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Novel Approach On Solubility Enhancement: Solid Dispersion a Brief Overview

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Abstract

Aim- 'Solid dispersion' means a mass of solid products which consist of at least two different components, generally a hydrophobic drug and hydrophilic matrix. Solid dispersion is used in pharmaceutical industry for increasing the absorption, dissolution rate and therapeutic efficacy of the drug. Hydrophilic polymers are the mainly used carrier for the preparation of solid dispersion. Melting method & Solvent evaporation method are two widely used approaches in preparing solid dispersion and solid solutions. Method- Solid dispersion are prepared by different methods like solvent evaporation method, hot melting method, fusion method etc. Solvent evaporation method is the widely used method in pharmaceutical application. In solid dipersion both drug and its carrier is agitated in a same common solvent, under vacuum, which is evaporated to produce a clear, solvent free film is remain left. Further the film is dried to constant weight. Result- Solid dispersion is the most used method to improve the solubility of poorly soluble drug in water. Solid dispersion helps to improve the bioequivalence and bioavailability. The increasing dissolvable property of solid dispersion is mainly because of amorphous form of drug is related with a higher energy state as contrast to its crystalline structure. Conclusion- Solid dispersion is a widely used method for distribute Lipid soluble drug by oral route. It is the most efficacious method to attain the aim of enhancement of dissolution of poorly water soluble drugs. Solid dispersion technique is used both in laboratory scale and at industrial scale also.

Keywords
solid dispersion, solvent evaporation, solubility, water soluble, melting method.

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INTRODUCTION

Novel drug delivery system is a new approach of drug delivery that describe the limitations of the conventional drug delivery. Novel drug delivery system is evolving, in order to reduce the drug degradation, drug adverse effect, and in order to increase the bioavailibity. The three main aim of novel drug delivery system (NDDS) is by implementing, selected to the targeted of site of action, sustained drug release and increased patient compliance. NDDS not only reduce the frequency of drug administration but it also minimizes the size of dose and frequency dosing also which lead to increase bioavailability. [1] The oral route of administration is the most preferred route due to its many advantages but many patients group such as elders, children's and patients who are mentally abnormal, have difficulties of taking

ordinary tablets. To overcome the above mentioned problems, Pharmaceutical technologist have put in their best efforts to develop a fast dissolving drug delivery tablets. i.e Orodispersible tablets. [2]

Two main strategies can be observed in enhancing the solubility of poorly water-soluble drugs. On the one hand, the drug is pre-solubilized in a liquid dosage form, like in self-emulsifying drug delivery systems or micro emulsions. When such formulations are released into the leumen of the gut, they disperse to form a fine emulsion, so that the drug remains in solution. Thus, the dissolution step, which often limits the rate of absorption of the drug, can be avoided on the other hand, the drug is transferred into its amorphous state, maximizing the surface area. [3]

solubility:

very soluble-	less than 1
freely soluble-	1-10
soluble-	10-30
sparingly soluble-	30-100
slightly soluble-	100-1000
very slightly soluble-	1000-10,000
insoluble-	greater than 10,000

Enhancement of solubility, dissolution rate and bioavailability of active compound is a very challenging task with a great relevance in active compound development. Among all newly discovered chemical entities about 40% drug are lipophilic. These poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. Around 40% drug shows poor water solubility that leads to poor bioavailability and low level of absorption. Solubility plays a major role for pharmaceutical drug formulation. Solubility mainly depends upon the solvent used as well as the pressure and temperature. [4]

Oral route is the most convenient route of drug administration, cost effectiveness, patient compliance and flexibility in drug design. The oral bioavailability depends upon several factors including dissolution rate, aqueous solubility, pre systemic metabolism and drug permeability. Poor bioavailability is the major problem for oral drug delivery system. For a new chemical entity low aqueous solubility is the major problem. Dissolution of drugs depends directly upon its solubility. Greater the solubility better will be the absorption hence it leads to good oral bioavailability. [5]

factors affecting on solubility: [4]

- Particle size
- Molecular size
- Temperature
- Polarity
- Pressure
- Temperature
- Nature of solute and solvent
- polymorphs

The dissolution of a substance may be described by Noye's Whitney equation.

dc/dt = (Cs-C) KDS/Vh …1

Where dc/dt is the rate of increase in Concentration, the concentration of drug in a bulk solution; K is a proportionality constant; D is the diffusion coefficient; S is the surface area of undissolved solid; V is the volume of the solution; h is the thickness of the diffusion layer; and Cs is the solubility of the drug in the solvent. If we consider a given drug under well-defined conditions (such as controlled liquid intake), we may assume that D, V and h are relatively constant values.

