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PARTICLE ENGINEERING TECHNIQUES TO ENHANCE DISSOLUTION OF POORLY WATER SOLUBLE DRUGS

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ABSTRACT

Poor aqueous solubility of a drug is an industry wide issue for pharmaceutical scientists in dosage form development. Numerous approaches have been developed for solubility enhancement of biopharmaceutical class II drugs (low solubility and high permeability). Particle engineering techniques are developed to modify the physicochemical, micromeritic and biopharmaceutical properties of the poorly soluble drugs and hence solubility. Various particle engineering processes like super critical fluid technology, cryogenic technology, nanomilling, evaporative precipitation into aqueous solution, melt sonocrystallization and cryo-vacuum; etc methods were developed based on the drug properties and requirement of nanoparticles characters. Patented nanomilling processes have come up based on the principles of pearl milling (nanocrystals), high-pressure homogenization (dissocubes, nanopure) and combined precipitation-homogenization (nanoedge). The use of these processes has improved *in vitro* dissolution rates and *in vivo* bioavailabilities of many poorly water soluble drugs. This review highlights several commercially available particle engineering processes recently reported in the literature for increasing the dissolution properties of poorly water soluble drugs.

Keywords: Nanoparticles engineering process, poorly water soluble drug, wet milling, high pressure homogenization, supercritical fluid, melt sonocrystallization.

INTRODUCTION

It is most difficult to develope a new molecule with good pharmacological activity and desired solubility and permeability. It has been reported that about 40 % of the compounds being developed by the pharmaceutical industry are poorly water soluble and out of which up to 40 % of pharmacologically active new molecules failed to reach market only due to their little or no water solubility[1]. Hydrophilicity and lipophilicity are two contradicting and often competing prerequisites necessary for the success of an experimental molecule as a commercial drug. From Noyes-Whitney equation, possibilities for improving drug dissolution are to increase the surface area of drug available for dissolution by decreasing the particle size of the solid compound and/or by optimizing the wetting characteristics of the compound surface[2]**.** Therefore, various formulation strategies have been investigated to improve solubility and dissolution rate of poorly water soluble drugs such as inclusion complexation with cyclodextrins, solid dispersion, salt formation, particle size reduction, use of surfactants, cosolvency, hydrotrophy etc. Modification of lattice structure or crystallinity to polymorphs, solvates, or anhydrous solids possess stability problem due to their metastable nature. Chemical approach to get water-soluble derivatives is costly because of need to demonstrate efficacy and safety of the new chemical species. The use of solubilizing excipients in drug solubilization is limited by their toxicity. Change of pH method may cause chemical instability and local tissue irritation or necrosis near the injection site at extreme pH conditions. Salt formation is used only for ionisable compounds and also the formed salts may also revert to respective acid or base forms in gastrointestinal tract. The miscibility requirement of cosolvents with water limits the capacity for the cosolvent to favorably interact with the hydrophobic solute where solubility is often exponentially related to the mole fraction of the cosolvent. High levels of surfactant can also lead to hypersensitivity reactions in certain individuals[3]. Because a molar excess of cyclodextrin must be added to drive the equilibrium toward complexation and due to their high molecular weight, large quantities of cyclodextrin may be required to reach the desired drug concentration. Micronisation increases the dissolution rate of drugs through increased surface area but it does not increase equilibrium solubility. Crystal and particle engineering strategies have notable potential to solve the problems of low aqueous solubility of drug substances. These methods are applicable not only to molecules of a specific physical and chemical nature, but to a wide range of crystalline materials, although a comprehensive knowledge of drugs at the molecular level is required to determine the appropriate approach to improve solubility and dissolution rate. In the present review different approaches of particle engineering technology are discussed to overcome solubility problem and successful delivery of the drug.

Crystal engineering

Crystal engineering offers numerous routes to improve drug solubility through crystallisation processes by forming co-crystals, metastable polymorphs, high-

energy amorphous forms and ultrafine particles. The formation of molecular complexes and co-crystals are important alternatives to salt formation, in case of neutral compounds or those having weakly ionizable groups[4]. The order for dissolution of different solid forms of drug is amorphous >metastable polymorph>stable polymorph. Co-crystallisation between two active pharmaceutical ingredients like aspirin or acetaminophen has also been reported[5].

Particle engineering

Particle engineering techniques are tools to modify the physicochemical, micromeritics and biopharmaceutical properties of the drug. Particle engineering processes includes use of super critical fluids, cryogenic technology, nanosuspension formation, evaporative precipitation into aqueous solution and melt sonocrystallization. Nanomilling can be done by precipitation, homogenization and combined precipitation-homogenization approach.

