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Review

Pharmaceutical Amorphous Nanoparticles

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ABSTRACT

There has been a tremendous revolution in the field of nanotechnology, resulting in the advent of novel drug delivery systems known as nanomedicines for diagnosis and therapy. One of the applications is nanoparticulate drug delivery systems which are used to improve the solubility and oral bioavailability of poorly soluble compounds. This is particularly important because most of the molecules emerging from the drug discovery pipeline in recent years have problems associated with solubility and bioavailability. There has been considerable focus on nanocrystalline materials; however, amorphous nanoparticles have the advantage of synergistic mechanisms of enhancing dissolution rates (due to their nanosize range and amorphous nature) as well as increasing supersaturation levels (due to their amorphous nature). An example of this technology is Nanomorph™, developed by Soliqus/Abbott, wherein the nanosize drug particles are precipitated in an amorphous form in order to enhance the dissolution rate. This along with other simple and easily scalable manufacturing techniques for amorphous nanoparticles is described. In addition, the mechanisms of formation of amorphous nanoparticles and several physicochemical properties associated with amorphous nanoparticles are critically reviewed.

Introduction

There has been an incredible increase in the identification of potential drug candidates based on the application of high-throughput screening techniques, genomics, combinatorial chemistry, and *in silico* computational approaches.[1-6] Of these potential drug candidates, about 40% do not have “drug-like” properties, such as good aqueous solubility and dissolution rates.[6-9] There are a number of approaches that are utilized to increase the dissolution rate and solubility and thus oral bioavailability of poorly soluble drugs. Traditional approaches to improve drug dissolution rate and solubility include salt formation, use of solubilizing excipients, and complexation agents. However, the success of these traditional approaches has been limited due to the taxing process of selection of highly soluble salts, as well as the requirement for large quantities of solubilizing excipients and complexation agents (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020966s022lbl.pdf).

Crystalline or amorphous nanoparticles are an attractive alternative approach to enhance the rate of dissolution and solubility of poorly soluble drugs. Discrete drug particles in the range of 100-1000 nm are defined as pharmaceutical nanoparticles.[10] An increase in the exposed surface area (or surface area-to-volume ratio) by particle size reduction causes an increase in dissolution rate and thus oral bioavailability.[11,12] In addition, according to the Kelvin equation, saturation solubility (in terms of vapor pressure) of the

Abbreviations used: ACN, amorphous chitin nanoparticles; API, active pharmaceutical ingredient; APTES, 3-aminopropyltriethoxysilane; BCS, Biopharmaceutics Classification System; CGN, K-carrageenan; CMC, carboxymethyl cellulose; cps, centipoise; CTAB, cetrimonium bromide; DLS, dynamic light scattering; DMC, dimethyl chitosan; DoE, design of experiment; DS, dextran sulfate; DSC, differential scanning calorimetry; DTAB, dodecyl trimethylammonium bromide; EPL, ε-polylysine; FDA, food and drug administration; FTIR, Fourier transform infrared spectroscopy; GAS, gas antisolvent; HMW, high molecular weight; HPC, hydroxypropyl cellulose; HPβCD, hydroxypropyl β-cyclodextrin; HPMC, hydroxylpropylmethylcellulose; LMW, low molecular weight; MβCD, methyl-β-cyclodextrin; MCC, microcrystalline cellulose; MCM-41, mobile composition of matter no. 41; MMA, methyl methacrylate; MPTMS, (3-mercaptopropyl)trimethoxysilane; NME, nanoporous membrane extrusion; NPs, nanoparticles; O/W, oil in water; PBS, phosphate-buffered saline; PCL, polyε-caprolactone; PEG, polyethylene glycol; PEI, poly(ethylene imine); PLA, polylactic acid; PLGA, poly(lactic-co-glycolic acid); PLM, polarized light microscopy; PM, physical mixture; PSu, propylene succinate; PVA, polyvinyl alcohol; PVP, poly(vinylpyrrolidone); PXRD, powder X-ray diffraction; RESS, rapid expansion of supercritical solutions; RH, relative humidity; SAS, supercritical antisolvent; SAS-EM, supercritical antisolvent enhanced mass transfer; SBA-15, Santa Barbara amorphous type material-15; SCF, supercritical fluid technology; SEM, scanning emission microscopy; SLS, sodium lauryl sulfate; STPP, sodium tripolyphosphate; TEM, transmission emission microscopy; TEOS, tetraethyl orthosilicate; T_g, glass transition temperature; THF, tetrahydrofuran; TMAOH, tetramethylammonium hydroxide; TMC, trimethyl chitosan; TPGS, tocopheryl polyethylene glycol succinate; TPP, pentasodium tripolyphosphate; TRPV1, transient receptor potential cation channel subfamily V member 1; USP, United States pharmacopeia; W/O/W, water in oil in water; YMCR, Y-junction microchannel reactor.

