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Role of Size of Drug Delivery Carriers in Pulmonary and Intravenous Administration with Emphasis on Cancer Therapeutics and Lung-Targeted Drug Delivery

Chetna Dhand,[a] Molamma P. Prabhakaran,[b] Roger W. Beuerman,[ac] R. Lakshminarayanan,[ac] Neeraj Dwivedi[d] and Seeram Ramakrishna[*be]

ABSTRACT

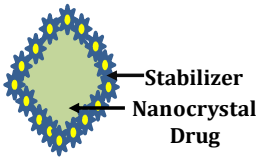
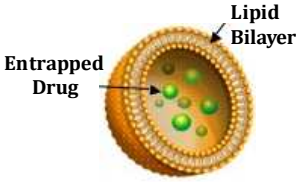
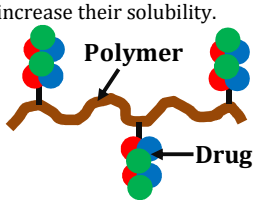
Designing a drug delivery system or fabricating efficient, triumphant and targeted drug carriers makes two different stories with trivial modifications in their designing parameters. Carrier geometry including its size and shape, chemical structure, surface chemistry and surface charge are among the key parameters that require optimization in order to achieve desired therapeutic behaviour. In this review, attempts have been made to give an overview about the effect of size of the drug delivery carrier on its biodistribution, target specificity, body clearance rate and most importantly on its therapeutic action. Pulmonary and intravenous drug administrations are mainly focused here with special emphasis on cancer therapeutics and Lung-Targeted drug delivery. Thus, this article highlights the significance of dimensional variations and sizes with regard to drug delivery carriers, to be appropriate for controlled and targeted drug delivery, prohibiting excessive therapeutic loss via various clearance routes and to overcome superfluous side effects and toxicity.

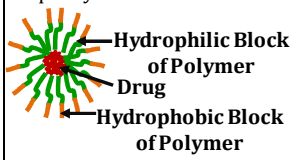
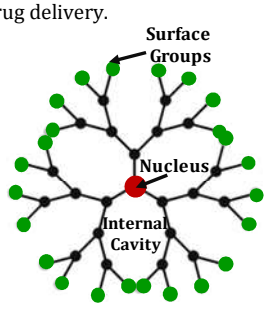
1. Introduction

Potential drug delivery system (DDS) is defined as the mechanism or strategy employed to introduce a therapeutic agent into the body.[1] The important challenge for the clinical translation of any DDS is to identify the optimal physicochemical parameters that simultaneously grant molecular targeting, immune evasion, and controlled drug release.[2] This mainly relates to the complex interdependence of DDS properties (composition, size, shape, surface charge, hydrophilicity, and ligand type and density), payload properties (drug type, solubility, loading, and release kinetics), and *in-vivo* physiological barriers to DDS trafficking (immune surveillance, particle extravasation, tissue penetration, and cellular uptake).[3] Thus, to acquire the appropriate amount of desired drug to the target organ/area without causing any side-effects and to prevent the induction of the drug resistance is a daunting task, but an important requirement in targeted DDS. Commercialization of nanotechnology in pharmaceutical and medical science have revolutionize this field and crafted a new era of nanomedicines.[4, 5] Highly efficient drug delivery, based on nanovehicles, could potentially reduce the drug dose needed to achieve therapeutic benefit, which, in turn, would lower the cost and/or reduce the side effects associated with particular drugs. Furthermore, nanoparticles size, shape and surface characteristics can be easily manipulated to achieve both passive and active drug targeting. Different nanoparticles based drug delivery carriers have been emerged in past few decades, viz., nanocrystals, liposomes, polymer micelles, dendrimers, polymer-drug conjugates etc.[4-12] Table 1 shows a compilation of the various commercialized nanocarrier based drugs available in the market with their detailed depiction.

Table 1 Most evaluated drug delivery nanocarriers for targeted drug delivery and their commercialized products.

