Nanotechnologies in drug delivery – An industrial perspective

D.V. Bazile

Drug Delivery Technologies and Innovation Sanofi R & D, Pharmaceutical Sciences Department,
13, quai Jules-Guesde, 94403 Vitry-sur-Seine Cedex, France
*Correspondence: didier.bazile@sanofi.com

The design and manufacture of objects in the 10-1000 nm range, referred to as nanotechnologies, has opened access to new drug delivery tools embracing a variety of applications. While some of these applications are simply based on the high level of dispersion (i.e. high surface/volume ratio) of the nano-objects, others involve constructs bearing multiple functionalities (encapsulation, long circulation, targeting), taking advantage of the compatibility of the nanoparticles size with the design of the drug delivery at the cellular and sub-cellular levels. This article is an attempt to analyze the current knowledge and impact of nanotechnologies in drug delivery, from an industrial perspective. Various aspects such as the routes of administration, raw materials, expected biopharmaceutical perfomances are considered, together with the different levels of differentiation of nanotechnologies, as compared to standard formulations. The needed degree of refinement of the understanding of the physico-chemistry and the biopharmacy of the nano-objects, together with the existence of methodological gaps to manage their quality, are discussed considering the specific context of the drug delivery challenge (colloidal dispersion versus targeting). Even though nanotechnologies were primarily envisaged for life cycle management, to avoid the combination of the risks associated to a new drug delivery system to the risks associated to a new drug, the scope of nanotechnologies is currently broadening with their development as enabling drug delivery technologies for biomolecules, and their use in translational sciences. The added value of nanotechnologies is also discussed in these contexts.

Key words: Nanotechnologies – Enhanced permeation – Retention effect.

Nanotechnologies can be defined as technologies aimed at designing and producing objects whose size ranges between few nanometers to few hundred of nanometers, as a function of the number of molecules assembled in the object [1]. Over the past two decades, nanotechnologies have been giving rise to a variety of applications in drug delivery [2-5]. Some of these applications are based on the high level of dispersion of nano-objects and their ability to quickly release the active molecule in a free (i.e. solubilized) form under dilution in the biological fluids [6, 7]. Some other types of applications take advantage of the compatibility of nano-objects size with the design of the drug delivery at the cellular and sub-cellular levels [8]. Some examples of nanotechnologies applications as listed in the *Table I* as examples, with no intent to be exhaustive.

To cope with the molecular/cellular resolution, the design of nanotechnologies-based products has been moving from the traditional compounding activity of formulation to a scientific expertise based on physicochemical and biopharmaceutical principles, and associated characterization tools [9]. Indeed, from a quality management perspective, nanotechnologies require, by design, a high degree of refinement of the understanding of the relationship between the physicochemical attributes of the product and the biodistribution and pharmacokinetics of the drug. However, the emergence of general

Table I - Examples of nanotechnologies applications in drug delivery.

Drug (tradename)	Company/Technology	Indication	Status
Oral route			
Rapamycin (Rapamune)	Wyeth-Elan/Nanocrystal	Immuno-suppressive	Marketed
Aprepitant (Emend)	Merck-Elan/Nanocrystal	Anti-emetic	Marketed
Fenofibrate (Tricor)	Abbott-Elan/Nanocrystal	Hypercholesterolemia	Marketed
Fenofibrate (Triglide)	Sciele Pharma Inc.-IDD P Skyepharma	Hypercholesterolemia	Marketed
Megestrol (Megace ES)	Par Pharmaceutical-Elan/Nanocrystal	Anti anorexic	Marketed
Intravenous route			
AmBisome	Astellas Pharma/Liposomes	Fungal infection	Marketed
Doxorubicin (Doxil)	Janssen Pharmaceuticals/PEGylated liposomes	Kaposi's sarcoma, metastatic breast and ovarian cancers	Marketed
Vincristine (Marqibo)	Talon therapeutics/sphingomyelin-based liposomes Optisomes	Acute lymphoblastic leukemia (ALL) and melanoma	Marketed
Paclitaxel (Abraxane)	Abraxis Biosc.	Metastatic breast cancer	Marketed
Doxorubicin (Livatag)	BioAlliance Pharm. Transdrug	Hepatocellular carcinoma	Ph. III
Camptothecin	Cerulean/Cyclosert	Non-small cell lung cancer	Ph. II
siRNA M2 subunit of ribonucleotide reductase	Calando Ph./Rondel	Solid tumors	Ph. I
Docetaxel BIND-014	Bind Biosc./Accurin	Solid tumors	Ph. I
siRNA PCSK9 synthesis inhibitor	Alnylam/Tekmira Lipid nanoparticles	Severe hypercholesterolemia	Ph. I
siRNA transthyretin inhibitor	Alnylam/Tekmira Lipid nanoparticles	Amyloidosis	Ph. II
Intramuscular route			
Paliperidone palmitate (Invega Sustenna)	Janssen Pharmaceuticals-Elan/ Nanocrystal	Schizophrenia	Marketed

rules giving rise to guidelines and practices is rendered difficult by the diversity of the applications (from simple colloidal dispersion to targeting of a specific cell type or sub-cellular compartment) and the variety of nano-objects and techniques used to characterize them in the publications. As a consequence, the physicochemical and biopharmaceutical context is considered case-by-case and the consistency between the analytical package and the expected performances is based on an approach built-in at a higher level.

