Review article

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A MINI REVIEW OF NANOCRYSTALS

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ABSTRACT

The advance of recent technology like high throughput screening, combinatorial chemistry and computer aid drug design, the drug innovation process has been considerably enhanced. However, new drug candidates often display poor aqueous or even organic medium solubility. Furthermore, many of them may have low dissolution rate and low oral bioavailability. Nanocrystal formulation sheds new light on advanced drug development. Due to small (nano- or micro- meters) sizes, the increased surface-volume ratio leads to intensely improved drug dissolution rate and saturation solubility. The simplicity in preparation and the potential for numerous administration routes allow drug nanocrystals to be a novel drug delivery system for specific diseases (i.e. cancer). In addition to the comprehensive review of different technologies and methods in drug nanocrystal preparation, suspension, and stabilization, we will also compare nano- and micro-sized drug crystals in pharmaceutical applications and discuss current nanocrystal drugs on the market and their limitations.

Keywords: Nanocrystals, Surfactant, Nano suspension, Dispersion media, Synthesis

INTRODUCTION

Nanocrystals are defined as crystalline particles of pure drug with sizes of not less than one dimension, which measuring smaller than 1000 nanometers (nm). Thin coating of surfactant is found to be stabilized or surrounded around them. In general, nanocrystals composed of 100% drug completely with the absent of carrier material [1]. They depend on quantum dots, which mean the particle size to be grouped as a nanoparticle and consist of atoms with the arrangement of a single- or poly-crystalline form. In addition, formation of nanosuspension will be observed if nanocrystals dispersed in a dispersion media. For examples, water, aqueous or non-aqueous media can be used as dispersion media, such as liquid polyethylene glycol and oils. According to the preparation methods, such as bottom-up technology, top-down technology, the forms of crystalline or amorphous in nature can be grouped by nanocrystals [2]. Moreover, nanocrystal technology provides an attractive and effective way to deliver poorly soluble drugs via parenteral route rather than oral route of administration [3]. On the other hand, nanocrystals also applicable toward wide variety of regions such as photovoltaics, photocatalysis, photobiology, and biomedical applications, including bioimaging, therapy, and tissue targeting for drug delivery.

Nanocrystals are termed as nanoparticles which have crystalline character. Thus, they have size with the nanometer range in crystal form. The process of refining crude oil into diesel fuel in order to manufacture filters can be achieved by nanocrystals. Besides that, nanocrystals are also a registered trademark of Elan Pharma International Ltd. for a technology that enhances the drug's bioavailability by rendering them as nanoscale particles. This subsequently could be suspended in liquids, convert into powder, pressed into tablets or encapsulated. Lastly, gold nanocrystals are of a molecular nature, maintaining their integrity in solution, as solids or thin films where they show crystalline order. While the analysis of laser-desorption mass spectrometric was established in the gas phase successfully. [4] Furthermore, solar panels can be generated if nanocrystals are layered and administered to flexible substrates. In general, hydrogen fuel cells can be worked more efficiently and required low cost to generate by the application of nanotechnology. This subsequently leads to lower prices for vehicles fueled by this type of alternative energy, as well as less energy is required to operate the generation of fuel cells [5]. According to the production technology, crystalline or an amorphous product can be produced during the processes of converting drug microcrystals to drug nanoparticles, especially when applying precipitation. In short, nanocrystal should not be considered as amorphous drug nanoparticle.

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PROPERTIES OF NANOCRYSTALS

Generally, nanocrystals of materials are acquired as sols. Sols that contain nanocrystals behave as classical colloids. For an instance, dispersion's stability related to the medium's ionic strength. Moreover, exceptional optical clarity is also exhibited by nanocrystalline sols. [6]. The fundamental purposes for the increased bioavailability and also increased dissolution velocity involve:

Increase of dissolution velocity by surface area enlargement:

In general, surface area can be enhanced by size reduction and thus lead to an enhanced dissolution velocity according to the Noyes-Whitney equation [7]. Hence, micronization is a convenient method to successfully increase the drug's bioavailability in a condition that the rate limiting step is contributed by dissolution velocity. The surface of particle is enhanced and therefore the dissolution velocity also increases. Hence, by moving from micronization further down to nanonization, the dissolution elocity can be achieved. In short, low saturation solubility is commonly related to low dissolution velocity in most cases.

