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Review on solid dispersion of poor water soluble drug by using natural polymers

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Abstract

Solid dispersion is a unique & most widely used approaches to enhance the solubility as well as dissolution rate especially BCS class II drugs. The main purpose of development of solid dispersion is improving oral absorption and oral bioavailability of poor water soluble drug by using natural gum. Solid dispersion is prepared by using solvent evaporation method, kneading method, melting method, and lyophilisation method etc. Natural polymer and its modified forms can be used as a best alternative for improving bioavailability of poor water soluble drug in solid dispersion. Most of natural polymer are hydrophilic and having high swelling capacity. Many natural polymers like cyclodextrin and carbohydrate are most extensively used as a carrier for enhancing the solubility and dissolution rate in solid dispersion. This review focus on various aspects of Solid dispersion and Solid dispersion of poor water soluble drug by using natural polymers.

Keywords: Solid dispersion, Solubilisation, natural polymer, Cyclodextrin, characterization

Introduction

The oral route is most preferred and simplest route for administration of drug. The patient compliance and drug treatment is usually more effective with orally route as compare to other route of administration¹. The development of poor water soluble drug for oral route is one of the most unique and greatest challenges for scientist of formulation in the pharmaceutical industry. Near about 40% new drug is create problem of poor water solubility in the pharmaceutical industry. Poor water soluble drug is slowly released, slowly dissolved and poor bioavailability that leads to required large dose for produce desirable pharmacological effect and sometime large dose is caused toxicity^[2]. So best option is solving solubility problemis enhancing solubility, dissolution rate of poor water soluble drug by solid dispersion technique. The solid dispersion is one of the best technique and method for enhancing the dissolution rate, solubility, and oral bioavailability of poor water soluble drug³. Because in which one or more active ingredient in an inert carrier or matrix in solid state⁴. Those drug having poor aqueous solubility they show poor bioavailability due to slow absorption because dissolution rate is slow⁵. The increasing the dissolution rate by size reduction or micronization but that create aggregation of particle problem which finally leads to poor wettability.

Some other approaches are like salt formation, solubilization by using co-solvent complexation with cyclodextrin and reduce particle size for increasing bioavailability of poor water soluble drug. The solubility problem is discuss above is solved by many author with the help of using number of natural polymer like Karaya gum KG, guar gum, alpha, beta and gamma) cyclodextrin, sorbitol, mannitol, urea, silica gel. The solubility is defined as a maximum quantity of solute that can be dissolved in certain quantity of solvent or quantity of solution at specific temperature. When solubility is increased that bioavailability is also increased. Solubility defined as:

Table 1: Definition of Solubility^[10].

Definition	Part of solvent required for one part of solute
Very soluble	< 1
Freely soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100
Slightly	100 – 1000
Very slightly soluble	1000 - 10,000
Insoluble	> 10,000

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BCS (Biopharmaceutics classification system) classify the drug into four classes on the basis of solubility and permeability. The solubility challenges are involved in class II and IV of BCS ^[10].

Table 2: BCS Classification of Drug.

Class	Permeability	Solubility	Examples
I	High	High	Metoprolol.
II	High	Low	Neteglinide.
III	Low	High	Cimetidin.
IV	Low	Low	Hydrochlorothiazide.

There has been natural polymer are used as a pharmaceutical excipient for oral used for the purposed of enhancement of dissolution rate, solubility and oral bioavailability of poor water soluble drug. Some natural polymer such as Hupu gum (HP), guar gum (GG), xanthan gum (XG), Karaya gum (KG), locust bean gum (LBG) ^[11].

1) Selection criteria of a carrier for solid dispersion ^[12].

Following some criteria that should be considered during election of carrier for solid dispersion.

- High water solubility carrier is selected because that improving the wettability and enhancing the dissolution rate.
- Carrier should be high glass transition because that improving the stability.
- Carrier should be minimal water uptake.
- Carrier should be soluble in all common solvent and with drug.
- Carrier should be low melting point.
- Carrier should be capable of forming a solid solution with drug.
- The viscosity of carrier is low and swelling capacity is high.

2) Approaches of Solid dispersion

The pharmaceutical researcher that focus on improving the oral

Bioavailability of active agents include:

1. Enhancing solubility and dissolution rate of poorly water soluble drugs.
2. Enhancing permeability of poorly permeable drugs ^[13].
Several Approaches for enhancement of drug dissolution/ bioavailability of poorly soluble drugs ^[14].

