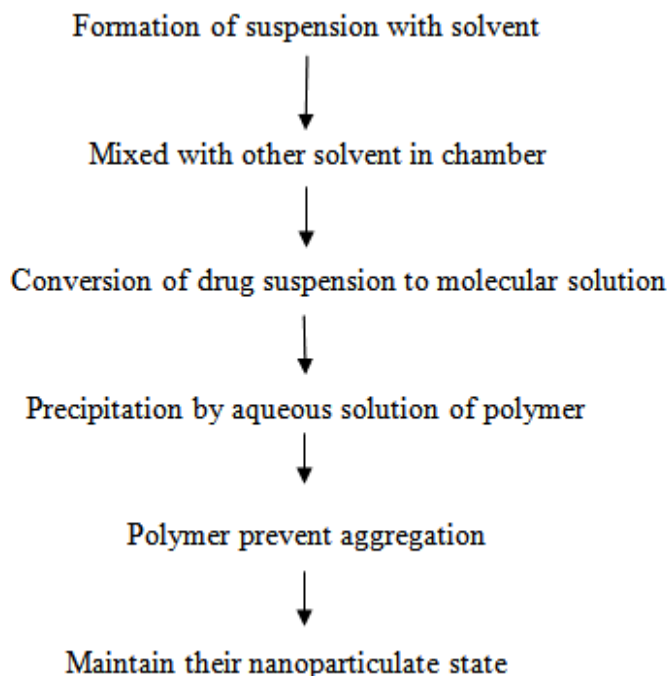
Solubility enhancement techniques:

1. **Nanonization:** Nanoemulsions present large o/w interfacial areas and radically low interfacial tensions. They have greater capacity to solubilize than simple solution of micelles. Being thermodynamically stable, Nanoemulsions hold an edge over unstable dispersions.

The ability of o/w Nanoemulsions to integrate hydrophobic drugs into the oil phase lends them more solubility. As per the literature, Nanoemulsions have made plasma concentration and bioavailability profiles of drugs more consistent. Nanonization are used for conversion of drug particle in to nano-crystals having the size of 200-600nm.

2. **Supercritical fluid recrystallization (SCF):** Those fluids have temperature and pressure greater than its critical temperature and pressure so as properties of gas and liquid. Example of supercritical fluid is carbon dioxide. These are compressible at temperature and pressure so as allow for alteration in density and mass transfer. By this method drugs are solubilize. It can be re-crystallized with reduction of particle size of pharmaceutical chemicals⁷.
3. **Use of surfactant:** Permeability and dissolution rate can be increased be surfactant. Absorption rate also be enhance due to increasing of particle size. Mechanism involves firstly wettability and then penetration of solvent in the particles of drug. Solubility of much poorly water soluble anti-microbial drugs can be increased by use of surfactant. Surfactant are three types; anionic, cationic and non-ionic. Anionic and cationic select over the non-ionic surfactant. It acts as good solubilizing agent.
4. **Evaporative precipitation:** This method involves phase separation for nucleation and growth of micro or nano particle occurs. For this technique low boiling point of solvents are selected and sufficient amount of drug is added after that solution is passed and pumped through tube which is heated under suitable temperature. Heated solution sprayed through atomizing nozzle and surfactants are added for reduction of particle size. Fine particles are generated which improve the solubility and permeability of drug⁸.
5. **Micronization:** Reduction of particle size occur so as increase of surface area which increase the dissolution rate and bioavailability of drug .The particle size after micronization is 1-10 microns. This method involves spray drying and attrition method.

6. **Sonocrystallisation:** This method used for the reduction of particle size by use of ultrasound and liquid solvent. It is a new method for increasing of solubility⁹.
7. **Nanomorph technology:** In this method crystalline state of less water soluble drugs change in to amorphous state^{10,11}.

Process:

8. **Homogenization:** Drug particles are reduced under high pressure and high velocity by applying of shear force. By this phenomenon drugs particles get dispersed. Homogenization depends on pressure and nature of drug.¹²
9. **Solid dispersion:** Chiou and Riegelman dispersions as “the dispersion of one or more active Ingredients in an inert excipient or matrix, where the active ingredients could exist in finely crystalline, solubilize, or amorphous stat”.

Solid dispersion is the most important method for improving of solubility of poorly water soluble drugs. It also increases the bioavailability by physical modification. Solid dispersion classified in to six categories; solid solution, eutectic mixtures, glass suspensions, amorphous precipitates, complex and above combinations.

