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Review

Nanocrystals for enhancement of oral bioavailability of poorly water-soluble drugs

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ARTICLE INFO

Article history:
Received 16 June 2014
Received in revised form
15 July 2014
Accepted 17 August 2014
Available online 27 August 2014

Keywords:
Nanocrystals
Bioavailability
Poorly water-soluble drugs

ABSTRACT

Nanocrystals, a carrier-free colloidal delivery system in nano-sized range, is an interesting approach for poorly soluble drugs. Nanocrystals provide special features including enhancement of saturation solubility, dissolution velocity and adhesiveness to surface/cell membranes. Several strategies are applied for nanocrystals production including precipitation, milling, high pressure homogenization and combination methods such as Nano-Edge™, SmartCrystal and Precipitation-lyophilization-homogenization (PLH) technology. For oral administration, many publications reported useful advantages of nanocrystals to improve *in vivo* performances i.e. pharmacokinetics, pharmacodynamics, safety and targeted delivery which were discussed in this review. Additionally, transformation of nanocrystals to final formulations and future trends of nanocrystals were also described.

1. Introduction

The poor solubility of drug is a major problem which limits the development of highly potent pharmaceutics. The drugs with low solubility lead to low oral bioavailability and erratic absorption which is particularly pertinent to drugs within class II of the Biopharmaceutical Classification System (BCS). Generally, the rate-limiting step for absorption of the drugs in this class is the dissolution velocity arising from low solubility. Although the drugs are high permeability, the poor solubility results in a low concentration gradient between gut and blood vessel consequent to a limitation of drug transport and oral absorption. Nowadays, there are a large percentage of drug compounds in drug development represents as poor aqueous solubility. Therefore, one of the most challenging tasks in drug development is to improve the drug solubility in order to enhance the bioavailability of these drugs. Several strategies have been employed to overcome these limitations. The approaches to increase the solubility and the available surface area for dissolution are classified as physical and chemical modifications. For the physical modification, the techniques include decreasing particle size (micronization, nanonization), formation of polymorphs/pseudopolymorphs (including solvates), complexation/solubilization (by means of using surfactants or cyclodextrins, conjugation to dendrimers, and an

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Peer review under responsibility of Shenyang Pharmaceutical University.
http://dx.doi.org/10.1016/j.ajps.2014.08.005

addition of co-solvents) and preparation of drug dispersions in carriers (eutectic mixtures, non-molecular solid dispersions, solid solutions). For the chemical modification, the used technique is the synthesis of soluble prodrugs and salts [1–5].

Particle size reduction has been a much smarter approach that can be applied to nonspecific formulation for many years. The micronization of drug leads to an increase in their surface area which proportionally increases in rate of dissolution and rate of diffusion (absorption). However, for very low solubility compounds the micronization fails to improve the saturation solubility and increase the bioavailability of the drug. Therefore, the further step to reduce the particle dimension to nanometer size range has been invented. Recently, particle diminution to the sub-micron range has emerged to be a powerful formulation approach that can increase the dissolution rate and the saturation solubility, subsequently improve the bioavailability of poorly water-soluble drugs and may also decrease systemic side effects. Over the last decade, drug nanocrystals are considered as a novel approach to improve the solubility of hydrophobic drugs since the technique is simple and effective which can quickly launch product to the market. The nanocrystals were invented at the beginning of the 1990s and the first products appeared very fast on the market from the year 2000 onwards. Additionally, drug nanocrystals are a universal approach generally applied to all poorly soluble drugs for the reason that all drugs can be disintegrated into nanometer-sized particles [6].

