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Review

Drug nanocrystals: *In vivo* performances

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ABSTRACT

Over the past few decades, there has been a considerable research interest in drug nanocrystal system as a pharmaceutical approach for poorly soluble drugs. At the beginning lots of works have been done to study various technologies associated with production of drug nanocrystals and their *in vitro* physical and chemical properties, such as morphology, formulation composition, stabilities, crystalline structure and enhanced solubility and dissolution velocity. Recently, *in vivo* behaviors of the nanocrystals have been generally studied in animals (including human), and the results proved that drug nanocrystals could be used as a versatile formulation to alter and improve the pharmacokinetic, pharmacodynamic and targeting properties of poorly soluble drugs. In this paper, *in vivo* performances of drug nanocrystals exhibited in animals in different administration route were reviewed, and the advantages of drug nanocrystals in the aspect of safety, pharmacodynamics, pharmacokinetics and targeting delivery were discussed in detail.

Contents

Abbreviations: AN, aqueous nanosuspension; Apo, apolipoprotein; AUC, area under the blood concentration–time curve; BCS, biopharmaceutics classification system; BMM, bone marrow-derived macrophage; CL, clearance rate; C_{max}, maximum plasma concentration; CNV, choroidal neovascularization; EPR, enhanced permeability and retention; GI, gastrointestinal; GIT, gastrointestinal tract; ICS, Inhaled corticosteroids; i.v., intravenous; IVIVC, *in vitro–in vivo* correlation; MPS, mononuclear phagocyte system; MRT, mean residence time; MTT, methyl thiazolyl tetrazolium; NSAIDs, non-steroidal anti-inflammatory drugs; PEG, polyethylene glycol; RBCs, red blood cells; RES, reticuloendothelial system; RITC, rhodamine B isothiocyanate; SDS, sodium dodecyl sulfate; T_{max}, time to maximum plasma concentration; Vd, volume of distribution.

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1. Introduction

At present about 40% of the drugs being in the development pipelines are poorly soluble, even up to 60% of compounds coming directly from synthesis are poorly soluble [1]. The poor solubility makes these drugs very difficult to perform the pharmacological screening of compounds for potential drug effects. It was reported that 70% of the potential drug candidates were discarded due to low bioavailability related with poor solubility in water before they ever reached the pharmaceutics department [2]. Many different techniques have been developed to overcome the solubility problem of poorly soluble drugs, *e.g.* solubilization, solvent mixtures, inclusion compounds, complexation and so on. A basic problem is that these formulation techniques can only be used to a certain number of drugs exhibiting special features required to employ the formulation principle (*e.g.* molecule fits into the cavity of the cyclodextrin ring, being soluble in certain organic agents) [3]. When it comes to drugs which are insoluble in both aqueous and organic media (drugs so-called 'brick dust drugs'), these approaches are often ineffective.

Over the past two decades, drug nanocrystal technology has been undoubtedly the highlight in pharmaceutical field. One of its major contributions is the benefits that can be gained by formulating poorly soluble drugs [4]. This approach generally produces dispersions of drug nanocrystals in a liquid medium (typically water), which are called "nanosuspensions". Nanosuspensions consist essentially of pure drug nanoparticles (100–1000 nm) and a minimum amount of surface active agents required for stabilization. At present, approaches developed to produce drug nanosuspensions mainly include the so called 'bottom up' (precipitation) and 'top down' (media milling, high pressure homogenization, *etc.*). The bottom up technology dissolves the drug in solvent, and then precipitates it by adding the solvent to a non-solvent. These techniques are not widely used because of some prerequisites, such as usage of organic solvents and the drug should be soluble at least in one solvent [5]. The top down technologies are disintegration methods, and so can be employed for all insoluble drugs including 'brick dust drugs'. Drug nanocrystals exhibit many advantages including high efficiency of drug loading, easy scale-up for manufacture, relatively low cost for preparation and applicability to various administration routes, such as oral [6], parenteral [7], ocular [8] and pulmonary delivery [9]. All these advantages have so tremendous impacts on promoting drug nanocrystals successfully from experimental researches to patients that several products have been launched into market (Table 1).