Type of Targeted Drug Delivery Carrier	Commercialized Drugs					
	Brand Name	**Active Integredient**	**Year of Approval and Licensed To**	**Indication**	**Mode of Administration**	**Ref.**
NANOCRYSTALS	Rapamune®	Sirolimus	2001 by Wyeth	Immunosuppressive	ORAL	4,6

Nanoscale formulation of the drug itself with outer thin coating/layer of non-ionic surfactant or polymeric macromolecule. It can function as its own carrier.  	Emend®	Aprepitant	2oo3 by Merck	Anti-emetic	ORAL	4,6
	Tricor®	Fenofibrate	2004 by Fournier and Abbott	Hypercholesterolemia	ORAL	4,6
	Megace®	Megestrol	2005 by Elan/Par Pharm	Anti-anorexia	ORAL	4,6
LIPOSOMES (30nm-20µm) Liposomes are self-assembled artificial vesicles developed from amphiphilic phospholipids. Liposomes are the most clinically established nanosystems for drug delivery due to their ability to entrap both hydrophilic and hydrophobic drugs.  	AmBsome® 80 nm	Amphotericin B	1995 by Glead	Severe Fungal Infections	INTRAVENOUS	7,8
	Depocyt® 200-300 nm	Cytarabine	2002 by Napp	Lymphomatous Meningitis	SPINAL	7,8
	Doxil® and Caelyx® 85 nm	Doxorubicin	1995 by Schering-Plough	Ovarian Cancer, Kaposi's Sarcoma and Breast Cancer	INTRAVENOUS	7,8
	Daunoxome® 45 nm	Daunorubicin	1996 by Diatos	Blood Cancer	INTRAVENOUS	7,8
	Visudyne®	Verteporfin	2000 by Novartis AG/QLT	Age Related Molecular Degeneration	INTRAVENOUS	7,8
POLYMER-DRUG CONJUGATE (6-15 nm) Polymer-Drug Conjugates indicates the drug molecules bound to the macromolecular structures to enhance their blood circulation time and to increase their solubility.  	Adagen®	Adenosine Deaminase	1993 by Enzon	Immunodeficiency Disease	INTRAMASCULAR	9,10
	Oncaspar®	L-Asparaginase	1997 by Enzon	Antineoplastic	INTRAVENOUS & INTRAMASCULAR	9,10
	Neulasta®	Pegfilginase	2002 by Amgen	Reduction of febrile Neutropenia associated with chemotherapy	SUBCUTANEOUS INJECTION	9,10
	PEG-Intron®	Interferon α-2b	2001 by Enzon, Schering-Plough	Hepatitis C	SUBCUTANEOUS	9,10

POLYMERIC MICELLES (20-150 nm) Polymer Micelles are the self-assembled core-shell nanostructures formed in aqueous solution consisting of amphiphilic block copolymers. Polymeric micelles have the advantage of having very small size over other nanocarriers which is really important for,percutaneous lymphatic delivery or extravagation from blood vessels into the tumor tissue. And also these micelles are having large loading capacity.  	Genexol-PM®	Paclitaxel	2007 by Samyang Biopharmaceuticals	Cancer chemotherapy	INTRAVENOUS	4
DENDRIMERS (5-10 nm) Dendrimers are the novel three dimensional, hyperbranched globular nanopolymeric architectures. Characteristics like Nanoscopic size, narrow polydispersity index, excellent control over molecular structure, availability of multiple functional groups at the periphery and cavities in the interior make them suitable and excellent candidate for targeted drug delivery.  	VivaGel® 3-10 nm	SPL7013, Dendrimer	Bacterial Vaginosis or Vaginal Microbicide for prevention of HIV and HSV Infections	2014 by Starpharma	TOPICAL	11
PROTEIN (ALBUMIN) NANOPARTICLES (130 nm)	Albraxane® 130 nm	Paclitaxel	Metablastic Breast Cancer	2005 by Abraxis Biosciences	INTRAVENOUS	12
LIPID COLLOIDAL DISPERSION (100-150 nm)	Amphotec® 122 ±48 nm	Amphotericin B	Fungal Infections	1996 by Sequus Pharmaceuticals	INTRAVENOUS	13

