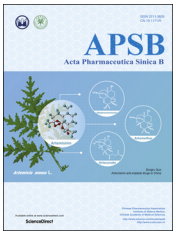
Acta Pharmaceutica Sinica B 2016;6(2):106–113

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



REVIEW

Injected nanocrystals for targeted drug delivery

Yi Lu[a], Ye Li[b], Wei Wu[a,*]

[a]*Department of Pharmaceutics, School of Pharmacy, Fudan University, Shanghai 201203, China*
[b]*Shaanxi Academy of Traditional Chinese Medicine, Xi'an 710003, China*

Received 29 October 2015; received in revised form 4 November 2015; accepted 16 November 2015

KEY WORDS

Nanocrystals;
Targeted drug delivery;
Biodistribution;
Ligand;
Stimuli response;
Encapsulation

Abstract Nanocrystals are pure drug crystals with sizes in the nanometer range. Due to the advantages of high drug loading, platform stability, and ease of scaling-up, nanocrystals have been widely used to deliver poorly water-soluble drugs. Nanocrystals in the blood stream can be recognized and sequestered as exogenous materials by mononuclear phagocytic system (MPS) cells, leading to passive accumulation in MPS-rich organs, such as liver, spleen and lung. Particle size, morphology and surface modification affect the biodistribution of nanocrystals. Ligand conjugation and stimuli-responsive polymers can also be used to target nanocrystals to specific pathogenic sites. In this review, the progress on injected nanocrystals for targeted drug delivery is discussed following a brief introduction to nanocrystal preparation methods, *i.e.*, top-down and bottom-up technologies.

*Corresponding author. Tel.: +86 21 51980084.
E-mail address: wuwei@shmu.edu.cn (Wei Wu).

Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

http://dx.doi.org/10.1016/j.apsb.2015.11.005

1. Introduction

More than 40% of drug candidates in the drug development process exhibit poor solubility, leading to poor and variable bioavailability[1]. The non-specific distribution of most drugs throughout the body results in side effects, further limiting their clinical use[2]. Targeting strategies based on nanocarriers are important solutions for these problems. Nanocarriers, *i.e.*, liposomes, nanoparticles, micelles and nanoemulsions, have been widely used to selectively deliver poorly soluble drugs to pathological tissues, organs or cells[3]. However, the intrinsic drawbacks, such as platform instability, limited drug loading, high manufacturing cost, scale-up difficulties, and quality control difficulties, contribute to the limited acceptance of these nanocarriers in clinic[4]. Only a couple of nanocarrier-based preparations are successfully marketed, *e.g.*, Doxil®, DaunoXome® and Abraxane®.

Development of nanocrystals emerged amid various shortcomings of existing delivery techniques for targeted therapy. Nanocrystals are drug crystals with particle size ranging from dozens to a few hundreds of nanometers, while in some cases, pure drug crystals may be physically stabilized by surfactants and/or polymers[5–7]. Absence of any carrier chemicals offer a theoretic drug loading up to 100%, typically 50%–90% (*w/w*)[8], leading to satisfactory therapeutic concentrations at low dose[9]. Toxic side-effects resulting from the encapsulating/solubilizing excipients also may be eliminated. Most importantly, physical instability issues inherent with other nanocarriers are largely circumvented by the nanocrystal formulation[10–12]. In addition, both top-down and bottom-up technologies have been well developed to prepare nanocrystals with desired particle size and size distribution, while the ease of scaling-up for nanocrystals can be proved by a dozen of commercial products[13].