Thus we can reduce equation (1) to:

dc/dt KS(Cs-C) …2

Equation (2) shows that the two variables, which may be controlled by

the formulation, are the surface area and the solubility of the drug. [6]

Approaches for enhancement of drug dissolution [4]

1. Physical modifications:
   - Micronization
   - Particle size
   - Polymorphs
   - Nanosuspension
   - Modification of crystal habit
   - Solid solution
   - Solid dispersion
   - Dispersion of drug in carrier
   - Pseudomorphs
   - Utilization of surfactant
   - Solubilization
   - Implication of eutectic mixture
   - Utilization of cyclodextrin
2. Chemical modification
   - Salt formation
   - Soluble pro drug approach
   - Change of pH
   - Complexation
   - Use of buffer
3. Miscellaneous methods
   - Hydrotrophy
   - Solubilizers
   - Use of surfactant
   - Co-solvency
   - Supercritical fluid process

Need of Solubility Enhancement in Pharmaceutical Development

Solubility is one of the important parameter in biopharmaceutical classification system (BCS), and solubility is the most important factor which controls the bioavailability of drugs. [7] In parenteral preparation solubility plays a major role. Pharmaceutical API's are mainly differentiating in terms of permeability and solubility by means of biopharmaceutical system of classification (BCS). The absorption of BCS class II drug can be significantly improved by optimization to the formulation by maintaining class II drugs in a solubilized condition at absorption site so it to gives a same absorption profile like that of class I molecules. For BCS class III & IV molecules, very limited formulations strategies are available because of their poor membrane permeability and their permeability can be significantly improved only because of chemical modification during optimization in API synthesis. [8] By increasing the bioavailability, less quantity of drug is required to produce the same therapeutic effect.

BCS classification

- Class I - high permeability, high solubility
- Class II - high permeability, low solubility
- Class III - low permeability, high solubility
- Class IV - low permeability, low solubility [9]

SOLID DISPERSION

Solid dispersion means dispersion of one or more active ingredients in an inert excipient or matrix (carrier), where the active ingredients could exist in finally amorphous, solubilized or crystalline state. [10] Solvent evaporation method and melting method are two widely used techniques in preparation of solid dispersions and. An amorphous solid dispersion is composed of two or more than two components, generally a carrier or matrix polymer, drug, stabilizing agent and or surfactant, due to this reason it is also called as ternary solid dispersion. [11]

Advantages-

- Generally solid dispersion is widely used.
- To reduce particle size.
- To improve the drug porosity.
- Improves wettability.
- To prepare fast disintegrating oral tablets.
- Maintain stability of unstable drugs.
- Supply liquid or gaseous compounds.
- Formulation of a fast releasing priming dose in order to attain a sustained release dose.
- Avoid polymorphic changes.
- It avoids pre systemic metabolism.
- Decreases the crystalline structure of drug in to amorphous form.
- To improve solubility of poorly water soluble drug.
- To obtain required release rate of drug.
- Mask bitter taste drug. [12]

Need of Solid dispersion

- It increased dissolution rate of a drug.
- It increases oral bioavailability of a drug.
- It improved the solubility and stability.
- It enhanced release of drug from ointment. [13]

Disadvantages

- instability.
- Changes in crystalline structure and a decrease in dissolution rate on ageing.
- Moisture and temperature have deteriorating effect on solid dispersion. [13]
- It is expensive method of preparation.
- Poor scale-up for the purpose of manufacturing. [12]

Application

- Increases bioavailability of drugs. [13]
- Increases dissolution rate and solubility of drugs.
- Formulate a fast release dosage form.
- Improved stability.
- To mask unpleasant taste and smell of drugs.
- Reduced side effect of drugs.
- Avoid undesirable incompatibilities.
- Stabilize unstable drugs.
- Formulate sustained release dosage form.
- Reduce pre systemic inactivation of drugs.