I. Physical modifications

- Particle size.
- Micronization.
- Nano suspensions.
- Modifications of the crystal habit.
- Polymorphs.
- Pseudo polymorphs
- Complexation/solubilisation.
- Utilization of surfactants.
- Utilization of Cyclodextrins.
- Dispersion of Drug in a carrier.
- Implication of Eutectic mixtures.
- Solid dispersions
- Solid solutions.

II. Chemical modifications

- Soluble prodrug approach.
- Salt formation.

III. Other ^[2]:

- Supercritical fluid method.
- Spray freezing into liquid and Lyophilization.
- Evaporative precipitation into aqueous solution.
- Solvent evaporation method.
- Hot melt extrusion.
- Electrostatic spinning method.
- Direct capsule filling.
- Polymeric Alteration.
- High- Pressure Homogenization.
- Lyophilization technique.
- Inclusion Complexes.

3) Natural polymer are used as carrier in solid dispersion ^[12].

Today many natural polymers have been evaluated for their used in new application. Some carrier are occurring from naturally which are easily soluble and dissolved in water and widely used in pharmaceutical formulation to enhance the dissolution rate of drug.

Different Natural polymer used as carriers for solid dispersions Category Example of carriers ^[12]:

1. Natural gums and its modified forms.
Example: Locust bean gum, Karaya gum, Guar gum, Xanthan gum, Hupu gum, *Aegle marmelos* gum etc.
2. Cyclodextrins.
Example: Alpha, beta & gamma Cyclodextrin, Hydroxypropyl beta-Cyclodextrin, Meta hydrated beta-Cyclodextrin.
3. Carbohydrates.
Example: Lactose, corn starch, Sorbitol, Mannitol, Chitosan, Maltose etc.
4. Miscellaneous.
Example: Gelatin, Egg albumin, Skimmed milk, Silica gel, Urea etc.

Natural gums and its modified forms

Natural gums, polysaccharides and their related derivatives of polymer are broadly used in pharmaceutical dosage form. Polysaccharide are hydrophilic in nature polymer and mostly choice of material because they are nontoxic and accepted polymer by regulatory authority. Natural polymer or gum like: guar gum, xanthan gum, locust bean gum etc. When used in minor quantity that increasing the dissolution rate due to low viscosity and high swelling capacity which offer the better alternative for these type of polymer. the dissolution rate is enhance because the formulation containing viscous carrier is generally low due to formation of gel layer on the hydrated surface which prevent the drug released during dissolution. The viscosity of carrier is reduce the dissolution rate. Modified gum is used in a way that swelling ability is remain same and viscosity is reduced and this can be enhance by heating.

Natural gums & method used for enhancing solubility of poorly water soluble drug.

1. Lovastatin (drug)
Locust bean gum and Modified locust bean gum. (Polymer).
Solvent evaporation (method).
Increased wettability, dispersibility and solubilization effect (mechanism).
2. Nimodipine (drug)

- Karaya gum, Modified gum karaya. (Polymer)
Co-grinding technique. (Method)
Increased wettability, dispersibility and reduced crystallinity. (Mechanism)
3. Licofelone (drug)
Modified guar gum. (Polymer)
Co-grinding mixture. (Method)
Swelling action result in increased surface area. (Mechanism)
 4. Cefixime (drug)
Guar gum (polymer)
Solvent evaporation (method)
Solubilization effect (mechanism)
 5. Gliclazide (drug)
Xanthan gum, Guar gum and Hupu gum (polymer)
Co-grinding mixture (method).
Swelling action result in increased surface area. (Mechanism).
 6. Gliclazide (drug)
Modified gum karaya (polymer).
Solvent evaporation (method).
Conversion of crystalline form to amorphous form (mechanism).
 7. Aceclofenac (drug)
Modified *Aegle marmelos* gum (polymer).
Physical mixture, co- grinding mixture (method).
Increased wettability, surface area and solubilization effect. (Mechanism).

Cyclodextrin

Cyclodextrin are belong to the category of carbohydrate but its broad application and role in dissolution enhancement. (CDs) are cyclic oligomer typically composed of 6-8 glucose unit. (CDs) are represent the class of solubilizing agent that a non-covalent dynamic complex with lipophilic molecules by inclusion. The inclusion complex is modified the physical property of drug or substance governed by the equilibrium constant between the free drug, free CDs, and complex of CDs-drug. Cyclodextrin is improve the stability of substance like: protein and peptide. The CDs are approved for pharmaceutical product can be classified into three major type but different only in the molecular weight and representative central cavity diameter.