Although invented for oral delivery to improve bioavailability of poorly soluble drugs, nanocrystals can be intravenously injected due to the nanoscale dimension. Due to lack of local mixing and initially insufficient volume of distribution, nanocrystals are not expected to dissolve rapidly in the blood upon i.v. administration, leading to improved biodistribution as compared to orally administrated nanocrystals[4]. The injected nanocrystals are recognized as exogenous materials and sequestered by mononuclear phagocytic system (MPS) cells. Consequently, nanocrystals in the blood stream are passively targeted to organs in which MPS cells are abundant, such as liver and spleen[14,15]. It has been reported that the sequestering and transportation of exogenous particles by MPS cells is very fast and efficient. Up to 90% of the injected dose is transported to liver and about 5% to spleen within 5 min after injection[9]. The phagocytotic uptake by MPS cells is triggered by the adsorbance of opsonins from the blood onto the nanocrystal surface. Surface modification with hydrophilic polymers, such as polyethylene glycol (PEG) and poloxamer, can reduce opsonization and thus prolongs the circulating time of nanocrystals in blood, facilitating tumor accumulation through enhanced permeability and retention (EPR) effects[9,16]. The targeting efficiency of nanocrystals may be further improved using ligand modification[17]. Besides tumor sites, targeting to other pathogenic sites like inflammation can be achieved by adopting stimuli-response strategies[16].

In this review, preparative methods for nanocrystals will be briefly introduced, followed by a detailed review on the progress of targeted drug delivery by nanocrystals. Polymer encapsulation to increase nanocrystal stability and immobilize ligands on the surface of nanocrystals will also be included.

2. Preparation of nanocrystals

2.1. Top-down techniques

High-energy mechanical forces are involved in the top-down approaches, which can be provided either by media milling (MM) (NanoCrystals®) or high-pressure homogenization (HPH) (IDD-P®, DissoCubes® and Nanopure®) to comminute large crystals[14,15]. The biggest advantage in top-down process is that it is a universal technique to prepare crystalline nanoparticles[6] and is flexible in production scale[18]. Thus, the process has been widely adopted to prepare commercial nanocrystals. Almost all commercial products were produced by NanoCrystals® except for Triglide® by IDD-P®. The disadvantage of this technology includes high energy and time consumption as well as contamination from the grinding media. For example, even with high pressure up to 1700 bar, 50–100 cycles of homogenization are still required to achieve the desired particle size and size distribution[5,11]; similarly, the milling time varies from hours to days, depending on the properties of the drug, the milling media, and the extent of particle size reduction[19,20]. Since contamination from the grinding media leads to unexpected side-effects, the top-down process may not be the optimal alternative to prepare nanocrystals for i.v. injection.

2.1.1. Media milling (NanoCrystals®)

A milling chamber, motor, recirculating chamber, coolant and milling media are the major components of the media mill (Fig. 1). In the process, the milling chamber is fed with a crude slurry containing drug, water and stabilizers, and agitated by the motor. Generally, the slurry occupies 2%–30% (*w/v*) volume of the milling chamber, while the milling media occupy 10%–50% (*w/v*) of the slurry. During agitation, the milling media roll over inside the chamber, generating high energy forces by shearing and impacting with drugs to reduce the particle size. The operation can be performed either in batch (discontinuous mode) or recirculation mode (continuous mode), depending on the scale. Recirculation is advantageous to reduce milling time and decrease particle size. The milling media can be retained in the chamber by media separators if recirculation mode is performed. Thermogenesis is severe due to the high energy generated during milling and long-term operation, leading to stability concerns. Therefore, the coolant is a necessity to control the temperature during the milling process.

2.1.2. High pressure homogenization (IDD-P®, DissoCubes® and Nanopure®)

During the process of HPH, drug suspensions are introduced into a high pressure homogenizer and forced to pass through a very narrow homogenization pathway in a sudden burst under high pressure (Fig. 2). Fracture of drug particles is achieved by cavitation, high-shear forces and collisions among particles. The process is generally composed of three steps: (1) dispersion of crude drug powders in pure solution or in solution containing stabilizer, (2) reduction of particle size by high-speed shearing or homogenization under low pressures, (3) high pressure homogenization to achieve the desirable particle size and size distribution. Based on the instruments and solution used, HPH can be further divided into three patented technologies: microfluidizer for IDD-P® technology, piston gap homogenizer for DissoCubes® (water) and Nanopure® (non-aqueous media).