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DRUGS DISSOLUTION ENHANCEMENT BY USING SOLID DISPERSION TECHNIQUE: A REVIEW

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ABSTRACT

The oral route of drug administration is the most common and preferred method of delivery due to the convenience and ease of ingestion. Oral bioavailability of a drug depends on aqueous solubility, drug permeability, dissolution rate, first pass metabolism. More than 40% new chemical entities (NCEs) developed in pharmaceutical industry are practically insoluble in water. Solid dispersion is a technique to enhance dissolution characteristics of drugs having poor water solubility. This technique can be applied to the preparation of solvent free solid dispersion. Supercritical fluids are those fluids whose temperature and pressure are greater than its critical temperature (TC) and critical pressure (TP). Various mechanism is involved in dispersion of solid technique. Various application is used for the dissolution of solid.

KEYWORDS: ***solid dispersion, techniques, mechanism and application***

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to the convenience and ease of ingestion. Oral bioavailability of a drug depends on aqueous solubility, drug permeability, dissolution rate, first pass metabolism. The solubility of a drug is a key determinant of its oral bioavailability and permeability. So, the major problems associated with drugs were its low solubility in the body fluids, resulting into poor bioavailability after oral administration. Poorly water-soluble compounds have solubility and dissolution related bioavailability problems. The "dissolution rate" is directly proportional to solubility of drugs.[1,2,3]

More than 40% new chemical entities (NCEs) developed in pharmaceutical industry are practically insoluble in water. These poorly water-soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity.[4,5,6]

Improvement in the dissolution rate of poorly soluble drugs after oral administration is one of the most crucial challenges in modern pharmaceutics. So, the "pharmaceutical researchers" focuses on two areas for improving the oral bioavailability of drugs which includes:[7,8,9]

(i) Enhancing dissolution and solubility of poorly permeable drugs.

(ii) Enhancing permeability of poorly permeable drugs.

So, the "Solid dispersion" has become an established solubilization technique for poorly water-soluble drugs in order to enhance the dissolution and oral bioavailability.[10,11] Although there are various techniques such as particle size reduction, micronization, physical modifications, complexation, solubilization, co solvency etc which can enhance solubility and dissolution rate of insoluble drugs but these techniques having some practical limitations, solid dispersion technique overcome these practical limitations.[12,13]

Solid dispersion though have numerous advantages, despite the advantages offered by the solid dispersions, the marketed products based on this technology are few. This is generally related to the poor predictability of solid dispersion behaviour due to lack of basic understanding of their material product.[14,15]

The term "Solid dispersion" is based on the concept that the drug is dispersed in an inert water-soluble carrier at solid state. By preparing solid dispersion, it is possible to provide better dispersibility and wettability of the drug by carrier material. Carriers which are soluble and dissolve in water at a faster rate are widely used in pharmaceutical industries. The increase in dissolution rate of the drug may be due to the increase in wettability, hydrophilic nature of the carrier and due to reduction in particle size. Fusion method has been used in order to prepare solid dispersion of active pharmaceutical ingredient by incorporating different carriers. So, several water-soluble carriers such as methyl cellulose, urea, lactose, polyvinyl pyrrolidone and polyethylene glycols and poloxamers etc are used as carriers for solid dispersion.[16,17,18]

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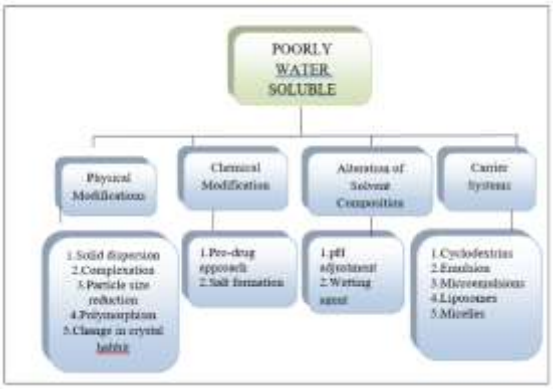

Fig 1. Approaches to increase solubility/dissolution

Ideal Candidate for Solid Dispersion

The poor solubility and low dissolution rate of poorly water-soluble drugs in the aqueous gastrointestinal fluids often causes insufficient bioavailability.[19,20] Especially for class II (low solubility, high permeability) substances according to BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in gastrointestinal fluids. For BCS class II drugs, rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the dissolution rate in turn increases the bioavailability for BCS class II drugs.[21,22,23]

