Journal of Controlled Release 272 (2018) 159–168

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Review article

Nanotherapeutics in oral and parenteral drug delivery: Key learnings and future outlooks as we think small

Puneet Tyagi, J. Anand Subramony*

MedImmune, LLC, USA

ARTICLE INFO

Keywords:
Nanotechnology
Immunotherapy
Sustained release
Nanorobots
EPR
Immuno-oncology
Nanocrystals
Drug targeting
API (active pharmaceutical ingredient)

ABSTRACT

Nanotechnology ushered the field of medicine in to a new era. Miniaturization, increased surface area, and the unique physicochemical properties in the nano dimension were explored for new applications. Pharmaceutical industry picked up the technology and early success came fast for oral drug delivery through improvement in dissolution properties of the active molecules. Many products were launched using the nanocrystal technology on the oral side. Further development of polymeric nanoparticles led to wide spread research of nanocarriers for parenteral delivery. While considerable efforts have gone in the last two decades for testing nanoparticles for tumor targeting, delivery into tumors has remained challenging and suboptimal. Inadequate in vivo models that didn't accurately reflect the age and vascularity of human tumors, and inability to reproducibly target therapeutic drugs to the tissue of interest due to intrinsic biodistribution of the particles and hence side effects, limited the number of studies that advanced to the clinic. Our article addresses the questions commonly asked by scientific researchers in nanomedicine: "Has nanoparticle technology yielded on its initial promise that scientists predicted towards improving therapeutic index and avoid toxicity by delivering molecules to target tissues or was it more of wishful thinking that had several roadblocks?" We answer this question by linking the relevance of nanoparticles to cancer immunotherapy. The advent of immunotherapy has begun to show the potential applicability of nanoparticles in a different light, to target the immune system. In this approach, nanoparticles may positively influence the immune system rather than create the targeted "magic bullet". Utilizing the intrinsic properties of nanoparticles for immune targeting as opposed to targeting the tumor can bring about a positive difference due to the underlying complex cancer mechanisms that can potentially overlap with the heterogeneous biodistribution of nanoparticles towards improving the acquired and innate immune responses. In this review, we have followed the progress of nanotechnology in pharmaceutical applications with key insights from oral and parenteral drug delivery, and how to modify our thinking to better utilize nanoparticles for immuno-oncology. In contrast to conventional "local" tumor targeting by nanoparticles, we propose a new mechanism whereby nanoparticles trigger priming of the T cells towards tumor destruction. The heterogenous biodistribution of nanoparticles lends itself to stimulating immune cells systemically in a "global" manner and with the right therapeutic combinations will be able to trigger tumor antigens to continually activate, retain memory effects and destroy tumor cells.

1. Introduction

Nanotechnology offers new possibilities for creating novel materials and for the development of unique pharmaceutical dosage forms and drug delivery systems. Nanoparticle systems are generally classified as nano-sized active drug particles or nano sized substrates that can encapsulate active pharmaceutical ingredients (API) within, complexed or conjugated, or synthesized in the nano-dimension. According to the U.S. Food and Drug Administration (FDA), a nanoparticle's dimension is 1–100 nm [1]. Nanotechnologies have been used to improve the functionality of APIs and excipients. Particularly for oral therapy, nanoparticle technologies can be used to process APIs by controlling particle size through bottoms-up crystallization or top-down milling to create unique nano-sized materials. The substantial improvements in the dissolution of oral APIs by nanoparticles has led to enhanced absorption and bioavailability [2]. For parenteral dosage forms, such as injections containing nanosuspensions, nanoparticles can increase the volume of distribution and hence alter the pharmacokinetic (PK) properties of active molecules [3].

Here is what we know and believe nanoparticles can do:

* Corresponding author at: One MedImmune Way, Gaithersburg, MD 20878, USA.
E-mail address: subramonya@medimmune.com (J.A. Subramony).

https://doi.org/10.1016/j.jconrel.2018.01.009
Received 6 December 2017; Received in revised form 11 January 2018; Accepted 11 January 2018

Nanoparticles offer improved dissolution capabilities for the APIs on the oral side and enable better partition of the APIs in the blood stream in the case of parenteral due to albumin and other binding mechanisms. Because many small-molecule drug candidates have potential toxicity due to high serum concentration (C_{max}) upon injection and during systemic circulation, encapsulating them in a nanoparticle delivery system allows their release be modulated via controlled release. Similarly, the rapid clearance of an API on injection can be overcome by suitable encapsulation and surface decoration of the nanoparticle with appropriate functional groups for slow release and increased circulation. Nanoparticle-based therapeutics can potentially decrease systemic toxicity and could improve efficacy by targeting a drug to a tumor site or by offsetting the drug's release [4]. Active drug targeting using nanoparticles, another approach for preventing systemic toxicity in APIs, involves anchoring the nanotherapeutics using a targeting ligand that can be an antibody fragment, peptide or a small molecule through surface functionalization. Active targeting relies on the interaction of targeting ligands with the overexpressed receptors (such as folates and transferrin) on the tumor cell surface. Active targeting helps with internalization of the API and its uptake into the tumor. Several publications have described the use of active targeting and the mechanisms of uptake [5].

