Enhancement of the solubility, bioavailability and absorption of poorly soluble drug candidates through nanotechnology- a review.

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ABSTRACT

Background: Orally administered drugs that transverse the intestinal membrane must be very soluble and lipophilic. This may not be so as most drugs are poorly soluble and thus possess poor bioavailability resulting in only a small fraction of the administered drugs absorbed into the systemic circulation and reach the target site. Thus, a major amount of the drug is wasted and the unabsorbed drug leads to undesired side effects in the gastrointestinal tract.

Objectives: The objective is to review some of the various drug delivery technologies used to formulate poorly soluble drug candidates through nanotechnology.

Methods: Formulating these compounds as pure drug nanoparticles is one of the newer drug-delivery strategies applied to this class of molecules. Nanocrystals, a carrier-free colloidal delivery system in nano-sized range, is an interesting approach for poorly soluble drugs. Several strategies are applied for nanocrystals production including precipitation, milling, high pressure homogenization and combination methods such as Nano- Edge™, SmartCrystal and Precipitation-lyophilization-homogenization (PLH) technology.

Results: Nanoparticle dispersions are stable and have a mean diameter of less than 1 micron. Drug nanoparticles have been shown to improve bioavailability and enhance drug exposure for oral and parenteral dosage forms. Nanocrystals provide special features including enhancement of saturation solubility, dissolution velocity and adhesiveness to surface/cell membranes.

Conclusions: Many publications reported useful advantages of nanocrystals to improve *in vivo* performances such as pharmacokinetics, pharmacodynamics, safety and targeted delivery which are discussed in this review.

Keywords: Nanoparticles, Nanocrystal Technology, Bioavailability, poorly water soluble compounds.

Amélioration de la solubilité, de la biodisponibilité et de l'absorption de médicaments peu solubles par nanotechnologie- bilan

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RESUME

Contexte: Les médicaments administrés par voie orale qui traversent la membrane intestinale doivent être très solubles et lipophiles. Cela peut ne pas être le cas étant donné que la plupart des médicaments sont peu solubles et possèdent donc une biodisponibilité médiocre, ce qui fait que seulement une petite fraction des médicaments administrés est absorbée dans la circulation systémique et atteint le site cible. Ainsi, une grande quantité du médicament est gaspillée et le médicament non absorbé conduit à des effets secondaires indésirables dans l'appareil gastro-intestinal.

Objectifs: L'objectif est de faire le bilan de quelques-unes des diverses technologies de livraison de médicaments utilisées pour formuler des médicaments candidats peu solubles à travers la nanotechnologie.

Méthodes: La formulation de ces composés en tant que nanoparticules de médicaments purs est l'une des nouvelles stratégies de livraison de médicaments appliquées à cette classe de molécules. Les nano-cristaux, un système de livraison colloïdal sans support dans une gamme de taille nanométrique, est une approche intéressante pour les médicaments à faible solubilité. Plusieurs stratégies sont appliquées pour la production de nano-cristaux, y compris la précipitation, le broyage, l'homogénéisation à haute pression et les méthodes de combinaison telles que Nano-Edge ™, SmartCrystal et la technologie de précipitation-lyophilisation-homogénéisation (PLH).

Résultats: Les dispersions de nanoparticules sont stables et ont un diamètre moyen inférieur à 1 micron. On a montré que les nanoparticules de médicament améliorent la biodisponibilité et augmentent l'exposition aux médicaments pour les formes posologiques orales et parentérales. Les nano-cristaux offrent des caractéristiques particulières, notamment l'amélioration de la solubilité de la saturation, de la vitesse de dissolution et de l'adhérence aux membranes de surface / cellulaires.

Conclusions: De nombreuses publications ont rapporté des avantages utiles des nano-cristaux pour améliorer les performances in vivo telles que la pharmacocinétique, la pharmacodynamie, la sécurité et l'administration ciblée, qui sont discutées dans ce bilan.

