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REVIEW ARTICLE

MODIFIED NATURAL CARRIER IN SOLID DISPERSION FOR ENHANCEMENT OF SOLUBILITY OF POORLY WATER SOLUBLE DRUGS

Shejul Amar*, Deshmane Subhash, Biyani Kailas

Department of pharmaceutics, Anuradha College of pharmacy, Sakegaon road, Chikhli, Dist- Buldana - 443201, Maharashtra, India

Corresponding Author's E-mail: amarshejul@gmail.com

ABSTRACT:

The solid dispersion is one of the most important and desirable technique of solubility enhancement, the use of natural carrier in solid dispersion gives prominent and ecofriendly results. Many carriers have limitations in enhancing solubility of poorly water soluble drugs due to their high viscosity and their hygroscopic nature, modifying natural gum at different temperature provides carrier which have low viscosity and high swelling capacity offers better alternative for natural carriers. Modification of natural gums also changes physical characteristics like swelling index, viscosity, water retention capacity and crystalline nature of powder into amorphous. It concludes that modified form of carrier always shows better desire properties for enhancing water solubility.

Keywords: Solid dispersion, Modified natural gums, Carriers, Solubility.

INTRODUCTION:

More than 90% of drugs approved since 1995 have poor solubility. Also More than 40% NCEs (new chemical entities) developed in pharmaceutical industry are practically insoluble in water, The solubility and dissolution properties of drugs play an important role in the process of formulation development hence Solubility is a major challenge for formulation scientist.[1,2,3]

The important aspect which may greatly affect the performance of the drug is solubility. This is an important physico - chemical property of drug, especially aqueous solubility. To exert better therapeutic efficacy or better bio-availability, the drug must be in solution state and to have drug in the solution state, it must have high dissolution rate and high solubility. Thus the bio-availability of poorly water soluble drug is often limited to its dissolution rate. A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption. Several methods have been introduced to overcome this problem.

STRATEGIES TO INCREASE THE SOLUBILITY OF DRUGS:

A) Chemical modification [4]

a) Salt formation

b) Prodrug formation

c) Polar group incorporation

B) Formulation approch

a) Reduction in particle size by

1) Micronization technique [5]

2) Nanosuspension formulation [6]

b) Modification of crystal habits[1]

c) Complexation of drug as [7]

1) Inclusion complex

2) Ion exchange complex

d) Solubilization and surfactants [8]

1) Micronization

2) Micelles formation

3) Formulation of self emulsifying drug delivery systems

e) Formation of solid dispersion with water soluble carries.[9]

FORMATION OF SOLID DISPERSION:

Solid dispersion is very important and practically simple technique which can overcome the limitations of the above techniques. It means that solid dispersion is the very important technique which can assure about the aqueous solubility of poorly water soluble drugs [10]

As per Chiou and Riegelman, the term solid dispersion as "a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures" the term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.[11, 12]

PHYSICO - CHEMICAL STRUCTURES OF SOLID DISPERSIONS:

The physico-chemical structures of these dispersions play an important role in controlling the drug release. Six representative structures have been outlined to represent type of interactions between carrier and drug: [12]

1. Simple eutectic mixtures.
2. Solid solutions.

3. Glass solutions and glass suspensions.
4. Amorphous precipitations in a crystalline carrier.
5. Compound or complex formation.
6. Combinations of above structures.