During the last decade of the 20th century lots of experiments have been done to study the manufacturing technologies of drug nanocrystals and their *in vitro* physical and chemical properties, such as procedure parameters, formulation composition, physical and chemical stability, crystalline structure, enhanced saturation solubility and dissolution rate, bioadhesion and so on. Some published reviews have well summarized and discussed results of these researches from different aspects [3–5,10–14]. In the last ten years more and more attentions were paid to the *in vivo* performances of nanocrystals in animals (including human) and many exciting findings were obtained. This review will specifically focus on these findings, including safety, pharmacokinetics, pharmacodynamics and targeting effects of drug nanocrystals. Some expanded studies of drug nanocrystals in recent years, such as moieties-modified polymer layers and cell-based drug delivery system will also be discussed in this review.

2. *In vivo* performances of nanocrystals in different administration route

2.1. Safety and toxicity

2.1.1. Safety issues of poorly soluble drugs

Safety is a primary issue for medicines, thus the toxicity assessment is the most important data for registration of a new medicine. For the poorly soluble drugs safety issue may be more troublesome. Due to their low solubility, a large amount of organic cosolvents or solubilizers should be added in most cases before they are formulated as injectable solution, which will result in unwanted side effects or even toxicities [15–17]. For examples, the Cremophor-EL – a solubilizer used in paclitaxel product Taxol® – is associated with serious side-effects such as hypersensitivity, nephrotoxicity, and neurotoxicity [18]. Renal injury occurring in the commercially available itraconazole injection Sporanox® is concerned with the cyclodextrin-solubilizing agents [19]. In addition, precipitation of the poorly soluble drugs from the non-aqueous formulation once it is diluted with blood is another potential problem [20]. Oral delivery, as a non-invasive route, is safe in most cases. However, the high and prolonged local concentration may be an issue involved in oral application of the poorly soluble drugs, especially for the irritative drugs such as non-steroidal anti-inflammatory drugs (NSAIDs). Similar issue may restrict the mucosa delivery, since precipitation of drugs on the mucosa surface resulting from the very limited dissolution will also cause local irritation [21].

2.1.2. Advantages of nanocrystal formulations in terms of safety

Drug nanocrystals are generally reported as a safe and well tolerated formulation in many administration route compared with the conventional products. This is mainly attributed to following advantages.

2.1.2.1. Fine particle size. As for the submicron delivery system, particle size is a crucial factor in determining whether or not it can be used in parenteral route. For i.v. injection the content of particles larger than 5 μm should be controlled strictly, because the smallest size of blood capillaries is about 5 μm. Existence of a high content of particles larger than 5 μm can lead to capillary blockade and embolism. Drug nanosuspensions, as colloidal aqueous dispersions, can be well tolerated in i.v. route in many reports. Fine particle size also helps improve safety of oral poorly soluble drugs in some cases, by increasing the distribution uniformity in the gastrointestinal (GI) fluid and avoiding the high and prolonged local concentration [22]. Nano-sized particles are also beneficial to a better toleration in the mucosa delivery, such

Table 1
Key characteristics of available commercial drug products based on drug nanoparticle technology.

Product/Company	Drug compound	Indication	Nano-sizing approach	Administration route	Date of FDA approval
Gris-Peg®/Novartis	Griseofulvin	Anti-fungal	Bottom up, coprecipitation	Oral	1982
Cesamet®/Lilly	Nabilone	Anti-emetic	Bottom up, coprecipitation	Oral	2005
Rapamune®/Wyeth [a]	Sirolimus	Immunosuppressant	Top–down, media milling	Oral	2000
Emend®/Merck [a]	Aprepitant	Antiemetic	Top–down, media milling	Oral	2003
Tricor®/Abbott [a]	Fenofibrate	Hypercholesterolemia	Top–down, media milling	Oral	2004
Megace® ES/Par Pharma [a]	Megestrol acetate	Appetite stimulant	Top–down, media milling	Oral	2005
Tridlide™/Skye Pharma[a]	Fenofibrate	Hypercholesterolemia	Top–down, high–pressure homogenization	Oral	2005
Invega Sustenna/Johnson & Johnson	Paliperidone palmitate	Antidepressant	Top–down, high-pressure homogenization	Injection	2009

[a] Cited from Elan, FDA Orange Book, SkyePharma.