Mots clés: Nanoparticules, technologie nanocristalline, biodisponibilité, composés peu solubles dans l'eau.

INTRODUCTION.

Solubility is an essential factor for drug effectiveness, independent of administration route.[1] It is well known that the majority of the new chemical entities coming directly from synthesis are poorly soluble.[2] Consequently, many of these substances have bioavailability problems after oral administration. Injections or infusions as intravenous aqueous solution are in most cases not possible because the low solubility in water would require a too large administration volume.[3] The use of solvent mixtures is often excluded as well, because more and more drugs are poorly soluble in aqueous media.[4] The use of nanotechnology as a drug-delivery approach for various difficult-to-formulate reagents is now prevalent. [5,6,7,8,9] In pharmaceutics, nanoparticles are typically defined as a discrete internal phase consisting of an active pharmaceutical ingredient having physical dimensions, less than 1 micron in an external phase.[3] Also, nanoparticles can be designed to form *de novo* when exposed to the appropriate biological fluid.[10] The pharmaceutical industry during the past three decades has developed and marketed several nanoparticulate pharmaceuticals with major emphasis on intravenous products—for example, intravenous nutritional fat emulsion (Intralipid®) and liposomal products (Doxil®, AmBisome®).

The inability to achieve high drug loading, the cost of ingredients and processing, and the restricted number of suitable excipients have hitherto limited the broader use of these formulation approaches. Elan's NanoCrystal® Technology, which focuses on poorly water-soluble drugs, has addressed many of these major concerns and has successfully expanded the scope and use of nanoparticulates or nanosuspensions to include the oral, inhalation, intravenous, subcutaneous (SC) and intramuscular (IM), and ocular routes of delivery. [11] Four oral products incorporating the NanoCrystal technologyare currently marketed in the United States and other countries: Rapamune®; Emend®, TriCor 145®, and MegaceES®. There are also other products in late-stage development delivered by oral, injectable, and inhalation routes using NanoCrystal Technology. Commercial success has spurred renewed interest in the area of nanoparticulate drug delivery, as evidenced by the establishment of several nanoparticle-based companies (Table 1) and a flurry of research activities in the past 10 years.

Table 1: Current industrial leaders in nanoparticle technology.

Formulation approaches for poorly water-soluble drugs	Company
Media milling nanonization	Elan Drug Technologies
Microfluidization/homogenization	Baxter
	SkyePharma
Supercritical fluid technology	Nektar
	Lavipharm
	RxKinetics
	Eurand
	Ferro
Alternative approaches	DENA
	Many academic interests

(Cortesy: Elan Drug Technologies)

The solubility challenge

It is estimated that 40% of active substances are difficult to formulate as a result of their lack of significant solubility in water. [12, 13, 14] If a molecule must penetrate a biological membrane to be absorbed, the molecule generally must possess some hydrophilic, hydrophobic or lipophilic characteristics. The classical approach to deal with this issue is to generate various salts of a poorly water-soluble molecule so as to improve solubility while retaining biological activity. Alternately, screening is continued to identify analogs or prodrugs with enhanced solubility. If successful, there would be little need to pursue a formulation approach that involves nanoparticle production. The problem is that, frequently, these approaches are not successful, and the molecule is abandoned early on in its development process or the product is launched with suboptimal properties including poor bioavailability, lack of fed/fasted equivalence, lack of optimal dosing, presence of extra excipients that pose limitations with respect to dose escalation, and ultimately, poor patient compliance. When these types of situations arise, a nanoparticle formulation approach has proven to be very useful and invaluable in all stages of the drug development and has opened opportunities for revitalizing marketed products with suboptimal delivery.