Selection of carrier

A carrier should have following characteristic for increasing the dissolution rate of drug: [14]

- Pharmacologically inert.
- It should be freely soluble in water.
- Soluble in various solvents.
- It should be chemically compatible with drugs.
- It should have low melting point and low vapour pressure.
- Non-toxic
- Enhance dissolution
- Improved stability
- Improve wettability

Selection of solvent

- It should be chemically inert. [14]
- Should be non-toxic.
- Readily evaporate at room temperature.
- Both carrier and drug must be dissolved in the solvent.
- Ethanol can be used because it is less toxic.

SOLVENTS USED IN SOLID DISPERSION [15]

- Methanol
- Chloroform
- Ethanol
- Water

- Acetic acid
- DMSO
- 1-propanol
- 2-propanol

POLYMERS USED

Polyvinyl Pyrrolidone:

Molecular weight ranges from 10000-70000. It is soluble in ethanol, chloroform, water and isopropyl alcohol. It is not suitable for melting method because its melting point is above 275. [15]

Cyclodextrins:

Cyclodextrin mask unpleasant taste of drug. It increases the drug stability. Cyclodextrin is mainly used to increase the solubility. It also decreases local tissue irritation.

Polyethylene Glycol:

The molecular weight of polyethylene glycol (PEG) is above 300000 also known as polyethylene oxides30[31]. They are obtained by reacting with ethylene oxide and ethylene glycol.

Phospholipids:

Phospholipid head group contain choline, inositol, glycerol esters[32], inositol phosphate, serine and ethanolamine. Monoacyl phospholipids is readily soluble in water. [16]

Poloxamers

They are surface active compounds used in pharmaceutical application. They are obtained by consecutive polymerization of ethylene oxide, propylene oxide and their derivatives. They are freely soluble in polar and non-polar organic solvents. Poloxamers are also known as pluronics.

Crospovidone

Crospovidone belongs to polyvinyl group which gets swells when dispersed into water.

Urea

It is the by product of human protein. It is good soluble in water and also shows good solubility in various organic solvents.

CLASSIFICATION OF SOLID DISPERSION [17]

1. Solid solution
2. Simple eutectic mixture.
3. Glass solution and glass suspension
4. Amorphous solid solution

Solid solution:

Solid solution is miscible in both liquid as well as solid state. Solid solution is of two types depending on the miscibility:

- Continuous solid solution: in this components are soluble in all proportion. The bonding strength is stronger.
- Discontinuous solid solution: in this the solubility is limited in nature.

Depending upon the molecular size solid solution are of two types substitutional and interstitial

Simple eutectic mixture:

It consists of two components which are completely miscible in liquid state but limited in solid state. Simple eutectic mixture is prepared by fusion of two melt components.

Glass solution and glass suspension:

In glass solution solute dissolves in the glassy system, a glass is a homogenous glassy system. It is characterized by brittleness and transparency. Glass refers to the mixture of pure chemical in glassy state.

Amorphous solid solution:

In amorphous solid solution the drug-polymer is cooled at that rate that it does not allow for crystallization of drug then the drug is trapped at its amorphous state or a solidified-liquid state. [17]

METHODS [18]

There are several techniques for the preparation of solid dispersion:

- Melting method
- Melt extrusion method
- Kneading method
- Solvent evaporation method
- Melt extrusion technique
- Lyophilization technique
- Co-precipitation method
- Spray drying
- Co-grinding method
- Melting solvent method

Melting method

In melting method both drug carrier is triturate in mortar and pestle and the mixture of drug and carrier is heated above their melting points, then cooled the mixture to get a congealed mass. It is then crushed and sieved.

Drug + water soluble carrier
↓
Melted directly
↓
Cooled and solidified the mixture with vigorous stirring in ice bath
↓
Solid mass was formed
↓
Crushed and then sieved

Melt extrusion method

In melt extrusion method both carrier an active ingredient is prepared by using hot stage extrusion. Drug concentration should be 40% (w/w)

Carrier and drug is melted
↓
Then extruded the mixture
↓
Granules formed
↓
Sieved the formed granules

Kneading method

In this method little amount of water is added to convert into paste, then the drug is added into paste and kneaded for a specified time and the kneaded mixture is dried and pass through sieve. This method is the most simple and common method, it has very high production cost.