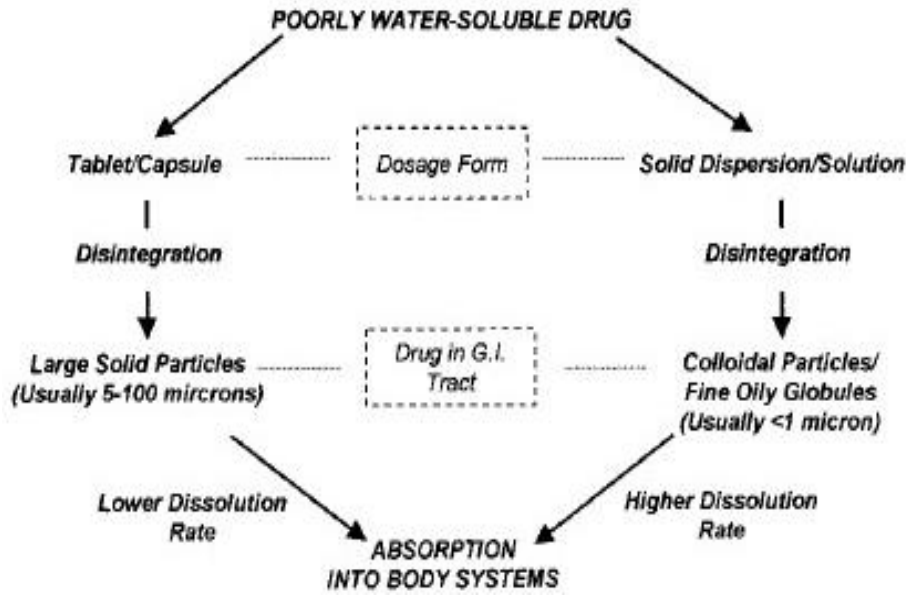

Fig.1. Schematic representation of bio-availability enhancement by Solid dispersion of poorly water soluble drug

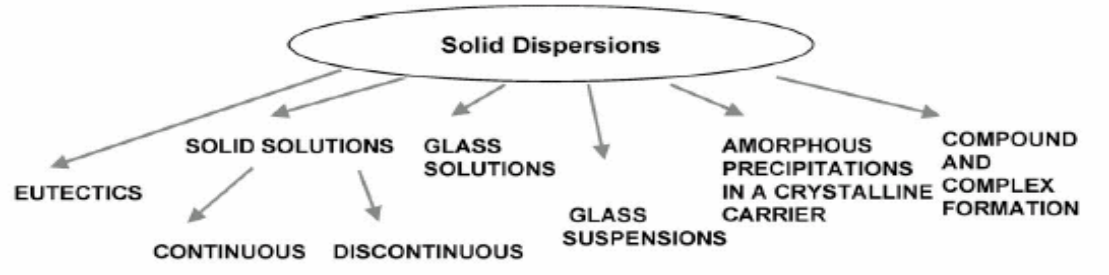

Figure 2 Categories of solid dispersions[13]

METHODS OF PREPARATION OF SOLID DISPERSION:

Various methods used for preparation of solid dispersion system. These methods are given bellow.

1. Melting method.
2. Solvent evaporation method.
3. Melting solvent method (melt evaporation).
4. Melt extrusion methods.
5. Lyophillization techniques.
6. Melt agglomerations process.
7. Electrospinning.
8. Super critical fluid (SCF) technology.
9. Kneading Method.
10. Spray Drying Method.
11. Dropping Solution Method.
12. Gel Entrapment Technique.

1. Melting method.

Drug and carrier accurately weighed are mixed using glass mortar and pestle. The mixture is heated at or above the melting point of all the components to achieve a homogenous dispersion. Then mixture is cooled to obtain a congealed mass. It is pulverized and sieved.[14]

2. Solvent evaporation method.

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to a constant weight.[14, 15]

3. Melting solvent method (melt evaporation).

This method includes the addition of drug into fixed amount of solvent, then the solution is incorporated into the melted form of polyethylene glycol below 70 ^{0}C. This method can be used for thermolabile drugs with high melting points. But it is limited to drugs with a low therapeutic dose, below 50 mg.[16,17]

4. Melt extrusion methods.

The advantage of this method is that the mixture is only subjected to an elevated temperature for about one minute which is good for thermolabile drugs. The drug-carrier mixture is typically processed with a twin screw

extruder. This mixture is melted and homogenized simultaneously and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder, The intermediates can then be further processed into conventional tablets.[18]

