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Solubility enhancement strategies for poorly water- soluble drugs in solid dispersions: A review

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Abstract :
Solid dispersions have been employed to enhance the dissolution rates of poorly water- soluble drugs. Many approaches have been investigated for the preparation of solid dispersions. This paper reports various solubility enhancement strategies in solid dispersion. The approaches described are fusion (melting), solvent evaporation, lyophilization (freeze drying), melt agglomeration process, extruding method, spray drying technology, use of surfactant, electro static spinning method and super critical fluid technology. The paper also highlights the potential applications and limitations of these approaches in solid dispersions.

Keywords: Water soluble drug; Spray drying technology; Electrostatic spinning; Super critical fluid technology

Introduction:

Drug substances are seldom administered alone, but rather as part of a formulation in combination with one or more non-medicinal agents that serve varied and specialized pharmaceutical function. The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all the drug substances and pharmaceutical ingredients to be used in fabricating the product. An important physical-chemical property of a drug substance is solubility, especially aqueous system solubility. A drug must posses some aqueous solubility for therapeutic efficacy. For a drug to enter the systemic circulation to exert a therapeutic effect must be in solution[1]. In recent tech- nologies, innovation of combinatorial chemistry and high throughput screening can effectively discover the seeds of new drugs, which present good pharmacological ac- tivities. However 35-40 % of these new drugs discovered by those technologies suffer from poor aqueous solubility[2-3].

The solubility/dissolution behavior of a drug is key determinant to its oral bioavailability, the latest frequency being the rate-limiting step to absorption of drugs from the gastrointestinal tract[4-6]. Consequently poor solubility results in low bioavailability, increase in the dosage, large inters and intra-subject variation and large variations in blood drug concentrations under fed versus fasted conditions. Improvement of oral bioavailability of poor water-soluble drugs remains one of the most challenging aspects of drug development. The techniques/ approaches that have commonly been used to over- come drawbacks associated with poorly water-soluble drugs, in general includes micronization, salt formation, use of surfactant and use of pro- drug [7-8]. However all these techniques have potential limitations.

Micronization has several disadvantages, the main one being the limited opportunity to control important characters of the final particle such as size, shape, morphology, surface properties and electrostatic charges. In addition micronization is a high-energy process, which causes disruptions in the drug s crystal lattice, resulting in the presence of disordered or amorphous regions in the final product. The amorphous regions are thermodynamically unstable and are therefore susceptible to recrystallization upon storage, particularly in hot and humid conditions[4, 9,10]. All poorly water-soluble drugs are not suitable for improving their solubility by salt formation. The dissolution rate of a particular salt is usually different form that of parent compound. However sodium and potassium salts of weak acids dissolve more rapidly than the free salts. Potential disadvantages of salt forms include high reactivity with atmospheric car- bon dioxide and water resulting in precipitation of poorly water-soluble drug, epigastric distress due to high alkalinity. Even though use of co solvent to improve dissolution rate pose problems such as patient compliance and commercilation[11-12].

Solid dispersion (SD) technique has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs[13-14]. The term solid dispersions has been utilized to describe a family of dosage forms whereby the drug is dispersed in a bio- logically inert matrix, usually with a view to enhancing oral bioavailability. Chiou and Riegelman defined these systems as the dispersion of one or more active ingredient in an

inert carrier matrix at solid state pre- pared by the melting (fusion), solvent or melting-solvent method.[15]

SOLUBILITYENHANCEMENTSTRATE- GIES IN SOLID DISPERSIONS

Various strategies investigated by several investigators include fusion (melting), solvent evaporation, lyophilization (freeze drying), melt agglomeration process, extruding method, spray drying technology, use of surfactant, electro static spinning method and super critical fluid technology.

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[16-17]. Another modification of the above method, wherein SD(s) 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 k30 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 SD with 0% apparent crystallinity[18].

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 over- come this problem Nakano et al [19] have described a method conceptualizing the formation of a SD 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.