Nanoparticle formulations

There are various ways in which nanoparticles of poorly water-soluble molecules are generated. [11,15,16,17] The approaches can be viewed as being a building-up approach through synthesis, [18] self-assembly[19, 20, 21] or precipitation of drug molecules.[15] Alternatively, nanoparticlescan be successfully generated using drug-fragmentation processes such as homogenization,[22,23] microfluidation,[24] or milling. Milling, which is the process used in generating Elan's NanoCrystal colloidal dispersions, is the recognized leader in the area of nanoparticulate research today. [3] No matter what approach is taken to generate drug nanoparticles,in comparison to particulates greater than 1 micron, surface area is increased (Figure 1).

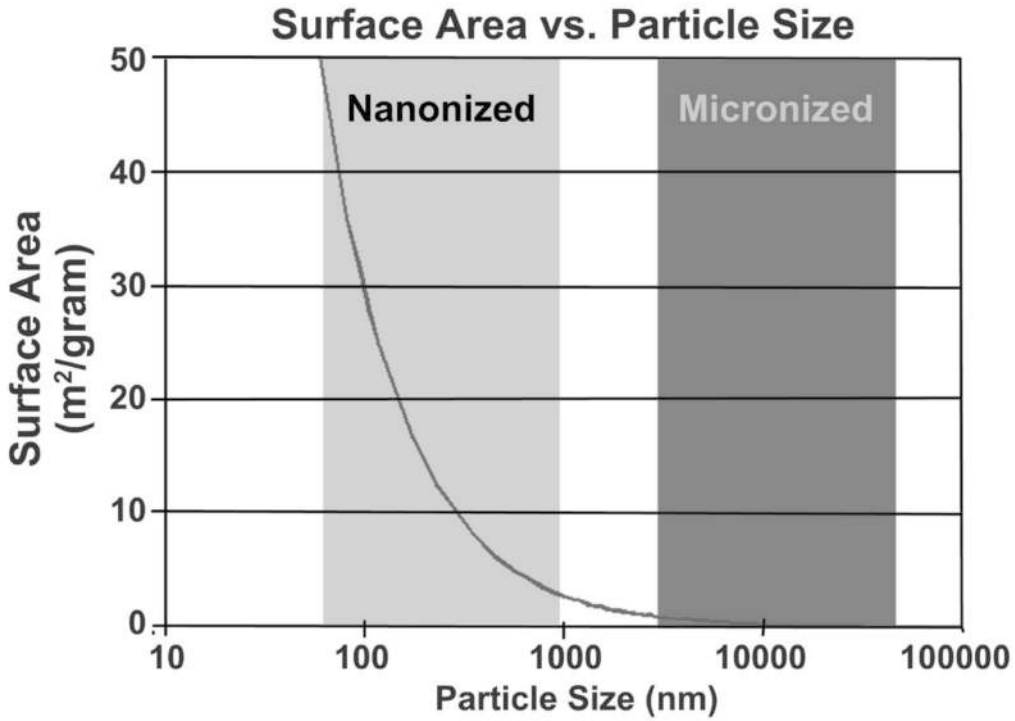

Figure 1: The plot demonstrates the increase in surface area obtained when solids are fractured from the micron-size range (microparticles) to the nanometer-size particles used in the various nanoparticle formulations to improve the performance of poorly water-soluble compounds (Cortesy: Elan Drug Technologies)

This increase in surface area and surface interactions can be positively used to enhance the dissolution rate and provide a platform for controlling the pharmacokinetic properties of the dosage form. However, unless properly dampened, this tremendous increase in surface energy can cause the nanometer-sized drug particles to spontaneously aggregate into a more thermodynamically stable state. Critical to the generation of physically stable nanoparticles is the use of various excipients that act to dampen or sensitize the surface energy of the nanoparticles by way of steric and/or ionic stabilization. An acceptable stabilizer should first be a reagent that is generally recognized as safe for the intended route of administration. Secondly, a stabilizer must have properties that allow it to properly wet the surface of poorly water soluble compounds. Finally, a stabilizer should possess properties so as to impart steric and/or ionic stabilization to the surface of the nanoparticles. It should be emphasized that surface stabilization does not necessarily involve chemical grafting of the surface stabilizer to the molecule. Stabilization is typically driven by the mere adsorption of the stabilizer to the surface of the poorly water-soluble compound.