5. Lyophillization techniques.

This method involve transfer of heat and mass to and from the product under preparation. In this method drug and carrier are co-dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.[16, 19]

6. Melt agglomerations process.

solid dispersions are prepared either by heating binder, In this technique the binder acts as a carrier, heating drug and excipients to a temperature above the melting point of the binder (melt in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray on procedure) by using a high shear mixer.[1]

7. Electrospinning.

In this process, a liquid stream of a drug or polymer solution is subjected to a potential between 5 and 30 kv and when the electric forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. As the solvent evaporates the fibers can be collected on a screen or a spinning mandrill. The fiber diameters depend on surface tension, dielectric constant, feeding rate and electric field strength.[20]

8. Super critical fluid (SCF) technology.

Commonly used in case of fluids whose temperature and pressure are greater than its critical temperature and pressure, allowing it to assume the properties of both a liquid and a gas. At near critical temperatures, SCFs are highly compressible, allowing moderate changes in the pressure to greatly alter the density and mass transport characteristics of a fluid that largely determines its solvent power. Commonly used SCFs are CO2, NO, ethylene, propylene, propane, ethanol, ammonia, water, n-pentane.[21]

9. Kneading Method.

A mixture of accurately weighed drug and carrier is wetted with solvent, kneaded thoroughly for some time in a glass mortar, the paste formed is dried and sieved.[22, 1]

10. 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.[23, 20]

11. Dropping Solution Method.

In laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature-dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape.[24]

12. Gel Entrapment Technique.

Carrier is dissolved in organic solvent to form a clear and transparent gel. Then drug 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.[25, 26]

IMPORTANCE OF NATURAL CARRIERS IN SOLID DIISPERSION

Research for alternative carriers has been increasing to suit for the industrial applications as well as to reduce the production cost and toxic effects. Recently, many natural polymers have been evaluated for their use in new applications.[27, 28]

Many carriers used in solid dispersions also cause problems due to their hygroscopic nature. Hence, continuous search for new carriers and new techniques is going on which will be useful for large scale manufacturing. Many polymers have limitations in enhancing solubility of poorly water soluble drugs due to their high viscosity. Use of polymers with low viscosity and high swelling capacity offers better alternative for these types of polymers. Use of natural polymer is more beneficial because of their low cost, biocompatibility, and biodegradability. Most of these polymers are hydrophilic in nature, and after absorbing they swell and form a viscous gel layer around the dosage form resulting into delayed/ sustained drug release.[27, 28, 29]

The properties of the carrier have a major influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug: [18, 30]

1. Soluble in water for fast release or insoluble for sustained release.
2. Physiologically inert.
3. Melting point should be not more than 200 ^{0}C.
4. Thermal stability up to its melting point.
5. Non-toxic, non-irritant.
6. Chemically compatible.

MODIFIED FORM OF NATURAL CARRIERS:

There are several natural carriers available for preparation of solid dispersion, but because of their characteristic limitations and undesired properties they need to be modified.

Generally natural carriers on heating at different temperature will leads to changes its characteristics like viscosity, water holding capacity, bulk and tapped density, swelling index, carrs index, and flow properties etc. such changes in characteristics may meet desired criteria needed by a ideal carrier for preparation of solid dispersion.[31]

Modification of natural carriers were done simply by placing Powdered carrier in a porcelain bowl and

subjected to heating in hot air oven for specified period of time and temperature, which leads to alter physicochemical properties of natural carrier .The prepared modified natural carrier was finally re-sieved and stored in airtight container at 25°C. [31, 32]

These carriers specially gums get charred on overheating and due to charring the active properties may lost and chances of change in colour, hence The prepared modified natural carrier must be identified as free from any altered colouration and charring.