Alpha CDs has molecular weight is 972 and central cavity diameter of around 5Å.

Beta CDs has molecular weight is 1135 and central cavity diameter of around 6.2Å.

Gamma CDs has molecular weight is 1297 and central cavity diameter of around 8Å.

Cyclodextrin and method for enhancing the solubility of poor water soluble drug.

1. Norfloxacin (drug).
Beta-Cyclodextrins, Hydroxypropyl gamma-Cyclodextrin (polymer).
Inclusion complexes by Freeze drying (method).
Formation of inclusion Complexes (mechanism).
2. Gliclazide (drug).
Beta-Cyclodextrins (polymer)
Inclusion complexes by kneading, coprecipitation, cogrinding, spray drying (method).
Formation of inclusion complex in solid state and reduction in crystallinity of the product (mechanism).

3. Carbamazepine (drug).
Hydroxypropyl beta-Cyclodextrin (polymer).
Inclusion complexes by solvent method (method).
Formation of inclusion Complexes (mechanism).
4. Danazol (drug).
Hydroxypropyl beta-Cyclodextrin (polymer).
Inclusion complexes by spray freezing (method).
Higher surface areas and stabilized inclusion complexes (mechanism).
5. Norfloxacin (drug).
Beta-Cyclodextrins (polymer).
Inclusion complexes by kneading method (polymer).
Formation of inclusion Complexes (mechanism).
6. Nimesulide (drug).
Beta-Cyclodextrin (polymer).
Inclusion complexes by kneading method (method).
Formation of inclusion Complexes (mechanism).
7. Satranidazole (drug).
Beta-Cyclodextrin (polymer).
Inclusion complexes by kneading method (method).
Reduction in crystallinity of the drug (mechanism).
8. Carbamazepine (drug).
Beta-Cyclodextrin (polymer).
Inclusion complexes by kneading method (method).
Decrease in crystallinity of the drug (mechanism).
9. Gliclazide (drug).
Beta-Cyclodextrin (polymer).
Inclusion complexes by liquid/liquid extraction and neutralization (method).
Increase in the drug Wettability (mechanism).
10. Piroxicam (drug).
Beta-Cyclodextrin (polymer)
Inclusion complexes by kneading, freeze drying, neutralization method (method).
Formation of inclusion Complexes (mechanism).

Carbohydrate

Carbohydrate are natural carrier that enhancing the dissolution rate of poor water soluble drug natural carrier like: lactose, soluble starch, mannitol, sorbitol, galactose, maltose, dextran, xylitol etc. when increasing the surface area of drug that leads to enhancement of dissolution rate.

Carbohydrates & methods used for enhancing solubility of poorly water soluble drug

1. Diazepam (drug).
Lactose (polymer).
Interactive mixing (method).
Increase in the surface area of drug directly exposed to the carrier material (mechanism).
2. Fentanyl (drug).
Coarse, mannitol (polymer).
Interactive mixing (method).
Increase in the surface area of drug directly exposed to the carrier material (mechanism).
3. Indomethacin (drug).
Fine Lactose (polymer).
Interactive mixing (method).
Dissolved lactose left an agglomerate structure of indomethacin with a much greater porosity and ability to disperse (mechanism).
4. Nifedipine (drug).
Chitosan, Chitosan glutamate (polymer).
Solid dispersion by solvent method (method).

Decreased drug crystallinity and size of the drug and wetting effect (mechanism).

5. Griseofulvin (drug).
Maltose, Lactose, Corn Starch (polymer).
Solid dispersion by roll mixing method (method).
Increase in the surface area of griseofulvin directly exposed to the carrier materials (mechanism).
6. Nifedipine (drug).
Mannitol (polymer).
Solid dispersion by hot melt method (method).
Improved wetting of drug crystal surface mainly due to attached mannitol particles which provoked the solubilizing effect (mechanism).
7. Rofecoxib (drug).
Mannitol, Sorbitol (polymer).
Solid dispersion (method).
Polar environment provided by the carrier (mechanism).