However, data from the descriptive literature presents a different picture. Even though several years of research have been devoted to the use of nanoparticles for parenteral applications, the ability to create reproducible tumor targeting nanoparticle has remained elusive due to various challenges. A recent review has looked into many of these challenges in a systematic way [6]. While looking at these difficulties, we discuss alternate ways of utilizing nanoparticles in immunotherapy due to their intrinsic features during biodistribution rather than where we would like them to go. We anticipate that the next wave of nanotherapeutics in immuno-oncology would require particles that can tackle and participate in competing events that go on during tumorigenesis, such as parallel processing of mechanistic pathways through different cell types (macrophages, dendritic cells), and heterogeneous signal transduction occurring away from the tumor in bone marrow and other places via killer cells for triggering positive immune responses.

In this review, we track the progress of nanotechnology in the last few decades (Fig. 1) which can be broadly classified into 4 different waves and describe the proven utility of nanoparticle technologies for oral products, nanocarriers for parenteral delivery and active targeting, and the next wave of utility in cancer immunotherapy.

2. Nanocrystals for oral delivery

Oral dosage forms such as tablets and capsules have been the choice of drug products over the years. Biopharmaceutical Classification System (BCS) [7] dictates the suitability of active pharmaceutical ingredients as candidates for oral dosage form development. Poor drug solubility of APIs is a major concern that limits the pharmaceutical development of oral dosage forms; about 40–60% of the early-stage discovery molecules are poorly soluble [8,9]. Poor solubility can also lead to erratic dissolution velocity and, eventually, unpredictable absorption and poor bioavailability.

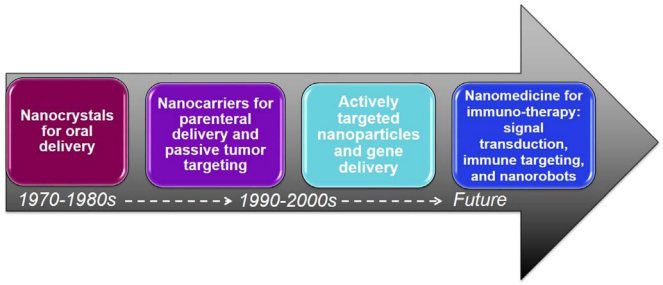

Fig. 1. Evolution of nanotherapeutics. Nanocrystals (Table 1) were utilized for bioavailability enhancement of oral drugs. Liposomes and other nanoparticle systems were developed as nanocarriers to improve solubility, distribution, and reduce toxicity of drugs (Table 2). While research continues on active targeting, current focus is more on delivering macromolecules such as RNA and DNA. The future of nanotherapeutics is expected to be immune targeting by nanoparticle robots, influenced by new learnings in immune biology.

Reductions in particle size to micron and submicron levels have been adopted in the last couple of decades to enhance rate of dissolution [10]. In comparison with micronization, reduction to the nano-size has proven to be a more powerful approach because it increases saturation solubility and dissolution velocity. The relationship between the drug's saturation solubility and the particle size is explained by the Ostwald–Freundlich eq. [11]:

$$\log \frac{Cs}{C\alpha} = \frac{2\sigma V}{2.303RT\rho r}$$

where Cs is the saturation solubility, Cα is the solubility of the solid, σ is the interfacial tension of the 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, and r is the radius.

The effect of particle size on solubility is not likely to be substantial for larger micron-sized particles, but it is pronounced for nano-sized materials [12,13]. Furthermore, increasing saturation solubility improves the concentration gradient between the gastrointestinal tract and blood, boosting the drug's passive absorption.

Reducing particles to nano-size also increases the drug's dissolution velocity, as explained by the Noyes-Whitney equation [14]:

$$\frac{dx}{dt} = \frac{DA}{h_d} \times (Cs - Ct)$$

where dx/dt is the dissolution velocity, D is the diffusion coefficient, A is the surface area, h_d is the diffusional distance, Cs is the saturation solubility, and Ct is the concentration around the particles.

2.1. Approaches to prepare nanocrystals for oral drug delivery

Nanocrystal preparations can be broadly categorized into those that are top down, in which large particles are broken down by attrition or cavitation, and those that are bottom up, in which nanocrystals are created by precipitation. Of the two approaches, the top-down approach using milling is by far the most commonly used.

2.1.1. Top-down approach

In this approach, large drug crystals are reduced to nano-size by a milling process or high-pressure homogenization. The classical wet-milling method is NanoCrystal Technology, wherein a ball mill, containing beads made of ceramic, stainless steel, or glass, generate shear force and impact to reduce the particle size of the drug suspension [3,15]. To stabilize nano-sized particles, stabilizers such as particle surface modifiers (surfactants) or hydro-colloids (hydroxyl propyl methyl cellulose) are added, which coat the surface of the nanoparticles to prevent crystal aggregation. NanoCrystal Technology was first used to develop sirolimus tablets, which was FDA approved in 1999 [16]. Many other drug products, such as fenofibrate (Tricor) and aprepitant (Emend), were subsequently developed using the nano-milling technology. Table 1 shows the list of products developed with nano-sizing technologies.

High-pressure homogenization is a high-energy disintegration process that involves passing the drug suspension through an orifice under high pressure. Particle size can be reduced through particle collision and/or cavitation [17]. Particle size reduction can be achieved by jet stream homogenizers, such as microfluidization (Microfluidizer, Microfluidics Inc., USA), or by piston gap homogenization, where nanocrystals are produced using pressures of up to 1500 bar. In the microfluidization process, frontal collision of fluid streams under high