1. Guar gum (modified)

Guar gum is also known as cluster bean, Guaran, Cyamopsis, Guarina. It is obtained from the seeds endosperm of Cyamompsis tetragaonolobus (Family Leguminoseae), gaur gum is better stabilizer and not self gelling. When cross linked with borax or calcium gel can be formed. Guar gum is highly soluble in water. Chemically, guar gum is a polysaccharide composed of the sugars galactose and mannose.[33, 34] Modification of gaur gum was done by heating at 125-130^{0}C for 2-3 hr, The results indicated that the viscosity of modified gaur gum was markedly lower when compared to gaur gum, the viscosity of 1% w/v solution of modified guar gum at 28°C is 1645 cps, which is about 3 times lower than that of gaur gum. Hence, the swelling and water retention capacity of modified gaur gum was not reduced significantly rather than that of the gaur gum. Due to the swelling nature of the carrier, the extensive surface of carrier is increased during dissolution, and the dissolution rate of deposited drug is markedly enhanced. Water retention capacity of carrier is the amount of water retained in it that indicates ability of carrier towards hydrophilic nature.[35]

In further study of Dissolution Rate Enhancement of Licofelone by Using Modified Guar Gum, it was absorbed that During the process of drug dissolution from ordered mixtures of drug and the hydrophilic carrier, when a drug-carrier particle comes in contact with the dissolution fluid, seeping of dissolution medium into the drug-carrier particle takes place, which initiates the formation of a stagnant gel layer of carrier around the particle.[35]

2. Xanthan gum (modified)

Xanthan gum is polysaccharide produced by bacterium xanthomonas campesttris. It is also known as Corn sugar gum, Grindsted, Keldent,Keltrol, Rhodicare S, Rhodigel, Vanzan NF, xanthani gummi,, Xantural. Xanthen gum is Soluble in cold water, insoluble in alcohol, ether and chloroform but soluble in mixtures of methyl alcohol and methylene and methylene chloride.[34, 36]

Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers, or preservatives, as precipita- tion occurs. Anionic and amphoteric surfactants at concentrations above 15% w/v cause precipitation of xanthan gum from a solution.[36]

Modification of xanthan gum was done by heating at temperature of 120^{0}C , it was observed that The swelling index and viscosity of modified xanthaan gum decreases with increasing temperature than xanthan gum. The viscosity of modified xanthen gum was makedly lower, but its swelling index is decreased and water retention capasity was increased. It may be due to the swelling nature of the carrier, the extensive surface of carrier is increased during dissolution. At higher temperature (120^{0}C) modified xanthan gum loose its structural arrangment and redues adhesive and cohesive force of attraction which helps to retain water and decease viscosity

3. Hupu gum (modified)

Hupu gum or Gum kondagogu (GKG) is a naturally occurring polysaccharide derived as an exudate from the tree (Cochlospermum gossypium). Basically it is a polymer of rhamnose, galacturonic acid, glucuronic acid, b-D galactopyranose, a-D-glucose, b-D-glucose, galactose, arabinose, mannose and fructose with sugar linkage.[33]

Study on enhancement of dissolution profile of Pioglitazone HCl using Hupu gum and modified Hupu gum as carriers by solid dispersion technique. Modified hupu gum was prepared by heating at different temperature. The hupu gum and modified hupu gum were characterized for viscosity, swelling index and water retention capacity. Solid dispersion was prepared by cogrinding method using hupu gum and modified hupu gum in the ratio 1:1 and 1:2 respectively. The solubility data shows that solubility of Pioglitazone HCl is increases with hupu gum and found high in modified hupu gum, The FTIR and XRD study was also carried out. it was concluded that hupu gum which is more viscous than modified hupu gum resulted in formation of lumps of drug-carrier particles during dissolution, whereas pioglitazone HCl-modified hupu gum particles dispersed rapidly. The modified hupu gum at different temperature gives tremendous changes in structural bonding, cohesive and adhesive forces of attraction, crystallinity of drug etc. These changes are modified changes that help to lower the viscosity and swelling index. This change also increases water holding capacity which improves the wettability of drug and helps to dissolve the poorly water soluble drug.[37]