Miscellaneous

Some types of miscellaneous natural polymer are used as a carrier and play major important role in dissolution enhancement of poor water soluble drug like: silica gel, gelatin, skimmed milk and egg albumin etc. [12].

4) Classification of solid dispersion

A) On the basis of carrier used [14]:

1. **Generation of solid dispersion:** In which used of crystalline carrier such as urea, sugar which is mostly first carrier to be employed in solid dispersion. But they have disadvantageous of developing crystalline solid dispersion which were thermodynamically more stable and did not released drug fastly or quickly as compare to amorphous solid dispersion.
2. **Generation of solid dispersion:** In which using amorphous carrier instead of crystalline carrier. In which synthetic polymer are used like povidone (PVP), Polyethylene glycol (PEG), Polymethacrylate and also natural polymer based product are used such as hydroxyl propyl methyl cellulose (HPMC), Ethyl cellulose (EC), hydroxy propyl (HP) or Starch related derivatives like: cyclodextrin.
3. **Generation of solid dispersion:** Today most of dissolution profile can be improve if the carrier has surface activity or self-emulsifying property. in which IIIrd generation of S.D used of surfactant such as inulin, inutac SP1, compritol 888ATO, poloxamer as a surfactant carrier. The surfactant carrier is effective in originating high polymorphic purity and enhance *in vivo* bioavailability [4, 7, 15].

B) On the basis of solid state structure [14]:

Drug polymer exhibiting immiscible in fluid state

When drug and polymer are immiscible in their fluid state. It is expected that they would not exhibit miscibility on solidification. Such system may be regarded as similar to their corresponding physical mixture and enhance in dissolution performance may be owing to modified in morphology of drug and/or polymer due to physical transformation. Formation of crystalline or amorphous solid dispersion can be biased by the rate of solidification of mixture and the rate of crystalline of drug and/or polymer [16].

Drug polymer exhibiting miscible in fluid state

When drug and polymer miscible in their fluid state then the

mixture may or may not undergo phase separation during solidification thereby influencing the structure of solid dispersion [2].

Eutectic mixture

Eutectic mixture was first described in 1961 by sekiguchi and Obi. The eutectic mixture is formed by combination of drug and polymer are miscible in their molten state. But on cooling the crystalline as two distinct component with negligible miscibility. When drug and carrier are co-melted at their eutectic composition [16].

Eutectic mixture is defined diagrammatically below:

Crystalline solid dispersion

Crystalline solid dispersion is formed when the rate at which the drug is crystallize from drug polymer miscible mixture is greater than the rate at which drug polymer fluid mixture solidified [16].

Amorphous solid dispersion

When drug and polymer mixture is cooled at a rate that does not allow for drug crystallization then drug is kinetically trapped in its amorphous or solidified liquid state. These type of solid dispersion have the risk of potential for conversion to a more stable and less soluble form [4].

Solid solution

Solid solution is a binary mixture system comprising of solid solute molecularly dispersed in a solid solvent. Since the two component crystalline together homogenous one phase system. Solid solution also called as molecular dispersion or mixed crystal or melt [15].

1. According to the extent of miscibility

Of two components.

- i. Continuous solid solution.
- ii. Discontinuous solid solution.

2. According to molecular size of two molecular

Size of two molecules of solid solution.

- i. Substitution solid solution.
- ii. Interstitial solid solution.

Continues solid dispersion

In which component are miscible in all solvent this means the bonding strength between the two components is strong as compare to bonding strength between each molecule of individual component [15].

Discontinues solid dispersion

In which solubility of component in solvent is limited.

Substitutional crystalline solid dispersion

In which solid dispersion having crystalline in nature that why solute molecule can either substitute for solvent molecule in the crystal lattice between the solvent molecule. Substitution is only possible when the size of solute molecules is less than 15% from solvent molecules.

Interstitial crystalline sold dispersion

In which dissolved molecules is occupy the interstitial space between the solvent molecules in the crystal lattice [15].

5) Method of preparation of solid dispersion

- Melting method.

- Solvent evaporation method.
- Lyophilization technique.
- Melting solvent method.
- Melt extrusion method.
- Kneading method.
- Co-grinding method.
- Spray drying method.
- Dropping solution method.
- Effervescent method.
- Super critical fluid technology.

Melting method

In which drug and carrier are accurately weighing and mix with the help of mortar and pestle. After that mixture are heated at above melting point of all component that form homogeneous dispersion. After that the mixture is cooled that finally obtain a congealed mass. That mass is pulverised and seive^[1].

