

Nanoparticles for Superior Pharmacokinetics and Enhanced Efficacy

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Introduction

Solubility and permeability are the two most important factors that can significantly affect Pharmacokinetics (PK) of a drug. The Biopharmaceutics Classification System (BCS) classify drug molecules based on solubility and intestinal permeability. Sufficient balance of hydrophilicity and lipophilicity is required for a drug to be absorbed well. Drugs which are highly soluble may be limited by permeability or vice-versa. Similarly, a highly soluble drug given by intravenous (IV) route may have undesirable distribution or clearance. The use of nanoparticles has shown some promises in addressing these barriers to the usefulness of the drugs. Originally stemmed from the idea of increasing usefulness of existing small molecule anti-cancer agents, this method has gained popularity due to its ability to allow delivery of nucleic acids, peptides, or proteins for disease treatment [1]. Nanoparticles based drug delivery has enormous clinical significance as demonstrated by new nanoparticle based drug approvals like pegylated liposomes of doxorubicin. Altered distribution and slower excretion of this liposomal injection resulted in the AUC of doxorubicin hydrochloride liposome injection ~2-3 times more than the AUC for a similar dose of conventional doxorubicin hydrochloride [2].

Nanoparticle Encapsulating Agents and Processes Utilized

Essentially, nanoparticle encapsulating agents can be polymer-based or lipid-based. Polymer based agents offers the advantage of using diverse hydrophilic or hydrophobic polymeric materials to modulate the physicochemical properties of nanoparticles (i.e. surface charge and mucoadhesivity), encapsulation efficacy, drug release profile and biological behavior [3,4]. Polymer based nanoparticles are generally divided into three main classes. a) Polymer drug conjugates using natural agents like albumin, chitosan or heparin. Alternatively, these can be synthesized using synthetic agents like Polyethylene Glycol (PEG) and Poly-L-Glutamic Acid (PLGA). b) Polymeric micelles involves formation of micelles by using certain polymers like PEG as seen in Genexol-PM[®] {PEG-poly(D,L-lactide)-paclitaxel}. c) Dendrimers are another polymer based nanoparticles as exemplified by poly(amidoamine). Besides absorption, lipid-based nanoparticles offer good permeation due to the bilayer structure similarity to that of the cell membrane. Lipid-based nanoparticles can also be very useful in altering other significant PK parameters to increase drug's usefulness. Additionally, these liposome based lipid nanoparticles can

be pegylated to increase circulation half-life. Viral and carbon nanotubes are other examples of lipid based nanoparticles gaining importance in drug development [3,4].

Encapsulation Techniques

Different strategies can be applied to synthesize drug loaded nanoparticles. One of the most common techniques is the entrapment of drug in lipophilic polymeric nanoparticles. This strategy offers various advantages like drug protection, Sustained Release (SR) effect and good loading efficiency, however limited drug solubility in polymer, use of organic chemical and undesired reaction between drug and polymer can be disadvantageous. Similarly, drugs can be encapsulated using Aqueous Core Nanocapsules (ACN), where drug is solubilized in the core which is then released in a SR fashion [1].

Another encapsulation method involves adsorption of the drug on to the polymer surface. Important advantages of this technique involve less reaction potential between the drug and the polymer. Additionally, electrostatic interactions of drug with the polymer can be modified by appropriately selecting polymer so as to improve drug loading. However, adsorption technique makes drug more vulnerable to leak prematurely and may result in overall lower biological efficacy [1].

Applications

The nanoparticle approach of increased drug delivery can be applied to various different types of formulations: oral, topical, pulmonary, and parenteral.

For oral drug delivery, one example is the entrapment of doxorubicin hydrochloride with PLGA nanospheres. This type of application results in an increase of bioavailability by 363% and 6 fold increase in T_{max} [5]. These desirable PK features substantiate application of nanoparticle based drugs especially in cancer, which can be extended to other disease states like HIV and Hepatitis C.

Small size and higher penetration of nanoparticle also has important applications in topical drug delivery. Topical nanoparticle offers fewer side effects, controlled drug release over a prolong period of time, and bypass of first-pass metabolism.

Pulmonary administration is another area of drug administration that utilizes nanoparticles. It is more of a nanoparticulate strategy via micronization instead of drug encapsulation that is utilized. Smaller drug sizes enables better penetration in the lung either via IV administration (through microspheres), nebulize solution, or dry powder inhalation. An example of nanoparticle utilization for pulmonary administration is the microemulsion systems water/lecithin/propan-2-ol/iso-octane [6]. Since nanoparticles are small in

size, they are the ideal candidate for pulmonary administration. However, more trials and experiments will have to be carried out to cover safety concerns such as biodegradability of the drug, stability of the drug product, and ease of maintaining consistent particle size during manufacturing.

Parenteral nanoparticles have made significant progress with Food and Drug Administration (FDA) approved drugs already in the market and a significant numbers of drugs in advanced stages of clinical trials. One of the well-known examples of nanoparticles for parenteral delivery is doxorubicin hydrochloride liposome injection comprising of doxorubicin hydrochloride encapsulated in pegylated liposomes for intravenous administration [7]. The pegylated liposomes of doxorubicin hydrochloride liposome injection are formulated with surface-bound methoxypolyethylene glycol (MPEG) to increase blood circulation time and to protect liposomes from degradation by natural defense systems like Mononuclear Phagocyte System (MPS). Post-injection samples of the SLN-doxorubicin and conventional doxorubicin from rats are biopsied from liver, heart, lung, kidney, spleen, and brain then drug concentrations were measured. An increased AUC is observed in the lung, spleen, and brain with the SLN-doxorubicin, revealing enhanced lipophilicity of doxorubicin in certain distribution profiles [7]. Pegylated liposomes have a half-life of approximately 55 hours demonstrating their stability in blood. It has been shown that at least 90% of the drug remains liposome-encapsulated during circulation. It is hypothesized that because of their small size (~100 nm) and good circulation half-life, the pegylated doxorubicin hydrochloride liposomes are able to penetrate the altered and often compromised vasculature of tumors [8,9].

In summary, nanoparticles offers numerous advantages and a promising method of drug delivery such as enhanced physiological and biological stability, improved PK profile, and most importantly,

increased permeability as seen in cancer cells. Both the drug encapsulation and nanoparticulating strategies results in significant reduction in particle size that increases the drug permeability. Though the majority of the researches utilizing nanoparticle are still under clinical trials, the current results from all routes of administration showed positive results.

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