SOLVENT EVAPORATION METHOD

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 subtle 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 [20-21]. Many investigators studied SD of meloxicam[22], naproxen[23-24], rofecoxib[25], felodipine[21], atenolol [26], and nimesulide[27] using solvent evaporation technique. These findings suggest that the above-men- tioned technique can be employed successfully for improvement and stability of solid dispersions of poor water drugs.

Bhanbhun M Suhagic [28] suggested a method for prepa- ration of SD of etoricoxib employing solvent evaporation process wherein carrier s 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 SD(s) exhibited improved dissolution attributed to decreased crystallinity, improved wetting and improved bioavailability.

LYOPHILLIZATION TECHNIQUE

Freeze-drying involves transfer of heat and mass to and from the product under preparation [29]. This technique was proposed as an alternative technique to solvent evaporation. Lyophillization has been thought of 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. G.V.Betageri et al [30], Yalcin Topalogh et al [31], M El Badry et al [32] and M Fathy[33] have successfully investigated the potential applications of lyophilization in manufacturing of SD(s).

D J V Drooge et al[34] suggested spray freeze-drying as a potential alternative to the above-mentioned process to produces tetrahydrocannabino containing inulin based solid dispersions with improved incorporation of tetrahydrocannabino in inulin.

MELT AGGLOMERATI ON PROCESS

This technique has been used to prepare SD wherein the binder acts as a carrier. In addition, SD(s) are pre- pared

either by heating binder, drug and excipient 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 pro- cedure) by using a high shear mixer[35].

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[36].

The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of SD(s) by melt agglomeration. Since these parameters result 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[36].

EXTRUDING METHOD

The extruding method was originally designed as an extraction / casting method for polymer alloys in plastic industry, is now used to process cereals and functionalize food materials, such as tissue products from animal proteins[39]. Hot melt extrusion approach represent the advantageous mean of preparation of SD(s) by using the twin screw hot melt extruder where only thermo stable components are relevant[40]. The extruder consists of a hooper, barrel, a die, a kneading screw and heaters. The physical mixture is introduced into the hopper that is forwarded by feed screw and finally is extruded from the die[39]. The effect of screw revolution speed and water content on the preparation of SD(s) should be investigated, since these parameters have profound impact on the quality of SD(s). Nakamichi et al[41]studied that presence of kneading paddle element of screw results in super saturation on dissolution testing while slow revolution rate of screw and addition of the suitable amount of water increased rate of dissolution although no super saturation occurred. In addition, high screw speed high feed rate processes in comparison with low screw speed low feed rate processes caused an increase in extrudate radius and porosity and de- crease in mechanical strength and drug release rate from the matrix attributed to the expansion promoted under certain extrusion conditions[42].

To reduce the melt viscosity in the extrudate and to be able to decrease temperature settings, a plasticizer can be added to the formulation. Typically, conventional plasticizer such as triacetin or polyethylene glycol is used in concentration range of 5-30 % weight of the extrudate that lowers the processing temperature. Carbon dioxide can act as temporary plasticizer. During extrusion carbon dioxide is transformed in gaseous phase. As a consequence carbon dioxide escapes from extrudate and does not appear in final product[43]. The role of methylparaben[44] and sorbitol[45] has also been investigated as plasticizer in preparation of SD(s) in extrusion method.

This method has already been used successfully to pre- pare SD(s) of itraconazole and hydroxypropylmethylecellulose(HPMC) [46],indomethacin/lacidipine/nefidipine/ piroxicam/ tobutamide and polyvinylpyrrolidone (PVP) [47], itraconazole[48] and HPMC 2910/ Eudragit e 100 or a mixture of Eudragit E 100-PVP vinyl acetate 64 to improve solubility and dissolution rate of poor water soluble drugs.

SPRAY DRYING

The manufacture of milk powder was one of the first applications of spray drying when the method was developed in 1920. Today, spray drying finds great utility in pharmaceutical industry because of the rapid drying and specific characteristics such as particle size and shape of the final product. In addition, it is simple and cost effective, as it is 30-50 times less expensive than freeze-drying. It is an established method that is initiated by atomizing suspensions or solutions into fine droplets followed by a drying process, resulting solid particles. The process allows production of fine, dust free powder as well as agglomerated one to precise specifications. The operating conditions and dryer de- sign depends upon the drying characteristics of the product and require powder specifications [49-51].