It is worth mentioning that, up to now, key attributes are essentially addressed to support the preclinical proof-of-concept of the drug delivery approaches while their management to anticipate and mitigate the risks inherent to the nanoparticulate form is postponed to clinical development steps. This strategy may be not always applicable to nanotechnologies since both their tolerability and drug delivery performances are sometime tightly bound to the structure of the nano-object [10]. As a consequence, any change aimed at improving the safety profile may impact the performances. At the same time, due to the pioneering status of nanotechnologies and the lack of clinical experiences and of generally accepted rules to assess the safety, the countermeasure is to stick as much as possible to the raw materials and processes of the preceding preclinical and clinical studies, in an attempt to preserve the quality. In this context, a particular attention needs to be paid to the scale-up of the nano-object manufacturing process and an appropriate level of understanding of the physico-chemistry of the nano-object assembly is critical to mitigate the risks of unexpected deviation of the quality from the lab to the pilot scale. Here again, a good balance is needed between the drug delivery challenge (simple colloidal dispersion versus long circulating or ligand-based targeting), the management of the desired and undesired properties of the nanoparticulate forms, and the methodological efforts.

The goal of this paper is to address, from an industrial experience, a few points deemed worthy of consideration in the design of nano-objects and the management of their quality. The specific applications of nanotechnologies in translational science, enabling drug delivery technology and life cycle management are discussed in light of these general considerations.

I. POSITIONING NANOTECHNOLOGIES-BASED PRODUCTS VERSUS STANDARD PHARMACEUTICAL FORMS

Since nanotechnologies are still at an early stage, some uncertainties remain about the cost of goods of nano-objects manufacturing, the regulatory constraints that will be associated to their development and finally the chances of success of their marketing applications. Therefore, there is a need to specifically address the expected performances of nanotechnologies based products and to describe how they will differentiate from standard pharmaceutical forms from both the physicochemical and biopharmaceutical standpoints.

The picture may be significantly different as a function of the route of administration. For the oral administration of small molecules, milling of the crystalline particles down to the sub-micronic scale has been shown to dramatically accelerate the dissolution kinetics of the drug in the gastro-intestinal tract and, as a consequence, the bioavailability [2]. Nevertheless, other pharmaceutical technologies such as amorphization [11] or complexation with solubilizing excipients such as cyclodextrins [12] could offer workable alternatives, as a function of the physicochemical properties of the drug. At the same time, at the interface between research and development when the limitation of a drug candidate stands in its poor water solubility, another alternative is to go back to the screening step and to select a molecule exhibiting better properties [13]. In a translational approach, it may be appropriate to assess the credentials of the frontrunner in a nano-particulate form while pursuing the efforts to identify a back-up compound better adapted to a standard pharmaceutical form. Therefore, there is always a risk that the nanotechnologies based product will not give rise to the gold standard treatment at the end.

For the intravenous route, the ability to apprehend in an integrated manner the molecular, cellular and tissular features of the pathology and the better accessibility to the pharmacological target appear as opportunities for nanomedicines to surpass standard products [14]. In fact, an in-depth drug delivery exercise combining physicochemistry and biopharmacy is necessary to properly justify the extra efforts paid to deviate from standard pharmaceutical forms. At the same time, as importantly, the understanding of these drug delivery mechanisms is the starting point of the assessment of risks associated to the nanoparticulate form. It is important to realize that even if the amount of drug accumulated in the tumor [15, 16] or crossing the blood brain barrier [17-19], expressed in μg of drug per gram of tissue, can be significantly increased using nano-carriers, the fraction of the dose directed to these particular compartments is, at the most, in the fraction of % range. Therefore, there is a need to manage the remaining part of the dose, i.e. to anticipate and control their accumulation in undesired organs and assess the associated potential safety issues. As a matter of fact, if the ability to diffuse through a leaky vasculature is the founding principle of the enhanced permeation and retention (EPR) effect, one may anticipate that nano-carriers may diffuse from the blood to other parts of the body where the vessels are leaky. Higher concentration of the drug in the macrophages, as compared to a standard solution, is also anticipated if the capture of the nano-carriers by the mononuclear phagocytes system (MPS) is quicker than the release of the drug from the carrier [20].

Finally, the biodistribution of the nano-carrier will be dependent upon the probability to explore a given organ/tissue and the ability of this particular compartment to extract the nano-object. In this approach, the physiologically based pharmacokinetics (PBPK) model [21, 22] provides an interesting methodology to apprehend the diffusion of the nano-carriers in the body, even though the methodological tools giving access to the estimation of the extraction factors in the tumor or in the brain need some adaptations [23]. Anyhow, it can be anticipated from the existing data that the magic bullet concept will apply to a small fraction of the dose and that a proper control of the remaining part will be key to further exploit the potential of nanotechnologies.

These principles associated to the intravenous route may also apply when the oral delivery is not based on the standard solubility/permeability description of the biopharmaceutic drug classification [24] such as administration of hydrophilic drugs [25] or highly lipophilic drugs directed to the lymph [26]. As a function of the expected performances, the deliveries in the eye [27, 28] or in the ear [29] may fall into the category taking advantage of the high level of dispersion, or the category based on the delivery design at the cellular level. In this latter case, an integrated approach between delivery and pharmacology is needed, not only to secure the assets of the nanotechnologies approach, but also to better assess the risks associated to the nanoparticulate form.

II. INVOLVEMENT OF DEVELOPMENT STAKEHOLDERS

It is important to realize that nanotechnologies have been introduced in pharmaceutical innovation through a formulation and material design approach. As a consequence, it is crucial for the chemistry manufacturing and control (CMC) department to interface with the other development stakeholders (pharmacologists, pharmacokineticists, toxicologists, clinicians) to clarify with them what makes nanotechnologies different from standard pharmaceutical dosage forms.

The administration of submicronic drug crystals illustrates how the comparison with a standard formulation and the risks assessment are highly dependent on the route of administration.

In the context of the oral route, the use of submicronic drug crystals may be considered as moving particles size reduction a step further

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