Drug nanocrystals are nanoscopic crystals of parent compounds with the dimension of less than 1 μm. They are composed of 100% drug without carriers and typically stabilized with surfactants or polymeric steric stabilizers. A dispersion of drug nanocrystals in an outer liquid medium and stabilized by surface active agents is so-called nanosuspensions. The dispersion medium can be water, aqueous or nonaqueous media e.g. liquid polyethylene glycol (PEG) and oils. The nanosuspensions can be used to formulate compounds that are insoluble in both water and oil and to reformulate existing drugs to remove toxicologically less favorable excipients. Additionally, the poorly soluble drugs enable to be formulated as nanosuspensions alone, or with a combination of pharmaceutical excipients [2,4,7].

2. Special features of nanocrystals to enhance oral bioavailability

Poorly soluble drugs encounter biopharmaceutical delivery problems such as low bioavailability after oral administration, low penetration of the drug into the skin, large injection volume for intravenous (i.v.) administration and undesired side effects after i.v. injection when using traditional formulations. Drug nanocrystals possess outstanding features enabling to overcome the solubility problems including an increase in saturation solubility, an increase in dissolution velocity, and an increased adhesiveness to surface/cell membranes [6].

These features are resulted from transferring of particle size from macroparticle to nanodimension that changes their physicochemical properties on the basis of nanotechnology. A detailed description of the physical background of these effects is shown below.

2.1. An increase in saturation solubility (C_s)

In general, saturation solubility is a compound-specific constant, which is depending on physicochemical properties of the compound, dissolution medium and temperature. However, this definition is only valid for drug particles with a minimum particle size in the micrometer range. Furthermore, the saturation solubility is also a function of the crystalline structure (i.e. lattice energy) and particle size. The polymorphic modification with highest energy and lowest melting point leads to the best solubility. Occasionally, homogenization process generates amorphous fraction with high inner energy that contributes to an increased solubility of the substance. For the particle size aspect, the saturation solubility is also a function of particle size when a critical size is below 1–2 μm. The saturation solubility increases with decreasing particle size below 1000 nm. This phenomenon can be explained by the Kelvin and the Ostwald–Freundlich equations.

The Kelvin equation (Eq. (1)) is originally used to describe the vapor pressure over a curved surface of a liquid droplet in gas (aerosol). A decrease in the particle size of liquid droplet contributes to an increase in curvature of the surface and the increasing vapor pressure. The situation of a transfer of molecules from a liquid droplet to a gas is comparable to the transfer of molecules from a solid nanocrystal to a liquid dispersion medium. Therefore, the Kelvin equation is also applicable to explain the relation between the dissolution pressure and the curvature of the solid particles in liquid. The dissolution pressure is equivalent to the vapor pressure. At saturation solubility state, the dissolving molecules and recrystallizing molecules are equilibrium. The dissolution pressure can be increased with increasing curvature (decreasing particle size). Therefore, the equilibrium is shifted toward dissolution, and thus the saturation solubility increases. The curvature is especially immense when the particle size is in the nanometer range.

$$\ln \frac{P_r}{P_\infty} = \frac{2\gamma M_r}{rRT\rho} \tag{1}$$

where P_r is the dissolution pressure of a particle with the radius r, P_∞ is the dissolution pressure of an infinitely large particle, γ is the surface tension, R is the gas constant, T is the absolute temperature, r is the radius of the particle, M_r is the molecular weight, ρ is the density of the particle.

The Ostwald–Freundlich equation (Eq. (2)) directly describes the relation between the saturation solubility of the drug and the particle size.

$$\log \frac{C_s}{C_\alpha} = \frac{2\sigma V}{2.303RT\rho r} \tag{2}$$

where C_s is the saturation solubility, C_α is the solubility of the solid consisting of large particles, σ is the interfacial tension of substance, V is the molar volume of the particle material, R is the gas constant, T is the absolute temperature, ρ is the density of the solid, r is the radius.

From the Ostwald–Freundlich equation, it obviously shows that the saturation solubility (C_s) of drug increases with a decrease in the particle size (r). However, this effect is not substantial for larger particles but will be pronounced for materials that have a mean particle size of less than 1–2 μm, especially well under 200 nm [2–4,8–11].