SD(s) of loperamide and peg 6000 were prepared by this technique, wherein solutions containing different concentrations of loperamide relative to the total amount of solid were spray dried. After spray drying, the

dispersions were dried at 40^0C under vacuum until constant weight. Solvent used was dichloromethane. The prepared SD(s) exhibited higher dissolution rates than that of pure crystalline loperamide[52]. Chouhan et al [53] studied the suitability of this technique for prepara- tion of SD(s) of glibenclamide polyglcolized glycerides. This study revealed the improvement in solubility and dissolution rates, also improvement in the therapeutics efficacy of amorphous glibenclamide in SD(s) was ob- served. Some other investigators [54-55] also reported im- provement in solubility and dissolution rate.

The frequent use of the organic solvent in spray drying pose problems such as residues in products, environ- mental pollution and operational safety as well as corporate problems such as capital investment. Tanno et al [56] described a process for producing the SD(s) of poorly water-soluble drugs using water-soluble polymer dispersion and/ or water-soluble polymer solution and the plasticizer solution by using 4-nozzle spray gun.

The spray drying technique is a useful method to obtain spherical particle and narrow distribution. The role of porous materials such as calcium silicate, controlled pore glass and porous cellulose is appreciated to formulate solid dosages forms because they confer special characteristics such as decrease of melting point and a decrease in the crystallinity of drug entrapped in pores. In addition, porous materials control polymorphs and sta- bilizes meta-stable crystals in SD(s) under sever storage conditions. Moreover, porous silica has been re- ported to improve solubility and dissolution rates of indomethacin and tolbutamide [57-58].

THE USE OF SURFACTANT

The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, adsolubilization, detergency, enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions[59-60].

Recently a new class of surfactants, gelucires have been proposed with different melting points and HLB (hydrophilic and lipophilic balance) values. Gelucire excipients have been used in the formulation of semi solid dispersions. They are solid waxy materials, which are amphiphilic in character. Gelucires are the saturated polyglycolized glycerides consisting of mono-, di-, and triglycerides and of mono- and di-fatty acid esters of polyethylene glycol. The nature and proportion of each component are specific to a given grade of gelucire. Gelucires with low HLB can be employed to decrease the dissolution rate of drugs and higher HLB ones for fast release. Gelucire 44/14 and gelucire 50/13 are two examples of this synthetic group where 44 and 50 rep- resent melting point, while 14 and 313 represent HLB values of gelucire respectively 61-62. Solid dispersions of antiviral agent uc-781-polyethylene glycol 6000- gelucire 44/14 and UC-781- PEG 6000-gelucire 44/14- PVP k 30 were studied. Improvement in solubility, dis- solution and stability was observed [63-64].

Labrasol, of same chemical nature as gelucire, is a clear liquid surfactant with a HLB of 14. Solid dispersions of piroxicam with labrasol have also resulted in improved solubility and dissolution when compared with pure drug The amphiphilic poly (ethylene oxide)-poly (propylene oxide)- poly (ethylene oxide) (PEO-PPO-PEO) block polymers, known as poloxamer or pluronics represent an- other class of surfactants. These are available in vari- ous molecular weights and PEO/PPO ratios, and hence offer a large variety of physico-chemical properties [65]. These block polymers are extensively used in the phar- maceutical industry as defoaming agents, gelling agents, detergents, dispersing agents, emulsifying agents and solubilizing agents[66]. When used in relatively high quantities, poloxamer imparts sustained-release properties to solid dosage forms, by forming a lipid matrix[67].

Solid dispersions using pluronic f- 68 (a type of poloxamer) as a carrier were studied for improving the dissolution and bioavailability of abt-963, a poorly water-soluble compound. Results showed that the solid dispersion substantially increased the in vitro-dissolution rate of ABT-963. A significant increase of oral bioavailability compared with conventional capsule formulation was also reported[68].