Increase in saturation solubility:

The saturation solubility c_s is a constant bases on the compound, the dissolution medium and the temperature. In general, powders that obtained from daily life and have a size within the range of micrometer or above are considered acceptable. However, the saturation solubility is also a function of the particle size for the case of below a critical size of 1–2 μm. In addition, it enhances if the particle size shows a decreasing of below 1000 nm. Hence, the enhancement of saturation solubility can be exhibited by drug nanocrystals. This involves two benefits:

The improvement of dissolution velocity is generated. This is because dc/dt is proportional to the concentration gradient $(c_s – c_x)/h$, where c_s is represented by saturation solubility; c_x is related to bulk concentration; while h is termed as diffusional distance.

The increased saturation solubility followed by the absorption by passive diffusion will enhance the concentration gradient between gut lumen and blood [1].

Moreover, the lipid droplets' vapour pressure in a gas phase increases if surface's curvature improves as well according to the Kelvin equation [8]. This subsequently will result in lowering size of particle. In general, each liquid has its compound specific vapour pressure. Therefore, phenomenon that showed vapour pressure increased will be affected by the available compound-specific vapour pressure. For an instance, the condition of transferring molecules from a liquid phase to a gas phase is in concept similar to the transferring of molecules from a solid phase to a liquid phase. Besides that, the vapour pressure is considered to be equivalent to the dissolution pressure. The molecules dissolving and molecules recrystallizing show an equilibrium in the state of saturation solubility [9].

Synthesis of nanocrystals

The traditional way involves typical metal salts and a source of the anion, which is related to molecular precursors. There are most semiconducting nanomaterials feature chalcogenides, such as SS− and pnicnides, such as P3−. Furthermore, silylated derivatives such as bis(trimethylsilyl)sulphide, (S(SiMe3)2 and tris(trimethylsilyl)phosphine, (P(SiMe3)3) are the sources of these elements.

In general, some methods are used to solubilize and subsequently stabilize the growing nanocrystals by the application of surfactants or polymeric stabilizers. Furthermore, atomic diffusion will contribute to nanocrystals so that they can exchange their elements with reagents in some cases [10]. According to some reports, synthesis of a large variety of nanocrystals with different chemistries and properties and with low dispersity had been discussed. For instances, noble metal, magnetic, semiconducting, rare-earth fluorescent, organic optoelectronic semiconducting and conducting polymer nanoparticles can be included. In addition, this technique is depended on a general phase transfer and separation mechanism appearing at the interfaces of the liquid, solid and solution phases occur during the synthesis. Therefore, it is believed that a simple and convenient route can be provided by methodology to a variety of building blocks for assembling materials with novel structure and function in nanotechnology [11**]**.

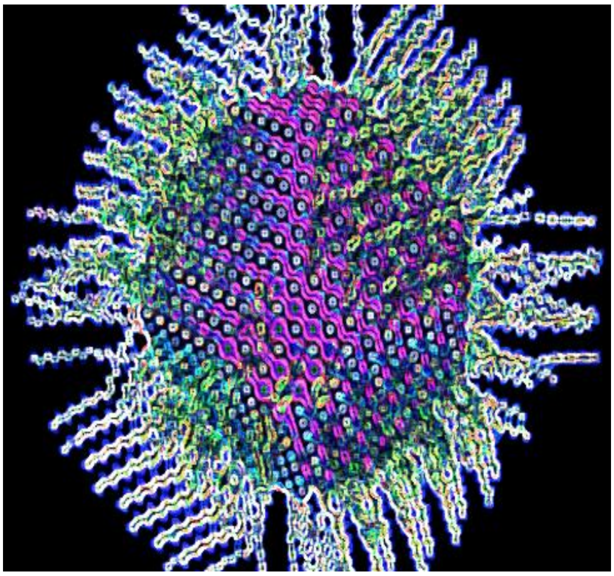

Figure 1: Shows surface chemistry of nanocrystals.

