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REVIEW ARTICLE

A RECENT APPROACH FOR SOLUBILITY AND BIOAVAILABILITY ENHANCEMENT: SOLID DISPERSION

Patel Chirag J*[1], Prof. Satyanand Tyagi[2], Dadarwal Poonam[3], Mangukia Dhruv[3], Pravin Yadav[3], Sojitra Ishita[4], M. Srujan Kumar[5], Anil K. Gupta[6]

[1]Editor-in-Chief, Tyagi Pharmacy Association (TPA) & Scientific Writer (Pharmacy), Chattarpur, New Delhi, India-110074.

[2]President & Founder, Tyagi Pharmacy Association (TPA) & Scientific Writer (Pharmacy), Chattarpur, New Delhi, India-110074.

[3]Department of Pharmaceutics, Maharishi Arvind Institute of Pharmacy, Mansarovar, Jaipur, Rajasthan, India-302020.

[4]Department of Pharmaceutics, Parul Institute of Pharmacy, Vadodara, Gujarat, India-391760.

[5]Department of Pharmaceutics, Samskruti College of Pharmacy, Ghatekesar, Hyderabad, Andhra Pradesh, India-501301.

[6]Research Scholar, Bhagwant University, Institute of Pharmacy & Research Center, Ajmer, Rajasthan, India-305004

ABSTRACT

Currently only about 8% of the new molecules have both high solubility and permeability. The drugs therapeutic efficacy depends upon the bioavailability and ultimately upon the solubility. Improving oral bioavailability of drugs those given as solid dosage forms remains a challenge due to solubility problems. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include nanonization, sonocrystallization, micronization, supercritical fluid method, spray freezing into liquid and lyophilization, evaporative precipitation into aqueous solution, use of surfactant, use of salt forms, solvent deposition, use of co-solvent, hydrotropy method, solubilizing agents, modification of the crystal habit, co-crystallisation, complexation and drug dispersion in carriers. Among several methods, solid dispersion has attracted attention of the researchers for previous 50 years. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug.

KEY-WORDS: Solid dispersion, Solubility, Carrier, Drug

INTRODUCTION:

In general the oral route of drug administration is the most common and preferred method of delivery as it is the simplest and easiest way of administering drugs [1, 2]. There are strong evidences that oral administration produces equally good clinical results, has fewer complications, is less costly and causes less patient inconvenience. Most of the new chemical entities (NCE) under development now-a-days are intended to be used as a solid dosage form that originates an effective and reproducible *in vivo* plasma concentration after oral administration due to many advantageous features of this rout like, greater stability, smaller bulk, accurate dosage and easy production [1, 3]. But the fact is most NCEs are poorly water soluble drugs, not well-absorbed after oral administration and the oral delivery of such drugs is frequently associated with low bioavailability, high intra- and inter-subject variability, and a lack of dose proportionality [4].

A drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Therefore, pharmaceutical researcher's focuses on two areas for improving the oral bioavailability of drugs include: (i) enhancing solubility and dissolution rate of poorly water-soluble drugs and (ii) enhancing permeability of poorly permeable drugs [5, 6]. It has been estimated that 40% of new chemical entities currently being discovered are poorly water soluble [7, 8]. To overcome the problems associated with oral absorption and bioavailability issue, various strategies have been utilized including prodrug formation (Murtha and Ando, 1994) complexation, microcapsulation, the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrines, nanoparticles, solid dispersions, self emulsifying drug delivery system etc. However ahead of all, solid dispersion is the most promising method to the scientists due to the ease of preparation, ease of optimization and reproducibility of the manufacturing method [1, 4].

Chiou and Riegelman defined these systems as the dispersion of one or more active ingredient in an inert carrier matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method [9, 10]. Earlier studies show that solid dispersion systems increased the drug dissolution due to improved solubility, wettability and dispensability using hydrophilic carriers [11].

Advantages [12, 13]:

1. Enhancement of the active agent bioavailability to a desirable extent.

*Corresponding author: Patel Chirag J

2. Homogeneous distribution of small amount of drug at solid state is possible to attain.
3. More acceptable to patients than solubilization product, since solid dispersion rises to solid oral dosage forms instead of liquid as solubilization products.
4. Avoiding polymorphic changes and the consequent bioavailability problems.
5. Transformation of liquid or gaseous form of the drug in to solid form is possible.