A. SUPERCRITICAL FLUID TECHNOLOGY

Super critical fluid technologies may reduce particle size and residual solvent content in one step and allow a certain control of particle size, particle size distribution, habit, morphology and polymorphic nature[6]. Particle formation is one of the most researched areas of super critical fluid (SCF) application[7]. Super critical carbon dioxide (SC CO_2) is most widely used because of its low and easily accessible critical temperature (31.2° C) and pressure (7.4 MPa), non-flammability, non-toxicity and inexpensiveness. These methods use super critical fluids either as solvent or antisolvent and/or dispersing fluid.

I. Rapid expansion of supercritical solutions (RESS)[8]: A solution of the poorly water soluble drug in a supercritical fluid is rapidly depressurised through a nozzle causing rapid nucleation of fine particles (neat or composite)[9]. In RESS, a drug is dissolved in SC CO_2 with surfactants and then this solution is sprayed over aqueous solution through nozzle leading to rapid nucleation of the supercritical fluid dissolved drug, forming fine particles with narrow size distribution in short time. This method for solubility enhancement has been investigated for phenacetin[10]and ibuprofen[11]. But drawback of this technique is that of low solubility of some drugs and surfactants in supercritical CO_2. However, this process is advantageous due to the absence of organic solvent and the uniform condition of particle formation. For SCF-insoluble polar compounds[12], a new approach called rapid expansion from supercritical solution with a non-solvent (RESS-N) is used wherein a drug dissolved in a SCF containing a cosolvent is sprayed through a nozzle to atmospheric pressure. The cosolvent significantly increases the solubility of the insoluble polar drug of interest in SC CO_2.

II. Supercritical anti-solvent (SAS): In this process, a solution of the drug in an organic solvent is contacted with a supercritical fluid that causes solid drug precipitation by anti-solvent effect[13]. Due to the intensive mixing and the absence of phase boundary, improved mass transfer and high supersaturation can be achieved[14]. This SAS process has been used for solubility enhancement of camptothesin[15] and sulfamethoxazole.[16]

III. Gas antisolvent (GAS): Intensive mixing of poorly water soluble drugs solution and CO_2 gas in large vessel causes rapid nucleation of drug to form micronized drug particles. A precipitator is partially filled with the drug solution and then gas is introduced at the bottom to achieve a better mixing. Drawback of this technique is that particle size and size distribution are difficult to control. In most cases, mother liquor cannot be completely removed and additional drying processes are required. In spite of these drawbacks, several drugs and explosives were successfully processed in this manner[17, 18].

IV. Precipitation with compressed fluid anti solvents (PCA): In this process, poorly water-soluble drug and/or polymer solutions are atomized into a chamber containing compressed CO_2 where two liquids collide and intense atomization into micronized droplets occurs. Microparticles or nanoparticles of drugs are formed by two way mass transfers: extraction of the organic solvent into CO_2 and CO_2 diffusion into the droplets. This technique of drug micronization has been investigated for phenytoin[19] and soy lecithin[20].

V. Particles from gas-saturated solutions (PGSS): The compound(s) melted/dissolved in a compressed gas and then rapidly expanded towards a low-pressure vessel causes precipitation of solid fine particles of insoluble drug[21]. This can be achieved because of the lower melting temperature of polymers in high pressure CO_2 atmosphere. This PGSS technique has been tried for nifedipine[22] and others[23].

VI. Solution enhanced dispersion by the supercritical fluids (SEDS): In this technique, the organic solvent solution of drug is impacted by a high velocity SCF causing high frictional surface forces and disintegrating solution to micro droplets. The main advantage of SEDS over the other SCF-based techniques is the direct control over the mean size and size-distribution of the product by controlling the pressure, temperature, and flow rates. A wide range of materials have been prepared as microparticles and nanoparticles using the SEDS process including salmeterol xinafoate[24], salbutamol sulphate[25] and insulin[26].

B. CRYOGENIC TECHNOLOGIES

Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with high degree of porosity at very low temperature conditions. Cryogenic inventions can be defined by the type of injection device (capillary, rotary, pneumatic, ultrasonic nozzle), location of nozzle (above or under the liquid level) and the composition of cryogenic liquid (hydrofluoroalkanes, N_2, Ar, O_2, organic solvents). After cryogenic processing, dry powder can be obtained by various drying processes like spray freeze drying[27], atmospheric freeze drying[28], vacuum freeze drying[29] and lyophilisation[29].

I. Spray freezing onto cryogenic fluids: Briggs and maxwell[30] invented the process of spray freezing onto cryogenic fluid. In this technique, the drug and the carrier (mannitol, maltose, lactose, inositol or dextran) were dissolved in water and atomized above the surface of a boiling agitated fluorocarbon refrigerant. Sonication probe can be placed in the stirred refrigerant to enhance the dispersion of the aqueous solution.

