Promises and challenges in the engineering of nanosized active pharmaceutical ingredients

The advances in the field of nanotechnology have revolutionized the field of delivery of poorly soluble active pharmaceutical ingredients (APIs). Nanoparticles refer to solid colloidal three-dimensional particles in the size range from (1 to 1000) nm. 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. Commercially, the first approved product employing nanoparticle formulation was ABI-007 (Abraxane®; American BioScience Inc., Santa Monica, CA). Nanotechnologies have been used for the treatment of several diseases such as cancer, tuberculosis, etc. 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.

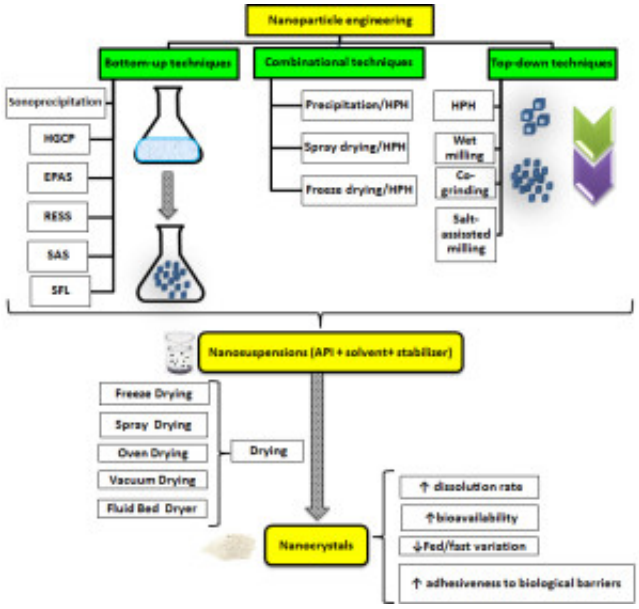

Fig. 1. Schematic showing different strategies to engineer nanosized active pharmaceutical ingredients

The existing production techniques of nanosized APIs are mainly classified into bottom-up techniques, top-down techniques, and a combination of both (Fig. 1). Nanoparticle engineering is a promising tool to resolve many current issues associated with poorly soluble APIs, such as those related to poor solubility and dissolution rate. Converting nanosuspensions into solid dosage forms

also can solve many problems related to API development such as poor bioavailability. However, the industrial scale production of nanosized systems is still a challenge. This is, in part, because most of the technologies that have been utilized to enhance the dissolution rate of poorly soluble APIs via the nanosizing route produce amorphous systems, which are metastable and possess tremendous challenges during processing, making them unfavourable in the pharmaceutical industry. Additionally, serious difficulties could be associated with the preparation of nanosized APIs, such as separating the nanosized APIs from surfactants, low formulation yield, contamination with microsized particles, and those related to the ability to re-suspend the nanosized APIs after drying. Particle size reduction of APIs into a nanosized range also remains challenging due to the aggregation of the high surface area nanosized particles. In the context of pulmonary API delivery, such aggregation results in a low emitted dose of the nanosized API upon inhalation, poor flow properties, and extreme powder handling difficulties. DPIs containing nanoparticle powder formulations have a major drawback, which is their aerodynamic diameter being unsuitable for prober inhalation delivery. This leads to a low API delivery efficiency due to a large fraction of the inhaled dose being exhaled. The low API loading efficiency and the difficulties associated with scaling the process up are also limitations of the nanosized pulmonary delivery systems. Additionally, there are few safety concerns related to the long-term inhalation of stabilizers used during the preparation of nanocrystals. It is also very imperative to control the residual solvents and cytotoxic excipients and the potential adverse effects of nanoparticles on pulmonary structure and function. Therefore, there is an increased need for innovative nanosizing technologies that can produce crystalline APIs with both high stability profiles and enhanced dissolution rates. The optimization of nanosizing processes using Quality by Design methods might open new horizons for the development of nanosized pharmaceutical formulations. 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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Publication

Recent advances in the engineering of nanosized active pharmaceutical ingredients: Promises and challenges.
Kaialy W, Al Shafiee M
Adv Colloid Interface Sci. 2015 Dec 8