Limitations [12, 14, 15]:

1. Poor stability of dosage from.
2. Laborious and expensive method of preparation.
3. Reproducibility of its physico-chemical properties.
4. Aggregation, agglomeration and air adsorption during formulation.
5. Difficulty in pulverization and sifting because of their tacky and soft nature.
6. Decrease in dissolution rate with aging ford.

CLASSIFICATION OF SOLID DISPERSIONS [5]:

Solid dispersions can be classified into simple eutectic mixtures, solid solutions, and physical mixtures of microcrystalline drug dispersed in carriers. A simple eutectic mixture consists of two compounds that are completely miscible in the liquid state but only to very a limited extent in the solid state. A eutectic mixture of a sparingly water soluble drug and a highly water-soluble polymer or carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline component and these components are assumed to crystallize simultaneously in very small particulate sizes and thus increases the rate of dissolution of a poorly water-soluble drug. Solid solution consists of a solid solute dissolved in a solid solvent. In solid solution, particle size is reduced to molecular level. Solid solutions of lower drug concentrations generally give faster dissolution rate, and the drug dissolution improves markedly with an increase in molecular weight of a water-soluble polymer such as PEG. Solid solutions can be further classified into three categories based on their miscibility into continuous versus discontinuous solid solutions.

The solid molecules may be dispersed in the solvent in three fashions these are: (a) substitutional crystalline; (b) interstitial crystalline; and (c) amorphous solid solutions.

MANUFACTURING PROCESSES FOR PREPARATION OF SOLID DISPERSIONS:

Various methods deal with the challenge of mixing a matrix and a drug, preferably on a molecular level, while matrix and drug are generally poorly miscible. During many of the preparation techniques, de-mixing (partially or complete) and formation of different phases is observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted. It was already recognized in one of the first studies on solid dispersions that the extent of phase separation can be minimized by a rapid cooling procedure. Generally, phase separation can be prevented by maintaining a low molecular mobility of matrix and drug during preparation. On the other hand, phase separation is prevented by maintaining the driving force for phase separation low for example, by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible.

1. Solvent Evaporation Method [9]:

The solvent-based process uses organic solvent to dissolve and intimately disperse the drug and carrier molecule. Identification of a common solvent for both drug and carrier can be problematic, and complete solvent removal from the product can be a lengthy process. Moreover suitable alterations in the concentrations used for solvent evaporation may lead to large changes in the product performance. In addition large volumes of Solvents are generally required which can give rise to toxicological problems. Many investigators studied solid dispersions of Meloxicam, Naproxen, Rofecoxib, Felodipine, Atenolol, and Nimesulide using solvent evaporation techniques. These findings suggest that the above-mentioned technique can be employed successfully for improvement and stability of solid dispersions of poor water drugs. Bhanbhun M Suhagic suggested a method for preparation of solid dispersions of etoricoxib employing solvent evaporation process wherein carrier is poly ethyl glycol (PEG) and PVP along with drug were dissolved in 2-propanol to get a clear solution and solvent was evaporated. The prepared solid dispersions exhibited improved dissolution attributed to decreased crystallinity, improved wetting and improved bioavailability.

2. Melting method/ Fusion method [5, 9]:

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term fusion method is preferred. The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The fusion process is technically the less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state. This process employs melting of the mixture of the drug and carrier in metallic vessel heated in an oil bath, immediately after fusion, the sample are poured onto a metallic plate which is kept at ice bath. A modification of the process

involves spray congealing from a modified spray drier onto cold metal surface. Decomposition should be avoided and is affected by fusion time and rate of cooling. Another modification of the above method, wherein solid dispersions of Troglitazone- polyvinyl pyrrolidone (PVP) K-30 have been prepared by closed melting point method. This method involves controlled mixing of water content to physical mixtures of Troglitazone PVP K-30 by storing at various equilibrium relative humidity levels (adsorption method) or by adding water directly (charging method) and then mixer is heated. This method is reported to produce solid dispersions with 0% apparent crystallinity. On the other hand, the fusion process does not require an organic solvent but since the melting of sparingly water-soluble drug and water-soluble polymer entails a cooling step and solid pulverizing step, a time consuming multiple stage operation is required. To overcome this problem have described a method conceptualizing the formation of a solid dispersions as the solid-to-solid interaction between a sparingly water soluble drug, nilvadipine and water soluble polymer which, unlike conventional production method, comprises mixing a sparingly water soluble drug and water soluble polymer together under no more than the usual agitation force with heating within the temperature region not melting them, instead of heating the system to the extent that the two materials are melted , the sparingly water soluble drug can be made amorphous to have never been achieved by any dry process heretofore known.