TYPES OF SOLID DISPERSIONS

I. On the basis of carrier used.

II. On the basis of their molecular arrangement.

I. On the basis of carrier used: On the basis of carrier used solid dispersions can be classified into three generations:

a) First generation: First generation solid dispersions were prepared using crystalline carriers such as urea and sugars, which were the first carriers to be employed in solid dispersions. They have the disadvantage of forming crystalline solid dispersions, which were thermodynamically more stable and did not release the drug as quickly as amorphous ones.[24,25,26]

b) Second generation: Second generation solid dispersions include amorphous carriers instead of crystalline carriers which are usually polymers. These polymers include synthetic polymers such as povidone (PVP), polyethylene glycols (PEG) and polymethacrylates as well as natural products-based polymers such as hydroxylpropylmethyl-cellulose (HPMC), ethylcellulose, and hydroxypropylcellulose or starch derivatives like cyclodextrins.[27,28]

c) Third generation: Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties. Therefore, third generation solid dispersions appeared. The use of surfactant such as inulin, inutec SP1, compritol 888 ATO, gelucire 44/14 and poloxamer407 as carriers was shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability.[29,30,31]

Biopharmaceutical Classification System of Drugs

The drug substances are categorized into 4 classes based on their solubility parameters and permeability to bio membranes. Such classification system is known as BCS system. The BCS is an experimental model that measures permeability and solubility under prescribed conditions. BCS is used as a tool in drug development in various pharmaceutical industries.[32,33,34]

The BCS defines three dimensionless numbers; dose number, dissolution number, absorption number.

In BCS, class II drugs having low solubility and high permeability and BCS class IV drugs having low solubility and low permeability. So, solid dispersion technologies are particularly used for improving the oral absorption and bioavailability of BCS class II and BCS class IV.[35,36,37]

Techniques for Solid Dispersion

There are various methods for solid dispersion: -

I. Fusion method

This method is also known as "melting method". This method was first proposed by 'Sekiguchi and Obi' in 1961, to prepare fast release solid dispersion dosage forms. It involves the preparation of a physical mixture of drug and a water-soluble carrier, heating it until it melted. The melted mixture is then solidified and cooled rapidly in an ice- bath under vigorous stirring.[38,39,40]

II. Solvent evaporation method

This method is used for the first to dissolving both the drug and carrier in a common solvent ant then evaporate under vacuum to produce a solid solution. In this method, the physical mixture of the drug and carrier is added in a common solvent, which is evaporated until a clear, solvent free dried mass is left. Mixing is at molecular level is preferred because this leads to optimal dissolution properties.[41,42]

III. Melting solvent method (melt evaporation method)

In this method the drug is dissolved in a suitable liquid solvent and the solution is directly Incorporated into the melt carrier (PEG) which is then evaporated until a clear, solvent free film is left. The film is further dried to a constant weight. This method has advantages of both the melting and solvent methods.[43,44,45]

IV. Hot - melt extrusion

This method is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. In this method the physical mixture of drug and carrier is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets or powder etc.[46,47,48]

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V. Supercritical fluid technology (SFT)

This technique can be applied to the preparation of solvent free solid dispersion. Supercritical fluids are those fluids whose temperature and pressure are greater than its critical temperature (TC) and critical pressure (TP).[49,50] The most commonly used supercritical fluids (SCFs) includes carbon dioxide, nitrous oxide, water, methanol, ethanol, ethane, n-hexane and ammonia. Carbon dioxide is most commonly used. In this technique the drug and the carrier are dissolved in a common solvent. When the solution is sprayed, the solvent is rapidly extracted by SCFs, resulting in precipitation of solid dispersion particles on the wall and bottom of the vessel.[51,52,53]

VI. Electrospinning method

It is a process in which the solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir.[54,55,56] The reservoir contains a polymer solution or melt and a conductive collection screen. This technique has tremendous potential for the preparation of nanofibers and controlling the release of biomedicines. It is simplest and cheapest process so it can be utilized for the preparation of solid dispersions in future.[57,58,59]

VII. Melt agglomeration method

This technique has been used to prepare the solid dispersion where the binder acts as a carrier. Solid dispersions are prepared either by heating the binder, 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 excipients (spray-on procedure) using a high shear mixture.[60,61,62] Melt- in procedure gives higher dissolution rates than spray-on procedure with poloxamer 188, PEG 3000 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. Melt-in procedure also results in the homogenous distribution of drug in agglomerates.[63,64,65]

VIII. Spray drying method

This method was initiated by atomising suspension or solution into fine droplets followed by a drying process. It is a useful method to obtain spherical particles and narrow distributed particles. In this method drug and carrier is dissolved in a volatile organic solvent with the help of magnetic stirrer to get a clear solution.[66,67,68] Solvent is evaporated at 40^{o}C under reduced pressure by using vacuum evaporator. Dry mass is obtained in a dessicator over anhydrous calcium chloride for 1-2 days depending upon the removal of solvent. The product is then crushed, pulverized and sieved through a suitable mesh size.[69,70,71]

IX. Lyophilization technique

This is a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion. In order to get porous, amorphous powder with a high degree of interaction between drug and cyclodextrins, lyophilization technique is considered suitable.[72,73,74]

X. Use of surfactants

Adsorption of surfactants on solid surface can modify their hydrophobicity, surface charge, and also interfacial processes such as dispersion/flocculation, floatation, wetting, solubilization, detergency etc. surfactants have been reported to cause salvation/plasticization, manifesting in reduction of melting point of active pharmaceutical ingredients, glass transition temperature and combined glass transition temperature of solid dispersions. Because of these unique properties surfactants have attracted the attention of investigators for preparation of solid dispersions.[75,76,77]