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drug is dependent on the drug particle size (which translates to the curvature effect). Theoretically, reduction in particle size will cause an increase in drug solubility.[13] However, the actual increase in saturation solubility for "nanocrystalline suspensions" (colloidal size range 100-1000 nm) is marginal, approximately 2%-10% compared to unmilled particles. Thus, nanosized crystalline powders may not be a useful approach for solubility-limited drugs (i.e., solubility is rate limiting for oral bioavailability).[14] In the case of amorphous formulations, the solubility of the drug is increased over the crystalline form due to its high energy state (higher Gibbs' free energy).[15-17] However, amorphous formulations are unstable and will convert to the stable crystalline form over pharmaceutically relevant timescales.[18] Generally, amorphous drugs have been formulated as microsized solid dispersions prepared using techniques such as spray drying and hot melt extrusion. For both these techniques, the drug is stabilized in a polymer matrix with a higher glass transition temperature than the neat polymer. Recently, nanosized amorphous formulations, namely "nanoamorphous," have been utilized to enhance the dissolution rates and solubilities of poorly soluble drugs. Theoretically, combining nanotechnology and amorphization approaches may offer absolute or synergistic effects in terms of solubility and dissolution rates. The advantage of amorphous versus crystalline nanoparticles is the considerably higher kinetic solubility of amorphous nanoparticles, which can be as much as 10-fold to 1600-fold. Although a significant amount of research has been carried out on amorphous nanoparticles, there are no marketed drug products available, till date. The major formulation challenge associated with amorphous nanoparticles is their stability, which depends on active pharmaceutical ingredient (API) properties such as the melting temperature (T_m), T_m/T_g ratio, and the properties of the polymer or stabilizer utilized.[19-23] Amorphous systems have higher free volume or enthalpy as well as high Gibbs-free energy. Accordingly, these systems are unstable and tend to crystallize to a stable polymorph of the drug, which typically would have lower solubility. The crystallization time of an amorphous drug is a kinetically controlled process (which can vary from seconds to years) and depends on several factors such as storage temperature and moisture content. Various approaches have been used to stabilize the amorphous form of drugs. For example, crystallization inhibitors (high T_g polymers) can be added and the formulation may be stored at low temperature (50°C below the drug T_g) and low moisture/humidity conditions.[16]

Broadly, there are 2 basic methods to manufacture nanoparticles: (1) a "top-down approach" (i.e., milling/grinding of the particles to achieve the required size) and (2) a "bottom-up approach" (i.e., precipitation of drug from a solvent to an antisolvent system).[11] The top-down approach is very time consuming and usually leads to crystalline particles, whereas the bottom-up approach is less time consuming and usually leads to amorphous particles due to fast evaporation of the solvent and thus precipitation of the API as amorphous particles. The manufacturing techniques employed for amorphous and crystalline nanoparticles are listed in Table 1.

The mechanism by which nanoparticles improve the dissolution rate and bioavailability of poorly water-soluble APIs (Biopharmaceutics Classification System [BCS] Class II and II/IV) is the enhanced surface area to volume ratio as described by the Noyes-Whitney equation.[43] According to the Noyes-Whitney equation, the dissolution rate J is given by the following equation;

$$J = \frac{DA}{h}(C_s - C)$$

where J is the dissolution rate, D the diffusion coefficient of drug, A the surface area of the dissolving solid, h the thickness of the diffusion layer, C_s the saturation solubility of the compound in the dissolution medium, and C the concentration of the drug in the medium at different time points during dissolution.

Increase in the surface-to-volume ratio and thus the dissolution rate of nanoparticles improves their pharmacokinetic properties in terms of increased rate and extent of release and absorption; rapid onset of action; reduced side effects, and improved clinical performance.[11,43,44] Concurrently, the drug saturation solubility is increased as theoretically predicted by the Ostwald-Freundlich equation as below:

$$ln\frac{C_{s,r}}{C_{s,\infty}} = \frac{2\gamma V_m}{rRT}$$

where $C_{s,r}$ and $C_{s,\infty}$ (g/L) are the solubility of drug particles with radii r and $r = \infty$ (m), respectively, c the interfacial tension between the drug particles and the medium (N/m), V_m the drug molar volume (m^3/mol), R the gas constant (8.314 J/mol K), and T the absolute temperature (K).

The importance of crystalline nanosuspensions to the pharmaceutical industry can be judged by the fact that 17 formulations are already on the market and approximately 10-15 are in different stages of clinical trials (Tables 2 and 3).[34] However, one of the major concerns with nanosuspension formulations is the preservation of their physical and chemical stability in aqueous medium.[51,52] Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings being a liquid dosage form, nanosuspensions are more susceptible to both physical instability (due to crystal growth and agglomeration) and chemical instability (due to degradation of the API(s)), when compared to solid dosage forms. In fact, of all the marketed formulations, only Megace ES is in the suspension form (nanoparticulate suspension of megestrol acetate). All others are prepared as nanosuspension-based solid dosage forms, as a way to overcome instability problems. Liquid nanosuspensions can be converted into solid dosage forms by drying to obtain a powder of nanosized drug particles, which can be processed into conventional dosage forms such as tablets or capsules. Spray and freeze drying are the most common methods of removing water from aqueous systems.[51,52]

Terminologies in Solid-State Pharmaceuticals

Solid Solution

If the API is molecularly dissolved in the solid excipient matrix, it is termed a solid solution. In crystalline solid solutions, the API can occupy crystal lattice sites or the interstitial spaces. If the formulation is amorphous, such as when the API is dispersed in an amorphous polymer, the API is distributed at random between the excipient molecules, and can be present as amorphous particles or in molecular solution.[53]

Solid Dispersion

If the API is dispersed as crystalline or amorphous particles in the solid excipient matrix, it is termed a solid dispersion. The matrix may be either a small molecule or a polymer. The dispersed state may include many forms such as eutectic mixtures, crystalline/glass solutions, and amorphous/crystalline suspensions.[53]

Amorphous Solid Dispersions

Amorphous solid dispersions are dispersions of amorphous drug, which is in the molecularly dispersed state (i.e., as a glass solution) in the amorphous polymer matrix.[45]