3. Melt agglomeration on process [9]:

This technique has been used to prepare solid dispersions wherein the binder acts as a carrier. In addition, solid dispersions are prepared either by heating 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) by using a high shear mixer. A rotary processor has been shown to be alternative equipment for melt agglomeration. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of solid dispersions by melt agglomeration. Since these parameters results in variations in dissolution rates, mechanism of agglomerate formation and growth, agglomerate size, agglomerate size distribution and densification of agglomerates. It has been investigated that the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition the melt in procedure also results in homogenous distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles.

4. Hot-melt Extrusion [9, 16]:

For pharmaceutical systems, several research groups have recently demonstrated that the hot-melt extrusion technique is a viable method to prepare granules, sustained release tablets, and transdermal and transmucosal drug delivery systems. Molten thermoplastic polymers during the extrusion process can function as “thermal binders and/or drug release retardants” once they exit the extruder and solidify. For film processing, a polymer can be shaped into a film via the heating process rather than through the traditional solvent-cast technique. The process has been useful in the preparation of solid dispersions in a single step. Hot-melt extrusion method is used in the preparation of various dosage forms in the pharmaceutical industry such as preparation of sustained release pellets. The drug carrier mix is filled in the hopper and is conveyed, mixed and melted by the extruder.

The die then shapes the melt in the required form such as granules, pellets, films or powder that can be further processed into conventional tablets or capsules. The advantages of hot-melt extrusion include lower temperature and shorter residence time of the drug carrier mix (< 2 minutes), absence of organic solvents, continuous operation possibility, minimum product wastage, good control of operating parameters and possibility to scale up. Oxygen and moisture may be excluded almost completely for substances prone to oxidation and hydrolysis. The disadvantages are few and mainly relate to negative effects of shear force. A fast-release dosage form of carbamazapine was prepared using lactose as a hydrophilic filler and PEG 4000 as a binder at a temperature below its melting point. Solubility and the dissolution rates of 17-ß-estardiol hemihydrate was improved using PEG 6000, polyvinylpyrrolidone (PVP), or a vinylpyrolidone/vinyl acetate-copolymer and Sucroester WE15 or Gelucire 44/14 employing this process. Highly enhanced dissolution rate from extruded powder containing 10% 17 ß-estardiol hemihydrate 50% PVP and 40% Gelucire 44/14 was preserved when processed into tablets and met the United States Pharmacopoeia (USP) XXIII requirements. For pharmaceutical applications, hot-melt extrusion offers many advantages over traditional processing techniques.
The advantages are as follows,

a. Fewer processing steps are needed and thus, time-consuming drying steps are eliminated.
b. There are no requirements on the compressibility of the active ingredients and the entire procedure is simple, continuous, and efficient.
c. Neither solvents nor water are used in this process.
d. The bioavailability of the drug substance could be improved when it is dispersed at the molecular level in hot-melt extruded dosage forms. To produce the pharmaceutical dosage forms via hot-melt extrusion, a pharmaceutical grade polymer must be selected that can be processed at a relatively low temperature due to the thermal sensitivity of most drugs. All components must be thermally stable at the processing temperature during the short duration of the heating process.
e.The intense mixing and agitation during processing cause suspended drug particles to disaggregate in the molten polymer, resulting in a more uniform dispersion of fine particles.

5.Electrostatic Spinning Method [5, 9]:

The electrostatic spinning method technology used in the polymer industry combines solid solution/dispersion technology with nanotechnology, this technology is now applied in the pharmaceutical field. Electro spinning is a process in which 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 containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor s cone). Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to the collection screen via the electrostatic force. The Coulombic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited by the viscosity increase, as the charged jet is dried. Water-soluble polymers would be useful in the formulation of immediate release dosage forms, and water-insoluble (both biodegradable and nonbiodegradable) polymers are useful in controllable dissolution properties. Fabrics generated by water-soluble carriers could be used in oral dosage formulations by direct incorporation of the materials into a capsule. Itraconazole/ HPMC nanofibers have been prepared using this technique. Electro spun samples dissolved completely over time, with the rate of dissolution being dependent on the type of formulation presentation and the drug: polymer ratio. Because the technique has been successfully used in other fields, this technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest. The technique can be extended in the pharmaceutical industry for the preparation of solid dispersions.