Another consideration for obtaining a physically stable nanoparticle formulation is the ability to control the phenomenon referred to as Ostwald ripening. Ostwald ripening results from uncontrolled precipitation or crystallization of the active, leading to particle-size growth following stabilization. [26, 27, 28] Ostwald ripening can be eliminated and/or reduced by controlling a number of formulation parameters such as particle size, particle-size distribution, solids content, choice of stabilizer, and a fluid phase with minimal potential to solubilize the poorly water-soluble compound. For instance, if a poorly water-soluble compound is an acid or a base, the pH of the fluid phase can be adjusted so as to minimize ionization; that is, acids would be processed under more acidic conditions, and free bases would be processed at a higher pH. Nanoparticle dispersions generated using Nanocrystal technology consist of drug and stabilizer, and most commonly, the fluid phase is water. These dispersions are processed using a high-energy media mill with highly cross-linked polystyrene, which provides a highly durable milling media resulting in efficient processing of crude drug crystals to homogenous nanoparticle–nanocrystalline dispersion with a particle size approximately 1 micron or less. The key characteristics of Nanocrystal formulations for poorly water-soluble molecules are:

· the versatility of the approach: suitable for many different classes of compounds, provided the aqueous solubility that is less than 10 mg/ml.
the potential to achieve formulations with high drug loading: 300 mg/g or (30% w/w).
·a drug-to-stabilizer ratio on a weight basis typically 10:1 or lower: 30% drug to 3% or lower stabilizer concentration.
·usefulness for all routes of administration: oral, pulmonary, intravenous, Subcutaneous, Intramuscular, and ophthalmic.
·the ability to be readily post processed into most commonly used dosage forms: tablets, capsules and sterile products.
·proven technology: four marketed products in the United States, Europe, and Canada.

Biological benefits of nanoparticles

As previously discussed, the property of nanoparticle formulations that make this approach highly beneficial is related to the surface properties imparted on nanometer-sized entities. Although in recent years, tremendous emphasis and focus have been placed on nanotechnology research, as early as 1906: Ostwald published “The World of the Neglected Dimensions, “wherein colloidal nanoparticles exhibited special properties that resided between the molecular and the material sciences. [10] In practice, applying Nanocrystal Technology or one of the alternate nanoparticle formulation approaches to the many formulation and performance issues associated with poorly water-soluble compounds in the pharmaceutical industry provide many benefits. These benefits can be categorized into three major areas: formulation-performance improvements related to enhanced dissolution, safer and more patient-compliant dosage forms, and the potential for dose escalation for improvements in efficacy.[3]

Improved performance of nanoparticles

The activity of a compound depends on its ability to

dissolve and interact with the relevant biological target, either through dissolution and absorption or receptor interaction. The poor bioavailability of poorly water-soluble molecules that are not permeation-rate limited can be attributed to dissolution-rate kinetics. [3] The dissolution rate is directly proportional to the surface area of the drug, according to the Noyes-Whitney model for dissolution kinetics. [29] Drug crystals reduced in size from 10 microns to 100-nm particles generate a 100-fold increase in surface-area-to-volume ratio. This increase in surface area has a profound impact on the bioavailability of the molecule (Figure 1). For oral drug delivery, drug crystals must dissolve to be absorbed. Although there are some reports that uptake of nanoparticulate materials can be mediated by various cellular or paracellular processes[30, 31] improving absorption remains the primary means for increasing the bioavailability of a poorly water-soluble compound [32].If the bioavailability of a poorly water-soluble compound is dissolution-rate limited, approaches that afford delivery using nanometer-sized particles of drug improve bioavailability by enhancing dissolution rate. [15, 25, 33, 34, 35, 36, 37] This maximizes the amount of soluble drug that is free to be absorbed. This is especially true for poorly water-soluble compounds absorbed at a defined region of the gastrointestinal tract.