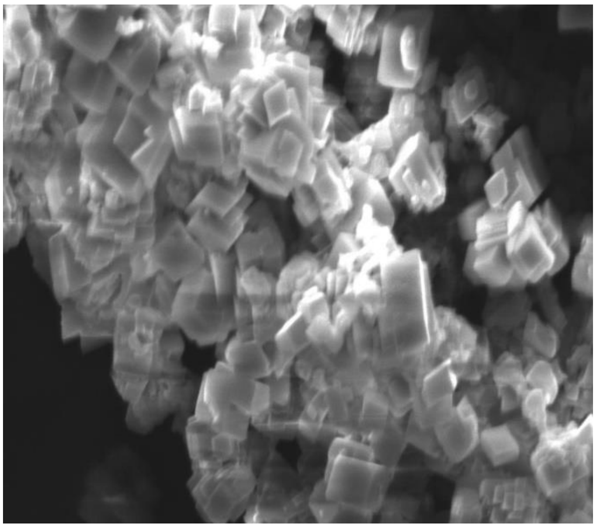

Figure 2: Shows SEM image of nanocrystals.

Preparations of Nanocrystals

Precipitation methods:

Preparation of hydrosols that developed by Sucker is one of the precipitation methods to produce nanocrystals. The technology is termed as "via humida paratum" (VHP). In general, this process is used to prepare ointments with finely dispersed, precipitated drugs, which was already discussed in the old pharmacopeia. For an instance, a solvent is used to dissolve the drug and subsequently transferred to a non-solvent. Thus, the finely dispersed drug nanocrystals in the precipitation form will be generated [12].

Milling methods:

In this method, the classical nanocrystals technology produces particle size diminution by the application of a bead or a pearl mill. Ball mills are prepared for the generation of ultra-fine suspensions [13].

Homogenization methods:

In addition, production of nanocrystals using homogenization methods involves three significant technologies, such as microfluidizer technology, piston gap homogenization in water and in water mixtures or in nonaqueous media technology. It can be done with microfluidizer jet stream homogenizers.

Applications of nanocrystals

In biological staining and diagnostic regions, the application of fluorescent probes can be achieved by semiconductor nanocrystals. In general, the nanocrystals show the characteristics of tunable, narrow, symmetric emission spectrum and are photochemically stable when compared with conventional fluorophores. Moreover, the dual-emission, single-excitation labeling experiment on mouse fibroblasts were conducted to manifest the benefits of the wide, continuous excitation spectrum. Lastly, these nanocrystal probes are therefore correlatively and may be superior to existing fluorophores in some cases [14].

In addition, possible future applications of nanocrystals include:

Hydrogen production, Pollutants and toxins discarded, Medical imaging, Drug manufacture, Protein analysis Flat-panel displays, Illumination, Optical and infrared lasers, Optoisolators, Magneto-optical memory chips Self-organized smart material [15].

CONCLUSION

Nanocrystal technology provides wide variety of advantages with only a little of disadvantages. The significant elements include particle size reduction and the increase in particle surface, curvature, and subsequently the enhanced dissolution velocity. In future, effective formulation technologies are required to make poorly soluble drugs to be more soluble and bioavailability. An enhancement in enrolment of products using nanocrystals will prone to an increased awareness in patients not willing to suffer from undesirable adverse effects. In short, it is paramount part of the work for the nanoparticles in future to achieve a prolonged or a targeted release by adjusting the surface of nanocrystals.

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