XI. Dropping Method

Dropping technique facilitate the crystallization of different chemicals, which is a new procedure for producing round particles from melted solid dispersions. A solid dispersion of a melted drug carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles.[78,79,80] 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. The dropping method does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation technique. This method also avoids the pulverization, sifting and compressibility difficulties.[81,82,83]

XII. Adsorption on Insoluble Carriers/ Fluidized Bed System/ Surface Solid Dispersion

The approach involves a fluidized bed coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce either granules ready for tableting or drug-coated pellets for encapsulation in one step.[84,85,86] The method has been applied for both controlled and immediate-release solid dispersions. Itraconazole coated on sugar sphere, is made by layering onto sugar beads a solution of drug and hydroxy propyl methylcellulose (HPMC) in an organic solvent of dichloromethane and ethanol.[87,88] A solid solution of drug in HPMC is produced upon coating (co- solvent evaporation) and controlled drying of coated beads in a closed Wurster process. As this thin film dissolves in water or gastric fluid, the molecularly dispersed Itraconazole is released at supersaturated concentration. HPMC acts as a stabilizer to inhibit recrystallization of the Itraconazole. The supersaturated solutions of Itraconazole are sufficiently stable to allow for absorption and distribution.[89,90]

XIII. Surface Active Carriers

A surface-active carrier may be preferable in almost all cases of the solid dispersion of poorly water-soluble drugs. Such carriers prevented the formation of the water insoluble surface layers by dispersing or emulsifying the drug in a finely divided state, which

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resulted in a high surface area of the drug.[91,92] The commonly used surface-active carriers in solid dispersions are Gelucire 44/14, vitamin E and Tween 80. One of the limitations of bioavailability enhancement by this method might be the low solubility of drug in available carriers.[93,94]

XIV. Solvent Melt Method

In solvent melt technique, the drug is dissolved in an organic solvent and mixed with the melted carrier. The solvent is then evaporated and the resultant product is pulverized to the desired size. This technique has been particularly useful for thermo labile drugs with high melting point and it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.[95,96]

XV. Kneading Technique

In kneading technique, a mixture of drug and carriers are wetted with water and kneaded thoroughly for 30 minutes in a glass mortar. The paste is dried under vacuum for 24 hours and then passed through sieve no.60 and stored in a desiccator. Solid dispersion involving PVP and valdecoxib were prepared by kneading technique. This method cannot be applied to all poorly water-soluble drugs.[97,98]

XVI. Inclusion Complexes

The improvement in solubilization ability within these water-soluble polymers/drug-included cyclodextrin (CD) aggregates requires less cyclodextrin to solubilise the same amount of drug, reducing the volume constraints present for non-aggregated CDs and increasing the range of delivery technologies available. Drug-CD complexes are commonly formed through either supersaturating a CD solution with drug and mildly agitating the solution for an extended period of time, or adding a mass of drug to a CD and solvent slurry and 'kneading' to produce a paste which is then dried and sieved. This method is not applicable to all poorly water-soluble drugs.[99,100,101]

XVII. Direct Capsule Filling

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug.[102,103] This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique.[104,105] However, Polyethylene glycol was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug. A surfactant must be mixed with the carrier to avoid formation of a drug-rich surface layer.[106,107,108]

XVIII. Spray drying

The solvent-based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule. In this methods drug and carrier is dissolved in a volatile organic solvent with help of magnetic stirrer to get a clear solution and solvent is evaporated at 400 ^{0}C under reduced pressure by using vacuum evaporator, obtained mass is dried in a desiccator over anhydrous calcium chloride for 1-2 days depending on the removal rate of solvent.[109,110] The product is crushed, pulverized and sieved through a suitable mesh number sieve. This technique was successfully employed for the preparation of solid dispersions of etoricoxib, carbamazepine and glibenclamide.[111,112]

XIX. Particle Size Reduction

The bioavailability of low solubility drugs is often intrinsically related to drug particle size. By reducing particle size, the increased surface area may improve the dissolution properties of the drug to allow a wider range of formulation approaches and delivery technologies.[113,114]

XX. Co-evaporates

In this technique, drug and copolymer are dissolved separately in same organic solvent and then these two solutions are mixed with further evaporation of solvent under either vacuum or using flash evaporation. Co-evaporates have mainly been employed for dermatological products.e.g., co-evaporates of hydrocortisone - PVP and betamethasone dippropionate– PVP.[115,116,117]

XXI. Co-precipitate

Co-precipitation is a recognized technique for increasing the dissolution of poorly water solubledrugs, so as to consequently improve bioavailability.[118,119] In this method nonsolvent is added drop wise to the drug and carrier solution, under constant stirring. In the course of the nonsolvent addition, the drug and carrier are co-precipitated to form micro particles. At the end, the resulted micro particle suspension is filtered and dried.[120,121]

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