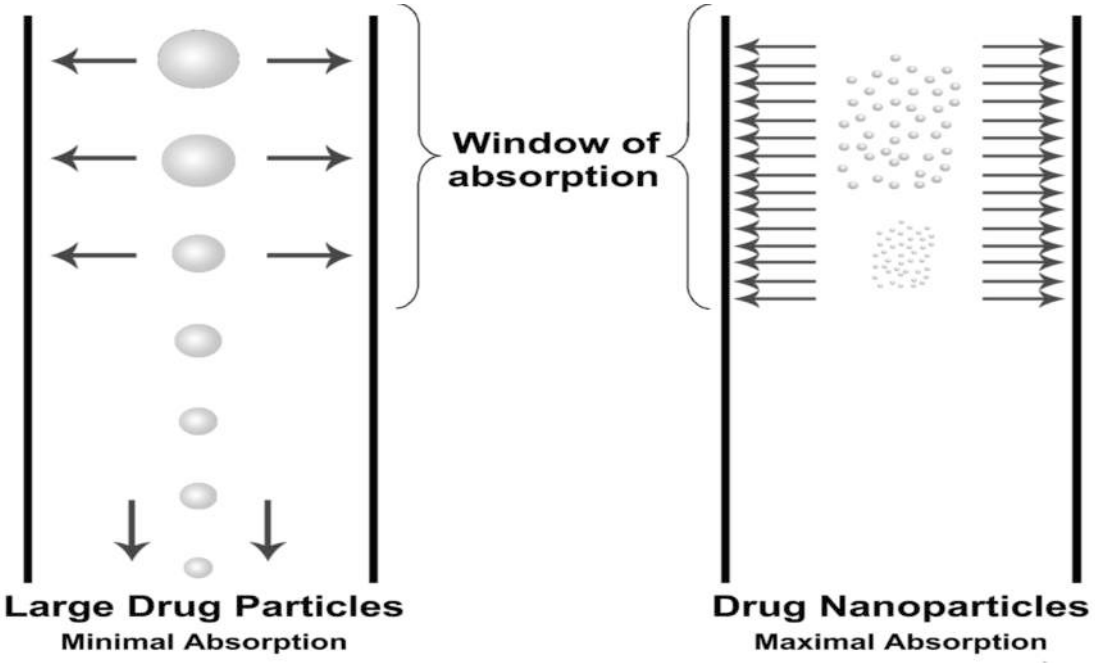

Figure2:The diagram demonstrates one of the primary issues associated with poorly water-soluble molecules whose bioavailability is dissolution-rate limited. On the left, large drug particles cannot adequately dissolve, which results in the inability to be absorbed. On the right, nanometer drug particles are rapidly dissolved during transit through the gut, thus maximizing absorption and improving bioavailability. (Cortesy: Elan Drug Technologies)

For instance, a large percentage of compounds are absorbed maximally at the duodenal–jejunal area.[38] If dissolution is not complete when the dosage form transits this area, bioavailability will be seriously compromised (Figure 3a). Similarly, if bioavailability depends on the nutritional state of the subject or is not dose proportional, nanoparticle formulations have been shown to reduce or eliminate such effects (Figure 3b and 3c).