Solid dispersion improves the solubility and dissolution rate by reducing of wettability and porosity. Solid dispersion can be prepared by solvent evaporation, hot melt extrusion, co-grinding and supercritical method and etc.¹³.

Classification of Solid Dispersion:

- a. First generation
 - Crystalline carriers
- b. Second generation
 - Polymeric carriers
- c. Third generation
 - Mixture of surfactant and polymers
 - Surfactants
 - Mixtures of polymers¹⁴

Preparation of Solid Dispersion: Solvent method used drugs and carriers but both should be soluble in solvent. Solvent can be evaporate by spray drying or freeze drying method. PVP-K30 can be used as carrier in ratio of 1:1,1:2,1:3,1:4 respectively dissolved in organic solvent. Solvent evaporate by heating. Remaining solid dispersed was kept in refrigerator and solidified, after that it powdered in mortar and then sieved. It stored as dried form¹⁵.

Advantage of Solid Dispersion:

1. Uniform distribution of drug molecules in to carriers is achieved by solid dispersions method.
2. It increases the wettability of drug molecules which improve the solubility of drugs.
3. Many carriers used in solid dispersion method like urea, colic acid, cellulose and bile salt are create the surface activity.
4. Carriers of solid dispersion have high porosity which improves the solubility by faster release of drug¹⁶.

Carriers used in Solid Dispersion:

1. **Polyethylene glycol (PEG):** PEG is used as carrier for preparation of solid dispersion of many drugs. Molecular weight of PEG is 1500-20000 generally used. When molecular weight of PEG is increased then viscosity is also increased which adjust the consistency of solid dispersion. PEG is water and many organic solvent soluble which are used in solvent evaporation method. PEG has low melting point below at 65°C which can be utilized for fusion method. It has good solubility property which improves the wettability. Polyethylene glycol formed by interaction of ethylene oxide with water¹⁷.
2. **Hydroxypropyl methylcellulose (HPMC):** It is cellular derivative, hydrophilic matrixes which are used as carrier for controlled drug release and solid dispersion preparation. It is nontoxic, cheap and easily compatible with other drug. It is available as many viscosity grades¹⁸.
3. **Polyvinylpyrrolidone (PVP):** PVP are used for preparation of solid dispersions by solvent evaporation method. It has good solubility and miscible with organic solvent. It is nonionic polymer achieve by polymerization. It is available as many grades like PVP K30¹⁹.

Characterization of Solid Dispersion: Solid dispersion can be analyzed by many methods; FTIR Spectroscopy-ray diffraction, electron microscopy, dissolution rate, differential scanning calorimetric (DSC) and differential thermal analysis (DTA)^{20, 21}.

Recent advancement: Medicament should be safe and effective for treatment of many diseases. The recent technology is available for changes in chemical modulation which improves the biological parameter. 90% of the drugs molecules are poorly water soluble and 40% of drugs are present in pharmaceutical industries which needs to improve in solubility and permeability process. In 2012, Food and Drug Administration approved the changes of dosage form by new formulation technology like changes in Ester or salt form, prodrug and chemical modification. These are comes under NDA's section^{22, 23}.

Solubility and permeability parameter of drug is very necessary for all category of drug because without solubilization drug particle cannot reach in to the blood circulation and cause the bioavailability and dissolution problem²⁴. Microemulsion technique is the most effective and recently introduce technique for improve in solubility, it has the low surface tension and small size which promote the absorption and permeation but it is apply for hydrophilic and hydrophobic drug.

Microemulsions are physically and chemically stable and mostly used in novel drug delivery system. Microemulsion system is dividing in to two category; water-in-oil and oil-in-water. In this system we use the surfactant and cosurfactant²⁵.

Poorly water soluble drug can be solubilize by improvement of synthesis method of complicated drug compound and make their changes in molecular structure²⁶. For improvement of solubility and dissolution rate, we can change in to formulation in different form like amorphous, crystalline solid and lipid formulation²⁷.

CONCLUSION: Solid dispersions are useful method for improving of solubility by increasing of dissolution characteristics. Many poorly water soluble drugs are available in pharmaceutical industry which needs to improve of solubility parameter. Most of the dosage forms are taken by orally which creates the problem in bioavailability. Many techniques are available for solubility enhancement like micronization, Nanonization, supercrystal fluid recrystallization, use of surfactant, evaporation precipitation, Sonocrystallization, Nanomorph technology and solid dispersion. Carriers are plays active role in solid dispersions.

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