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Historical perspective

Recent advances in the engineering of nanosized active pharmaceutical ingredients: Promises and challenges

Waseem Kaialy *, Maen Al Shafiee

School of Pharmacy, Faculty of Science and Engineering, University of Wolverhampton, Wolverhampton WV1 1LY, UK

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ABSTRACT

The advances in the field of nanotechnology have revolutionized the field of delivery of poorly soluble active pharmaceutical ingredients (APIs). Nanosized formulations have been extensively investigated to achieve a rapid dissolution and therefore pharmacokinetic properties similar to those observed in solutions. The present review outlines the recent advances, promises and challenges of the engineering nanosized APIs. The principles, merits, demerits and applications of the current 'bottom-up' and 'top-down' technologies by which the state of the art nanosized APIs can be produced were described. Although the number of research reports on the nanoparticle engineering topic has been growing in the last decade, the challenge is to take numerous research outcomes and convert them into strategies for the development of marketable products.

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Abbreviations: AFR, aerosol flow reactor; API, active pharmaceutical ingredient; ASES, aerosol solvent extraction system; AUC, area under the curve; BSA, bovine serum albumin; CQA, critical quality attributes; C_{max}, maximum plasma concentration; CSD, colloidal silicon dioxide; DCP, dibasic calcium phosphate anhydrous; DMA, dimethylacetamide; DPI, dry powder inhalers; DSC, differential scanning calorimetry; EPAS, evaporative precipitation into aqueous solution; Eq, equation; GAS, gas anti-solvent; HGAP, high gravity antisolvent precipitation; HGCP, high gravity controlled precipitation; HGRP, high gravity reactive precipitation; HIV, human immunodeficiency virus; HP-β-CD, 2-Hydroxypropyl-β-cyclodextrin; IV, intravenous; HPC, hydroxypropyl cellulose; HPH, high-pressure homogenization; ILC, inulin lauryl carbamate; IVIVC, *in vitro in vivo* correlation; MCC, microcrystalline cellulose; NSAID, nonsteroidal antiinflammatory drug; P-gp, P-glycoproteins; PLGA, poly(lactide-co-glycolide); PLM, polarized light microscope; PSD, particle size distribution; PVA, polyvinyl alcohol; PVP, polyvinylpyrrolidone; RPB, rotating packed bed; RESS, rapid expansion in supercritical fluid; SAS, supercritical anti-solvent; SCF, supercritical fluid; SLNs, solid lipid nanoparticles; SDS, sodium dodecyl sulfate; SEDS, solution-enhanced dispersion by supercritical fluids; SDC, sodium deoxycholate; SEM, scanning electron microscopy; SFL, spray freezing into liquid; SGF, simulated gastric fluid; SLS, sodium lauryl sulfate; TEM, transmission electron microscopy; TPGS, D–α–tocopherol polyethylene glycol succinate; TPP, tripolyphosphate; UWL, unstirred water layer; WGG, wheat germ agglutinin; XRPD, X-ray powder diffraction.

* Corresponding author. Tel.: +44 1902321139.
E-mail address: w.kaialy@wlv.ac.uk (W. Kaialy).

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1. Introduction

Nanoparticles refer to solid colloidal three-dimensional particles in the size range from 1 to 1000 nm [1]. Therapeutically, nanoparticles could be used as API carriers (vehicles) through dissolving, entrapping or adsorbing the API. Historically, nanoparticles have been developed for API delivery since the 1960s [2]. Commercially, the first approved product employing nanoparticle formulation was ABI-007 (Abraxane®; American BioScience Inc., Santa Monica, CA) [3]. Nanotechnologies have been employed for the treatment of several diseases such as cancer [4], tuberculosis [5,6], etc. Nanotechnologies have been used to improve the solubility of hydrophobic APIs by two main approaches. The first approach involves the production of nanocrystals using techniques based on down–up methods, top-down methods, or a combination of top-down and down–up methods. The second approach involves nanotechnology-based API delivery dosage forms such as polymeric micelles, nanosuspensions and/or nanoemulsions [7].

2. Solubility of nanosized APIs

APIs administered orally have to be in the solution state to be absorbed and consequently induce a therapeutic response. It is estimated that at least 40% of the newly identified APIs are low soluble materials [8], making the formulation of such compounds challenging in the pharmaceutical industry. Therefore, universal solubilization methods that can significantly improve the APIs' bioavailability are still highly desirable. In the literature, many techniques were used to improve the solubility of poorly soluble APIs, such as complexing APIs with cyclodextrins [9], conjugation to dendrimers [10], salt formation of ionizable APIs [11], solid dispersions [12], and lipid-based API delivery systems such as microemulsions and liposomes [13]. Nevertheless, some of these techniques were unsuccessful and thus the molecules were abandoned during early stages of development, or the product being launched exhibited suboptimal properties, including the poor bioavailability, the lack of fed/fasted equivalence, the lack of optimal dosing and the presence of extra excipients that pose limitations with respect to dose escalation, and ultimately a poor patient compliance [14].

Nanosized APIs proved promising properties in all stages of the API development process. According to the Nernst–Brunner/Noyes–Whitney equation [15–17], increasing the saturation solubility of an API will increase its dissolution rate from the pharmaceutical dosage form. This is described in Eq. (1) (Eq. 1; [18]).

$$\frac{dX}{dt} = \frac{A.D}{h}\left(Cs - \frac{Xd}{V}\right), \tag{1}$$

where dX/dt is the dissolution rate, Xd is the amount dissolved, A is the particle surface area, D is the diffusion coefficient, V is the volume of fluid available for dissolution, Cs is the saturation solubility and h is the thickness of the effective boundary layer. Based on the above equation, the decrease of particle size will increase the effective particle surface area (A), eventually leading to an enhanced dissolution rate and thus an increased API bioavailability [19]. The applicability of this theory has been verified by many researchers [20,21]. Additionally, according to the Prandtl equation (Eq. (2)), the decrease in particle size achieved for nanosized APIs will lead to a decrease in the thickness of the effective boundary layer, ultimately resulting in an increased API dissolution rate [22].

$$hH = k\left(\frac{\sqrt{L}}{\sqrt{V}}\right), \tag{2}$$

where L is the length of the surface in the direction of flow, k is a constant, V is the relative velocity of the flowing liquid against a flat surface and hH is the thickness of the hydrodynamic boundary layer.

Additionally to the enhanced dissolution rate explained above, nanosized APIs have increased saturation solubility compared to an un-milled product of the same API, as illustrated by Freundlich–Ostwald equation [23,24] (Eq. (3)).

$$Cs = C\infty e^{\left(\frac{2\gamma M}{\rho RT}\right)}, \tag{3}$$

where Cs is the saturation solubility of the nanosized API, $C\infty$ is the saturation solubility of an infinitely large API crystal, γ is the crystal-medium interfacial tension, M is the compound's molecular weight, r is particle radius, ρ is density, R is a gas constant and T is the temperature.

Based on the above equation, C_s is a function of the interfacial tension (γ) and therefore is a function of the interfacial energy G ($G = \sigma \cdot A$). High energy surfaces are likely to be created on the surface of the milled nanosized API particles compared to parent microsized particles. Such differences in the interfacial energy may contribute to differences in C_s between nanosized and microsized APIs [25]. For example, Ganta et al. [26] showed how the saturation solubility of Asulacrine has dramatically increased for milled preparations compared to un-milled preparations. The solubility increased with successive size-reduction steps and the highest solubility was achieved with a median particle size of 133 nm.