CHARACTERIZATION [12, 17-19]:

A number of techniques can be employed to identify the physical nature of the solid dispersions. No single method however, can furnish the complete information and hence a rational combination of the methods is preferred.

1. Thermal Analysis:

a. Thermo-microscopic Methods:

This is a visual method of analysis using a polarized microscope with a hot stage to determine the thaw and melting points of solids. The method is advantageous as small amount of sample is required and direct observation of the changes taking place in the sample through the thaw and melt stages. The technique has been used to support DTA or DSC measurement. It gives information about the phase diagram of binary systems.

b. Differential thermal analysis (DTA):

This is an effective thermal method for studying the phase equilibrium of pure substance or solid mixture. Differential heat changes that accompany physical and chemical changes are recorded as a function of temperature as the substance is heated at uniform rate. In addition to thawing and melting, polymorphic transition, evaporation, sublimation, desolvation and other types of changes such as decomposition of the sample can be detected. The method has been used routinely to identify different types of solid dispersion. The greatest advantage of using this technique is in constructing phase diagram of high reproducibility; a higher temperature range is permitted, greater resolution realest. A sample size of less than 1 mg can be used.

2. Differential Scanning Colorimetry (DSC):

In DSC, both the sample and reference materials are subjected to linear heating, but both are maintained at the same temperature. Here change in temperature is not recorded, but the heat flow into the system is recorded which is required to maintain isothermal conditions. The method is useful to study the behavior of crystallization and melting and deriving phase diagrams of solid dispersions.

3. FT-IR Spectroscopy:

FT-IR spectroscopy used to study the possibility of an interaction between drug and polymer in solid state.

Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix.

4. X-ray diffraction (XRD):

In this analytical tool, intensity of x-ray reflection is measured which is a function of diffraction method. The diffraction method is very important and efficient tool in studying the physical nature of solid dispersion which has been used in crystal structure studies in two different ways.

a. Single crystal x-ray crystallography dealing with the determination of bond angle and inter atomic distances.

b. Power x-ray diffraction dealing with the study of crystal lattice parameter, where the x-ray diffraction intensity from a sample is measured as a function of diffraction angles.

Thus, changes in diffraction pattern indicate changes in crystal structure. The relationship between wavelength, of the x-ray, the angle of diffraction, θ, and the distance between each set of atomic planes of crystal lattice, d, is given by equation: $M\lambda = 2d \sin \theta$, where M represent the order of diffraction.

5. Scanning Electron Microscopy:

It usually gives primary information of system and tells about the amorphous or crystalline nature of solid dispersions. The application of the electron microscope technique, however, usually limited to chemicals with high resolution.

6. Thermodynamic methods:

In this analysis, the phase diagrams of eutectic and solid solution systems give the value of heats of fusion, entropies and partial pressures at various compositions that helps to determine the solubility gap below the solid-liquid equilibrium temperature.

7. Dissolution rate determination:

The method involves comparing the in vitro dissolution rates of the solute component from a constant-surface tablet made from molecular dispersion (i.e., solid or glass solution) with a physical mixture of the same chemical composition.

The technique is simple to perform. It tells whether the solid dispersion has improved the dissolution rate or not. The degree of crystallinity can also be studied if it is carried out under standard conditions.

CONCLUSION:

Lipophillic molecules especially those belonging to the Biopharmaceutics Classification System (BCS) Class II and IV, dissolve slowly, poorly and irregularly, and hence poses serious drug delivery challenges like incomplete release from the dosage form, poor bioavailability etc. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. Solid dispersion technology is one of the possible modes that increase the solubility of poorly soluble drugs. Solid dispersion has set itself as a proven technology for the purpose with unique set of advantages and limitations. Due to the advantageous features of solid dispersions formulation scientists consider it as one of the most potential method of improving oral bioavailability, but changes in crystal behavior of drug and carrier particles during processing and storage limits the method to be commercially applicable. Improved understanding of physical stability of solid dispersions is the main driver for increasing future relevance of solid dispersions.

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