Solvent evaporation method

In which mixture of drug and carrier is dissolved in common solvent after that evaporated until clear the solvent is left is further dried to constant weight ^[15].

Lyophilisation technique

In this method transfer of heat and mass that form a product. The drug and carrier mixture is co-dissolved into common solvent, frozen and sublimed to obtain a Lyophilization molecular dispersion ^[11, 7].

Melting solvent method

In which the addition of at specific fixed amount of solvent and then that solution is incorporated into melted form of polyethylene glycol below 70°C. This method is also used for thermolabile drug with high melting point. But limited drug is required with low therapeutic dose (below 50 mg) ^[15, 11].

Hot melt extrusion method

This method is used for thermolabile drug. The drug carrier mixture is typically processed with a twin screw extrusion. After that mixture is melted and homogenised simultaneously and then extruded and giving shaped as tablet, granules, pellets, and other oral dosage forms ^[15, 6].

Kneading method

Drug and carrier are accurate weighed and this mixture are wetted with solvent. Kneaded with the help glass mortar as sometime that leads to paste and then sieved ^[15, 11].

Co-grinding method

In which drug powder and carrier are accurately weighed and sometime mixed by using blender at specific speed. The mixture is charge into the chamber of vibration ball mill for grinding ^[15].

Spray drying

Weighed accurate amount of drug and lipid carrier then dissolved in methanol to obtain clear solution. This solution is sprayed on lab scale with the help of dryer ^[11].

Dropping solution method

In lab scale the mixture if melted drug carrier is sock in pipette and then dropped onto plate. After solidified that form round particle. The size and shape of particle can be influence

by such factor like: viscosity of melt, size of subject is heated in hot air oven for specified period of time and temperature ^[11].

Effervescent method

In which sodium bicarbonate and organic acid (citric tartaric or succinic) react with each other to yield effervescent. But combining of both in poor soluble drug with organic acid that increased the dissolution and absorption rate of poor soluble drug ^[15].

Super critical fluid technology (SCF)

In which commonly solvent are used whose temperature and pressure are greater than its critical temperature and pressure. SCF are high compressible allowing moderate changes in the pressure to great alter the density and mass transport characteristic of fluid. Fluid commonly used in SCF NO, CO₂, propylene, propene, ethylene, ethanol, ammonia, water and n-pentene ^[11].

6) Characterization of Solid dispersion

Different type of molecular structure of drug in the matrix can be encountered in solid dispersion. Several type of technique is available to evaluate or investigated the molecular arrangement in solid dispersion. However most effort has been put into differential amorphous and crystal material. Many technique are available which detect the amount of crystalline material in solid dispersion ^[2, 7, 17].

- Differential scanning calorimetry.
- Powder X-ray diffraction.
- Infrared spectroscopy (IR)
- Isothermal Micro calorimetry
- Dissolution calorimetry
- Macroscopic techniques
- Confocal Raman Spectroscopy.
- Temperature Modulated Differential Scanning Colorimetry (TMDSC).
- *In Vitro* Dissolution Studies.
- Solubility Studies.
- Humidity studies.
- DSC (Tg, Temperature recrystallization).
- Dynamic vapor sorption.
- Saturated solubility studies.
- Polarized light optical microscopy.
- Hot stage microscopy
- Humidity stage microscopy ^[12, 13, 14].

7) Application of solid dispersion ^[15]:

- To enhance the absorption of drug.
- To dispensed liquid or gaseous compound.
- To formulate sustain released dosage form as fast released desirable dose.
- To stabilize unstable drug.
- To reduce side effect.
- To mask and unpleasant taste and smell.
- To convert liquid compound into formulation.

8) Some of marketed solid dispersion ^[18].

Valdocoxib (NSAID) solid dispersion.
Terbinafine hydrochloride solid dispersion.
Glimepiride solid dispersion.

Conclusion

Solid dispersion containing natural carriers which is low

toxicity in nature, biocompatible and easy available is an alternative and best choice for improving solubility of poorly water soluble BCS-II drug. Modification of natural carriers gives novel application to solid dispersion containing dosage forms. The modification helps to improve the ideal or desired properties of carrier without affecting their physical and chemical stability. There is need to explore utilization of various unexplored natural polymers in solubility enhancement.

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