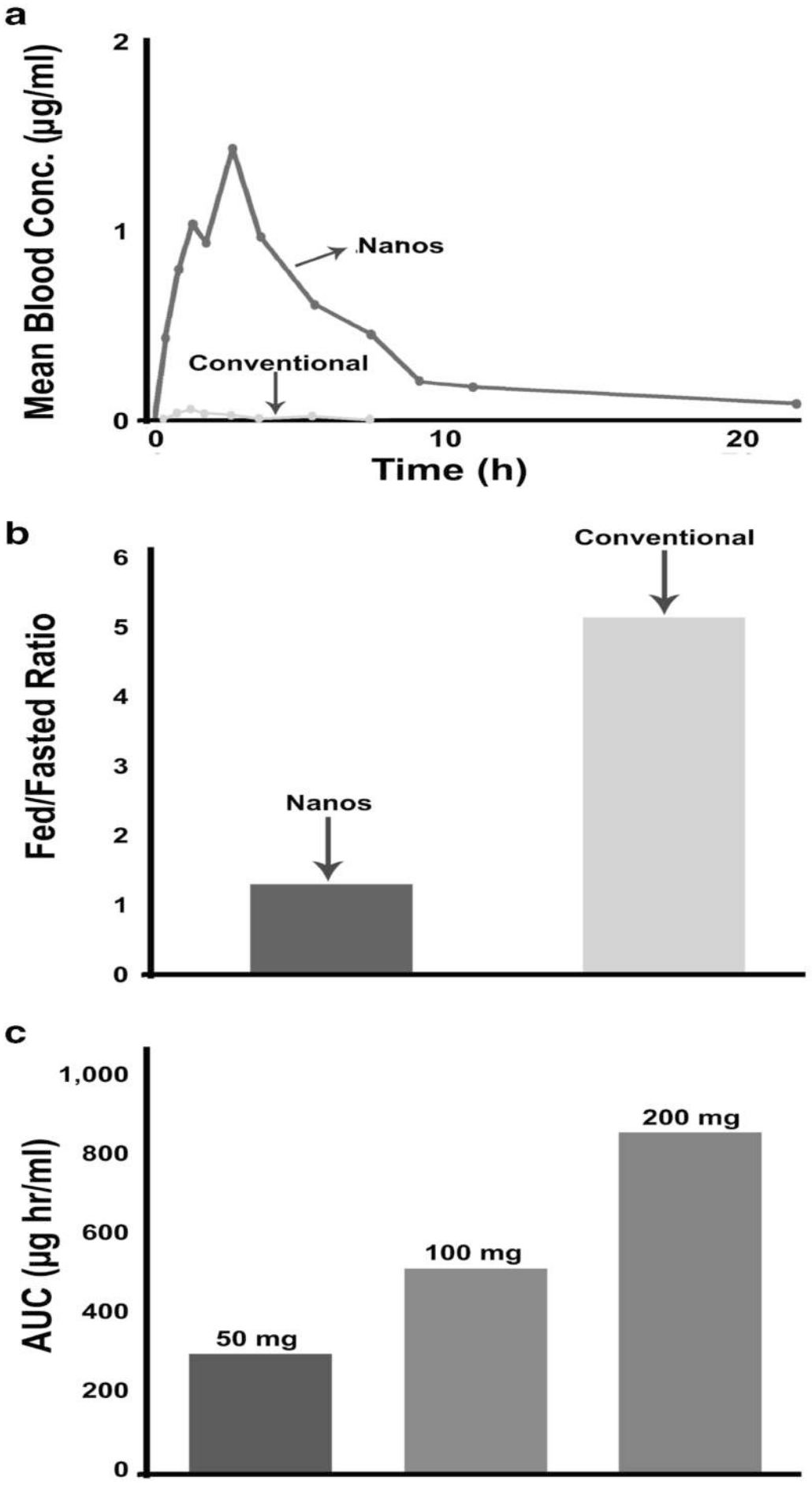
a
Mean Blood Conc. (µg/ml)
2
1
0
Nanos
Conventional
0
10
20
Time (h)
b
Fed/Fasted Ratio
6
5
4
3
2
1
0
Conventional
Nanos
c
AUC (µg hr/ml)
1,000
800
600
400
200
0
200 mg
100 mg
50 mg

Figure 3: Depicted are a few of the primary benefits observed when a poorly water-soluble compound is formulated using a nanoparticle approach. (a) The bioavailability of a poorly water-soluble model compound formulated as a nanoparticle dispersion (red) or as a conventional crude suspension (yellow). (b) The bar graphs show the comparison in the fed/fasted variation in bioavailability of a model compound when formulated as a nanoparticle dispersion (red) or as a crude suspension (yellow). Many poorly water-soluble molecules whose bioavailability is dissolution rate limited are not dose proportional. (c) A dose-escalation study is shown demonstrating dose proportionality for a nanoparticle formulation of a poorly water-soluble compound. (Courtesy: Elan Drug Technologies).