Solvent evaporation method [19]

In solvent evaporation method both carrier and drug are dissolve in a common solvent and the solvent is remove under vacuum to produce solid mass. In this method thermal decomposition of both carrier and drug can be prevented because it requires low temperature for evaporation of organic solvents. The major disadvantage of this method is that it requires a high cost.

Drug + carrier matrix (both dissolve in a common solvent)
↓
Solution formed
↓
Then evaporate the solvent
↓
Solid mass then formed is sieved
↓
Dried
↓
Solid dispersion

Lyophillization technique

In lyophillization technique transfer of mass and heat takes place for the product formation. It is the alternative technique of solvent evaporation method. In this drug and carrier are dissolved in a common solvent to obtain a lyophilized mass.

Co-precipitation method

In co-precipitation method the drug is added in carrier's solution. Then it is mixed by magnetic agitation and protected from light. Precipitate is then filtered and dried at room temperature. This method is widely used in industry.

Spray drying

In spray drying method both the drug and carrier is dissolvent in a suitable solvent then both the solution is sonicated to produce a clear solution which is then dried by using spray dryer. [20]

Co-grinding method

In co-grinding method both carrier and physical mixture of drug is blended at particular speed.

Super critical fluid process

supercritical process shows both gas and liquid properties above its pressure and critical temperature. The low pressure and temperature makes super critical process more effective for pharmaceutical application. It is economic method and also environment friendly and safe. [21]

carrier + drug
↓
Dissolve in CO_2 (as solvent)
↓
In expansion vessel sprayed by using nozzle
↓
Then particles are formed immediately because of low pressure
↓
Expanded mixture results in fast cooling

Melting solvent method

Drug dissolve in a suitable solvent
↓
Then add melt mixture of polyethylene glycol
↓
Evaporate the solvent
↓
Clear film is formed
↓
Dried the film
↓
weight

EVALUATION PARAMETERS [22]

- X-ray diffraction method
- Drug entrapment efficiency
- Spectroscopic method
- Thermal analysis
- Moisture sorption characteristics
- Dissolution testing
- Microscopic method
- Environmental scanning electron method
- Thermodynamic method
- Dissolution rate method
- Modulated temperature differential scanning calorimetry
- Particle size analysis
- Stability studies

x- ray diffraction method

It is a method of determining the arrangement the arrangement of atoms in crystal in which beam of x-rays are diffracted in many directions. The intensities and angles of these diffracted beams, produces 3D picture of the electron density within crystals. From that electron density the position atom can be determine as well as various other information.

Drug entrapment efficiency

EE% = actual drug content/theoretical drug content x 100

Spectroscopic method

Spectroscopy was studied the interaction of matter and radiation as a function of wavelength. Spectroscopy is used for the visible light.

Thermal analysis

In thermal analysis temperature between the sample and reference material is determined when both are incorporated to same heat. In thermal analysis physical property of substance is measured. [22]

Moisture sorption characteristic

Equilibrium moisture sorption = amount of moisture sorped at equilibrium/dry weight of material.

Dissolution testing

Dissolution testing are performed in ternary dispersion and binary dispersion. The test is performed according to USP 24 method.

Particle size analysis

Particle size analysis of solid dispersion can be done by electron microscopy. Sample of each batch is dispersed in phosphate buffer solution pH 7.4

Stability studies

The formulation is kept in amber color bottle, the bottle is tightly plugged with cotton and seal with aluminum. [23]

CONCLUSION

Solubility plays an important role for the oral drug release it is also important for parentral preparation. Solubility problem affected the bioavailability and dissolution of drug. There is numerous method for enhancement of drug solubility and solid dispersion is one of them. Solid dispersion has great advantage for preparation controlled drug delivery system and increasing the drug bioavailability. Solid dispersion technique is used both in industrial scale as well as laboratory purpose. For lipohillic drug solid dipersion is the best method delivery of drug by oral route. By solid dipersion method we can identify new carrier molecule. Selection of carrier and selection of suitable solvent is the important parameter for solid dispersion. Drug with poor aqueous solubility shows poor dissolution and absorption. Solubility of drug is one of the major challenging job pharmaceutical industry. Several surfactants and co-solvents are used to raise the solubility of poorly soluble drug. Selection of excipient and carrier also plays a major role for solubility enhancement. Reduction of particle size results in increase solubility and bioavailability. Greater the surface area more will be the solubility. Adjustment of pH principle applied both in parentral and oral formulation.

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