The characteristic FTIR peaks are preserved in the spectra of solid dispersion systems at almost same wave number. This indicates that there is no interaction between drug and carrier. In a XRD spectra of Pioglitazone HCl, modified hupu gum and solid dispersion containing modified hupu gum, The modified hupu gum was found amorphous in nature as there were few peaks with very weak intensities. In XRD, the series of sharp and intense diffraction peak indicated that, the crystalline nature of pure pioglitazone HCl. The crystalline peaks of optimized batches were found on low / negligible intensity at the same wavelength. It indicates that the crystallinity of pure drug was converted into amorphous form in solid dispersion. This happened might be due to use of amorphous modified hupu gum as carrier, which form high surface area dispersion.[37]

4. Locust bean gum (modified)

Locust Bean Gum (LBG) is also known as Carob Gum, obtained from the refined endosperm of seeds from the carob tree Ceretonia Siliqua L. It is an evergreen tree of the legume family. Carob bean gum is obtained by

removing and processing the endosperm from seeds of the carob tree. It is non-teratogenic and non-mutagenic according to Joint FAO/WHO Expert Committee on Food Additives held in Geneva, April'75. [33, 34]

Study was carried on solubility of poorly water soluble drug lovastatin (LS) by solid dispersion (SD) techniques using modified locust bean gum (MLBG) as a carrier. The result of swelling capacity and viscosity studies revealed that the modified forms possessed swelling properties similar to that of LBG but viscosity was decreased as a function of temperature and exposure time. However, it was observed that LBG samples were charred when heated at

140°C. In the preparation of MLBG, no further change in viscosity of LBG was observed by heating it at 120°C for 2 h. Hence, these conditions of heating at 120°C for 2 h were selected to prepare MLBG. The prepared MLBG was finally resieved (100 mesh) and stored in an airtight container at 25°C. The dissolution rate of LS from solid dispersions of LBG prepared by modified solvent evaporation method was low when compared with solid dispersions of MLBG because of high viscosity of LBG. Hence, various SD were prepared using MLBG than LBG to enhance the solubility of LS. Improvement in dissolution rate of LS by PM compared with pure drug might be the solubilization effect and wetting ability of the MLBG on LS.[27]

5. Khaya gum (modified)

Khaya gum is a polysaccharide obtained from the incised trunk of the tree Khaya grandifoliola family Meliaceae. It is known to contain highly branched polysaccharides consisting of D galactose, L-rhamnose, D-galacturonic acid and 4-O- methyl-D-glucoronic acid.[33, 34]

The work on the influence of modified gum karaya (MGK) on the oral bioavailability of a poorly water-soluble drug, nimodipine (NM), in comparison with that of gum karaya (GK) was carried out. A cogrinding method was selected to prepare mixtures of NM and GK or MGK in a 1:9 ratio (NM:GK/MGK). Differential scanning calorimetry (DSC), Fourier transmission infrared (FT-IR) spectroscopy, X-ray diffraction (XRD), solubility studies, and in vitro release studies were performed to characterize the properties of the cogrinding mixtures. No drug-carrier interactions were found, as confirmed by DSC and FT-IR studies. The XRD study revealed that the crystallinity of NM was identical in both the cogrinding mixtures and was decreased when compared to that of physi-cal mixtures or pure NM.[32]

Further work on enhancement of in vitro dissolution of poorly soluble drug glimepiride by preparing solid dispersions using modified gum karaya was carriedout. Low viscosity with comparable swelling characteristics as compared to GK of modified form of gum karaya may lead to improvement in dissolution behavior of solid dispersion batches. Also, the conversion of crystalline form of drug to amorphous form may be a responsible factor, which was further confirmed by DSC, FTIR studies, and X-RD studies.[38]

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 drug (BCS-II). 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.

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