For parenteral applications, one of the first questions that should be addressed is when a nanoparticle approach should be considered for a poorly water-soluble drug candidate. If the drug candidate requires an excessive amount of co-solvents or extreme pH conditions or is a low-potency molecule requiring a high dose, the nanoparticle approach would be of value. To reiterate, nanoparticle formulations basically consist of the drug, an external phase (which is typically water and a minimal amount of stabilizer), and a reagent that has a proven history of safe use for the intended application. Buffering and/or isotonicity agents can be added, provided they are compatible with the formulation and do not disrupt the colloidal stability of the nanoparticulate formulation.[3]

For sterility assurance, all current methods available have been applied (i.e., terminal heat, gamma irradiation, filtration, and aseptic production). The method of choice is dictated by the properties of the compound and properties of the colloidal dispersion so that the end product meets the appropriate specification for its intended purpose. In essence, the drug-particle formulation approach provides an opportunity to have safer, less toxic parenteral medications that lend themselves to opportunities for dose escalation, enhanced efficacy, and improved patient tolerability. A few examples demonstrating the benefits of using a nanoparticle technology such as Nanocrystal Technology for parenteral products in clinical studies have been published for intravenous [39] and pulmonary applications. [40] Preclinical studies have been published for subcutaneous (SC) [41,42,43] and IM. [44]

Applications of nanocrystal formulations.

In all cases, the formulations have proven to be well tolerated and provide alternate formulation approaches for poorly water-soluble therapeutics, thus broadening their applications and use. One final point that should be addressed is the potential alteration in biodistributional properties that can potentially result when a compound is dosed using a nanoparticulate platform. It is well established that various physical properties of a particulate carrier can affect tissue distribution. [45, 46, 47] The tissue distribution following intravenous injection of nanoparticulate carriers that involve encasement or encapsulation technology such as liposomes and various polymeric carriers have been extensively studied. [48, 49, 50] Size, surface, and shape are important if the intention is to target or avoid rapid uptake of the particulates by the mononuclear phagocytic system (MPS) of the lung, liver, spleen, and bone marrow.

For drug nanoparticles that do not involve encapsulation technology, tissue distribution is also dictated by the solubility of the compound. If a compound is soluble in the blood pool, the drug nanoparticle, on dosing, will exhibit a pharmacokinetic and tissue-distribution profile very similar to the compound dosed as a solution. [24, 41] Alternatively, if the compound is practically insoluble in the blood pool, when dosed, drug nanoparticles will behave very similarly to the other nanoparticulate platforms described above; that is, size and coating can be used to target or avoid the MPS system. [11, 17] This ability to use a particulate carrier to control tissue distribution of a compound can be beneficially used to direct high concentrations of drug to diseased sites while limiting exposure to healthy tissue.

CONCLUSIONS

Nanoparticle-formulation technologies have provided the pharmaceutical industry with new strategies for resolving issues associated with poorly soluble molecules. For new chemical entities, the technology has been of value when used as a screening tool during preclinical efficacy and/or safety studies. During development, robust nanoparticle formulations can be post-processed into various types of patient-friendly dosage forms that provide maximal drug exposure. For marketed products requiring life-cycle management opportunities, nanoparticle formulation strategies provide a means to incorporate an old drug into a new drug-delivery platform, thus opening new avenues for addressing unmet medical needs. The era of nanotechnology in the pharmaceutical industry has begun. During the next decade, it will be interesting to see if all the promises envisioned become a reality.

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