Table 1: It shows applications of various particle engineering techniques

S. NUMBER	TECHNIQUE	DRUG STUDIED	REFERENCE
1	Crystal engineering	Ibuprofen	41
2	RESS	Salicylic Acid, Paclitaxel Aspirin	42 43
3	RESSN	Aspirin, Paracetamol Lysozyme, Lipase	44 45
4	SAS	Camptothesin Sulfamethoxazole	15 16
5	GAS	Theophylline	18
6	PCA	Phenytoin Soy lecithin	19 20
7	PGSS	Nifedipine	22
8	SEDS	Salbutamol sulphate Insulin	25 26
9	SFL	Danazol	46
10	URF	Repaglinide	33
11	Controlled precipitation	Gemfibrozil Rifabutin	47 48
12	Nanocrystals	Theophylline	49
13	Microfluidization	Glipizide, Nifedipine Coenzyme Q_{10}	50 51
14	Dissocube	Compritol 888 ATO	52
15	Nanoedge	Itraconazole, Clofazimine	53
16	EPAS	Carbamazepine, Cyclosporine	54 55
17	Melt sonocrystallization	Salbutamol Sulphate Ibuprofen	56 57

II. Spray freezing into cryogenic fluids (SFL): The SFL particle engineering technology has been used to produce amorphous nanostructured aggregates of drug powder with high surface area and good wettability[31].It incorporates direct liquid–liquid impingement between the atomized feed solution and cryogenic liquid to provide more intense atomization into microdroplets and consequently significantly faster freezing rates. The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders.

III. Spray-freezing into vapor-over-liquid (SFV/L): Freezing of drugs solution in cryogenic fluid vapours and subsequent removal of frozen solvent produces fine drug particles with high wettability[32]. During SFV/L the atomized droplets typically start to freeze in the vapor phase before they contact the cryogenic liquid. As the solvent freezes, the drug becomes supersaturated in the unfrozen regions of the atomized droplet, so fine drug particles may nucleate and grow.

IV. Ultra-Rapid Freezing (URF) : Ultra-rapid freezing is a novel cryogenic technology that creates nanostructured drug particles with greatly enhanced surface area and desired surface morphology by using solid cryogenic substances. Application of drugs solution to the solid surface of cryogenic substrate leading to instantaneous freezing and subsequent lyophilization for removal of solvent forms micronized drug powder with improved solubility. Ultra rapid freezing hinders the phase separation and the crystallization of the pharmaceutical ingredients leading to intimately mixed, amorphous drug-carrier solid dispersions and solid solutions. This technique has been investigated for solubility enhancement of repaglinide[33].

C. NANOMILLING

Nanosuspensions by the virtue of their large surface area to volume ratio provide an alternative method to formulate poorly soluble compounds. Nanocrystal are produced by two approaches namely, ‘‘bottom up’’ methods and ‘‘top down’’ methods. The bottom-up approach involves dissolving drug in an organic solvent and then precipitation on addition of an antisolvent in the presence of a stabilizer. Nanomorph technology and hydrosols are examples of bottom up approach[34]. Top-down processes consist of size reduction of large drug particles into smaller particles using various wet milling techniques such as media milling (nanocrystals)[35], microfluidization[36,37] and high pressure homogenization[38]. Homogenisation can be performed in water (dissocubes) or alternatively in non-aqueous media (nanopure). A hybrid approach (nanoedge) employs both ‘bottom up’ and ‘top down’ approaches through microprecipitation and homogenization like of precipitation followed by a homogenisation to form nanosuspension[39]. Melt sonocrystallization is a bottom up approach in which ultrasonic energy is applied during the precipitation of water insoluble drugs for dissolution enhancement of poorly water soluble drugs[40]. The applications of various particle engineering techniques are shown in table 1.

CONCLUSIONS

The growing numbers of poorly water soluble drugs demand development of technologies for enhancing drug solubility. Various conventional techniques like cyclodextrin inclusion complexation, salt formation, cosolvency, hydrotrophy, solid dispersion, comminution and spray drying were being used but each were found with inherent problems of their efficacy or stability of final product. Novel technologies such as particle engineering by use of supercritical fluid, nanomilling and crystal engineering have been developed to improve drugs solubility. By using one of the above techniques, many lipophilic drugs can be formulated successfully so that in future it may be possible to utilize most of NMEs, no matter what their solubility is, if they are pharmacologically active. It is clear that the crystal and particle engineering strategies described in this review have notable potential to strengthen the available methods for addressing problems of low aqueous solubility of drug substances. These methods are applicable not only to molecules of a specific physical and chemical nature, but to a wide range of crystalline materials. The micronization of pharmaceutical materials is slowly becoming more popular, and the use of SCF technology to produce composite particles is increasing little by little. Combining SCF with special equipment methods such as spray drying, specialized nozzles, and freeze drying is useful for the production of functional particles, including drug substances. The combination of SC-CO2 technology with other technologies could potentially resolve these issues by taking a control of the physicochemical variables involved.

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