The presence of water and polar water-miscible solvent, a partially water-miscible solvent, a non- ionic surfactant, an anionic surfactant and cationic surfactant affect domain of the PEO-PPO-PEO block copolymer self- assembly[69].

Therefore, organic solvents and surfactants should be used with great care for preparation solid dispersion while using in combination with poloxamer.

Inutec SPI, a derivative of inulin prepared by the reaction between isocyanates and the polyfructose back- bone in the presence of a basic catalyst such as a tertiary amine or lewis acid, has also been evaluated as carrier in formulation of solid dispersions for a poorly water- soluble drug. Inutec SPI has low viscosity and stability effect on emulsion and suspension. Dissolution properties of SD(s) made up of itraconazole and Inutec SPI were improved in comparison to pure itraconazole or physical mixtures with Inutec SPI[4].

Hemant et al [70] and Sheen et al [71] studied that polysor- bate [80], a commonly used surfactant, results in improve- ment of dissolution and bioavailability of poorly water- soluble drug attributed to solubilization effect of surface active agent. Polysorbate 80 also ensues complete release of drug in metastable finely dispersed state having large surface area.

ELECTROSPINNING

Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle[72]. 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[73]. This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest[74-77]. This technique can be utilized for the preparation of solid dispersions in future.

SUPER CRITICAL FLUID (SCF) TECH NOLOGY

This technology has been introduced in the late 1980s and early 1990s, and experimental proofs of concept are abundant in the scientific literature for a plethora of model compounds from very different areas such as drugs and pharmaceutical compounds, polymers and biopolymers, explosives and energy materials, super- conductors and catalyst precursors dyes and biomolecules such as proteins and peptides. From the very beginning of supercritical fluid particle generation research, the formation of biocompatible polymer and drug-loaded biopolymer micro-particles for pharmaceutical applications has been studied intensively by a num- ber of researcher groups[78].

Since the first experiences of Hannay et al in 1879, a number of techniques have been developed and patented in the field of SCF-assisted particle design. These methods use.

SCFs either as solvent: rapid expansion from supercritical solution (RESS) or antisolvent: gas antisolvent(Gas) supercritical antisolvent (SAS), solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS). Conventional methods, i.e. Spray drying, solvent evaporation and hot melt method often result in low yield, high residual solvent content or thermal deg- radation of the active substance.

In the supercritical fluid anti-solvent techniques, carbon dioxide is used as an anti-solvent for the solute but as a solvent with respect to the organic solvent. Different acronyms were used by various authors to denote micronization processes: aerosol solvent extraction sys- tem (ASES), precipitation with a compressed fluid anti- solvent (PCA), gas anti-solvent (GAS), solution enhanced dispersion by supercritical fluids (SEDS) and supercritical anti-solvent (SAS). The SAS process involves the spray- ing of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing co-currently·

The use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient. In addition the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be car- ried out near room temperature. Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent. The reason for this depression is the solubility of the lighter component (dense gas) in the forming phase (heavier component) .

Wong et al compared the SD(s) of felodipine prepared by conventional solvent evaporation (CSE) and supercritical antisolvent precipitation (SAS) methods. The particle sizes of the SD(s) from CSE process increased at 1h after dispersed in distilled water. However the particle sizes of the SD(s) from SAS process were maintained for 6 h due to the increased solubility of felodipine. More- over, SD(s) form the SAS process showed a high dissolution rate of over 90% within 2 h showing the potential applications of SCE technology in preparation of SD(s)·

CONCLUSION

The solubility of drugs in aqueous media is a key factor highly influencing their dissolution rate and bioavailability following oral administration resulting in low bioavailability. Solubility enhancement of these drugs remains one of the most challenging aspects of drug development. A variety of devices have been developed over the years to enhance the drug solubility and dissolution of the drugs. The solid dispersion method is one of the effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs. Various techniques, described in this review, are suc- cessfully used for the preparation of SD(s) in the bench and lab scale and can be used at industrial scale also.

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