Excipients used in nano-technology assisted drug delivery systems.

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Editorial

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INTRODUCTION

The overall therapeutic benefit of an active pharmaceutical ingredient (API) is dependent on its potency and efficacy to deliver to the site of action. Drug delivery systems enable optimization of the latter by altering the physicochemical and/or biopharmaceutical properties of the API(s). Application of nano-technology for the prevention and the treatment of diseases has provided a wider platform for delivery of 'difficult to deliver' APIs. This increasing utilization of nano-technology assisted drug delivery systems (NADDS) has demonstrated wide-ranging benefits, from improvement in oral bioavailability to targeting of drug to specific tissues.

Nano-technology has been defined in a number of ways. The definition proposed by the National Nanotechnology Initiative of the US government encompasses three substantial points, that is (1) "research and technology development at the atomic, molecular, or macromolecular levels, in the length scale of approximately 1-100 nanometer (nm) range in any direction", (2) "creating and using structures, devices, and systems that have novel properties and functions as a result of their small and/or intermediate size" and (3) "ability to control or manipulate materials on the atomic or molecular scale" (1).

NADDS exhibit unique properties at the cellular, atomic and molecular level that are not present in the bulk material. This not only allows the alteration of the apparent aqueous solubility, permeability, bioavailability, potency and toxicity of the APIs, but can also enable their targeting to the site of action. These unique properties can be partially attributed to the increased surface to volume ratio of such systems (2). Distinct advantages offered by nano-technology based products have led to emergence of numerous drug delivery systems. On the one hand, there are systems that consist predominantly of the API (with some stabilizers) such as nanocrystals and nanocrystalline in solid dispersions, while on the other hand there are nano-carrier assisted drug delivery systems that consist of numerous ingredients, apart from the API. The latter may include polymeric nanoparticles, liposomes, self

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nano-emulsifying drug delivery systems, solid lipid nanoparticles and dendrimers. These systems have been extensively investigated for their delivery potential and some of them are commercially available as enabling technologies.

Marketing approval and commercialization of pharmaceutical products requires them to pass through a stringent regulatory review process. Traditionally, this regulatory pathway has concentrated on the safety and efficacy of the medicinal product. However, the contribution of sub-micron size particles to the unique properties of NADDSs, requires additional regulatory scrutiny. There has been a general lack of regulatory standards for the approval of NADDSs. As a result, USFDA has taken the lead in developing a framework for a guidance document for drug products utilizing nano-technology. A recent 'Guidance for Industry" issued by USFDA in June 2014, has set a two point agenda for "Considering Whether an FDA-Regulated Product Involves the Application of Nano-technology". For the purpose of guidance, "nano-technology products" mean products that contain or are manufactured using materials in the nano-scale range, as well as, products that contain or are manufactured using certain materials that otherwise exhibit related dimension-dependent properties or phenomena (3). Hence, apart from 'size', emphasis is also on the products that demonstrate 'dimension specific properties'. The current thinking, rather than adopting a restrictive view of size, focuses on "to identify and address potential implications for safety, effectiveness, public health impact, or regulatory status of the product". The presence of any of the above two criteria would invite additional scrutiny to identify and address consequences on safety, effectiveness and regulatory status.

Role of excipients in NADDSs

NADDSs pose unique challenges during their development and manufacture. Numerous excipients are used to reach nano-scale size, prevent aggregation during processing /shelf life and active targeting to the receptor site and examples of such excipients are shown in Table 1.

Table 1 Examples of excipients used in nano-technology assisted drug delivery systems

POLYMERIC NANO PARTICLES
sodium alginate
gelatine
polylactic acid
polyglycolic acid
dextran
SOLID LIPID NANO PARTICLES
tricaprin
tristearin
glyceryl monostearate
cetyl palmitate
palmitic acid.
EMULSIONS
soybean lecithin
egg lecithin
polaxamer 188
polysorbate 80
tyloxapol
VESICLE BASED SYSTEMS
phosphatidylcholine
distearoyl
dipalmitoyl phosphatidic acid
cholesterol
STABILIZERS
poly vinyl alcohol
poly vinyl pyrrolidone (PVP)
polyacrylic acid
hydroxypropyl methyl cellulose (HPMC).

Many of these excipients have been used traditionally in other applications and enjoy GRAS status. However, several others have no history of being used in previously approved products through a particular route of administration. This puts an additional regulatory burden for the approval of such products where, apart from the finished product, the excipient would also attract regulatory scrutiny.

Excipients have been traditionally used to facilitate conversion of APIs into medicinal products as these are expected to contribute towards processing, product performance and stability. Given the diversity of NADDS, such systems may require a specific three dimensional structure for their function. Even the simplest of such systems require excipients for the generation and maintenance of sub-micron size particles. Additionally, excipients may play a crucial role in increasing the absorption or active targeting. Consequently, the successful development of NADDSs requires a thorough understanding of physicochemical properties and functionality of the excipients.

Functionality of excipients used in NADDSs

The functionality of an excipient is defined as the function it performs in a formulation and the degree to which it meets the intended function. However, direct testing of functionality in a formulation or manufacturing process is not always possible. Therefore, the European Pharmacopoeia has recently introduced the concept of 'Functionality Related Characteristics' (FRC) in the non-mandatory section of the excipient monograph (4). A FRC is a controllable characteristic of an excipient that is shown to impact its functionality. It is now well understood that not only the API but excipients can alter the performance of NADDS. Hence, excipients used in NADDS require unique FRCs to enable the generation of well defined sub-micron structures necessary for NADDS.

The concept of FRCs can be explained by taking the example of stabilizing excipients used for nanocrystals. Polymers such as PVP and HPMC are used as steric stabilizers for nanocrystals. Steric stabilization involves adsorption of polymer(s) on the surface of API nanocrystals. This discourages contact between particles, thus preventing aggregation. The surface environment of both the polymer(s) and the nano crystals, influences adsorption effectivness. Polymer characteristics such as molecular weight, degree of branching and rate of hydration can directly influence its role as a steric stabilizer and could act as FRCs. However, the FRCs of the same polymer may change upon alteration in surface environment of the API nanocrystal. Hence, tailor-made FRCs could be required for excipients used in NADDS, as functionality can only be tested in the context of a particular formulation and its manufacturing process. This would be much more complex for multi-component three dimensional constructs, and would require a detailed orthogonal testing for identification of FRCs.

Nano-excipients

Nano-excipients are excipients existing in nanometer size range. These might be manufactured deliberately or generated unintentionally during manufacturing of NADDS. The process of manufacturing NADDS can have the potential of converting an excipient into its "nano" form. The existence of nano-excipients in finished drug products was recently highlighted by Moreton. This can alter the properties of the excipient, thereby enhancing its transport across biological membranes (5). Therefore, it is expected that nano-excipients would require additional safety evaluation in comparison to the non-nano excipients.

Nano-excipients and regulatory expectations

The thought process of USFDA in assessing nano-excipients is shown in the recently issued guidance document entitled "Assessing the effects of significant manufacturing process changes, including emerging technologies, on the safety and regulatory status of food ingredients and food contact substances, including food ingredients that are color additives"(6). This document touches upon the use of nano-technology in food substances. While ignoring the presence of nano-range particles in existing substances, the focus is on

an intentional alteration of particles to nanometer scale. Though a closer assessment of such products has been recommended, the final assessment of safety is to be based on the characteristics of the finished product and the safety of its intended use. However, it must be stressed that the yardstick applied to conventionally manufactured food substances cannot be blindly extrapolated to nano-engineered food substances.

This guidance document has also questioned the applicability of traditional safety tests of nano-engineered food substances. The need for developing validated *in vitro* toxicity assays for nano-engineered food substances has been stressed. This will enable meaningful safety assessment of nano-engineered food substances. It is reasonable to conclude that a similar philosophy should be adopted for nano-engineered pharmaceutical excipients.

CONCLUSION

Much research has been carried out on NADDS. Commercialization of these technologies would depend on how well they meet the criteria for safety and efficacy. In particular, upfront consideration of regulatory expectations not only from the delivery system but also the excipients, would ensure higher success rates. Looking forward nano-technology enabling excipients will witness intensive scientific investigations, as they have the capacity to contribute unique functionality to the drug products.

REFERENCES

1 National nanotechnology Initiative Strategic plan, National Science and Technology Council Committee on Technology Subcommittee on Nanoscale Science, Engineering, and Technology, Executive Office of the President of the United States, February 2014.

2 Desai N, (2012). Challenges in development of nanoparticle-based therapeutics, AAPS J 14 (2):282–295.

3 Guidance for industry: Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology, US FDA, U.S. Department of Health and Human Services, June 2014.

4 European Pharmacopoeia, Seventh edition (7.0) 2012. 5.15. Functionality-Related Characteristics of Excipients, 661-662.

5 Moreton C, (2010), Trends in Pharmaceutical Excipients: An Update, Am. Pharm. Rev., 13 (6), 22 – 27.

6 Draft Guidance for Industry: Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients That Are Color Additives; Availability, US FDA, U.S. Department of Health and Human Services, April, 2012.