The physicochemical properties such as size, shape and the surface characteristics of DDS are among the key parameters which should be considered beforehand on an engineering perspective while designing efficient DDS for any therapeutic agent via specific administration route. Venkataraman et al.[14] and Champion et al.[15] have already contributed a detailed review on the effect of shape of the drug delivery nano/micro-carriers on their therapeutic performance. Recently in 2013, Honary and Zahir et al. have published a detailed review on the effect of the zeta potential/surface charge of nano-drug delivery carriers on their drug delivery characteristics in two parts.[16-17] Being an equally worth-discussing parameter, there is not even a single review article available enlightening/revealing the effect of size of the drug carrier on its drug delivery characteristics except brief discussions. Size/dimension of the drug delivery carrier influence almost every aspect of its functioning and efficacy like its degradation, flow properties, renal clearance, hepatic filtration, tissue extravasation/Diffusion, endocytosis etc.[18] Exemplifying this, nanoparticles having size smaller than 10 nm can be easily cleared by kidney excretion and larger nanoparticle (>150 nm) have the higher tendency of being cleared-off by mononuclear phagocyte system (MPS), also known as reticuloendothelial system (RES).[19] Moreover it was shown that the liposomes of size 100-150 nm have higher potential to be the part of the blood circulation for longer time and also show high hepatic filtration kinetics than of liposomes of size >70 nm.[20-21] Size of the DDS also plays a vital role in deciding their accumulation at the tumor region through the enhanced permeability and retention (EPR) effect, which has been discussed in detail further on in this review.[22] As a physical parameter 'size' of DDS is critical in context of the drug target/site of action, cellular uptake/internalization mechanism and specialized therapeutic action.[23]

In the present review article, we highlight the importance of the size of the drug delivery carrier in deciding its biodistribution, target accumulation/specificity, body clearance rate and most importantly its therapeutic action. The spotlight has been more focused on two different mode of therapeutic administration: first is **pulmonary administration** (Targeting the lungs/other organs via pulmonary route/human respiratory tract) and second is **intravenous administration** with special emphasis on cancer therapeutics

along with lung-targeted intravenous administration (Targeting the lungs via blood circulation).

2. Effect of Size of Drug Delivery Systems on Pulmonary Administration

The physiology of the lung makes it an ideal target organ for drug delivery and likewise pulmonary route serve as the appropriate mode of administration due to its high solute permeability, large surface area for absorption with non-invasive characteristics and being a site with limited proteolytic activity.[24] During pulmonary administration, drugs are delivered locally into the lungs for treatment of respiratory diseases like asthma, lung cancer etc., which has the potential to reduce the dose-dependent drug toxicity.[25] Alternatively, systemic drug delivery can also be achieved by targeting the drug delivery carriers to the alveolar region where the drug can be absorbed through the thin epithelial cell layer and enter the systemic circulation.[26-27] This can be desirable to achieve a rapid onset of action by avoiding first-pass metabolism and for delivering of biotherapeutics, i.e. peptides and proteins, that cannot be delivered orally, owing to enzymatic degradation and poor intestinal membrane permeability.[28] Furthermore, the lungs can be targeted for delivery to specific lung cells, such as alveolar macrophages, for treatment of diseases such as tuberculosis.[29]

Human respiratory or the pulmonary system is divided into two main functional zone i.e. the conducting zone (consists of trachea, bronchi and bronchioles) and the respiratory zone (constituting airways and the alveoli). The human lung contains about 2300 km of the airways and 500 million of the alveoli that participate actively in the gaseous exchange process.[30] The surface area of the human lungs is estimated to be approximately 75-140 m^2 in adults.[31] The pseudostratified epithelium, which provides a barrier for absorption into the blood stream, varies differently in different parts of the lungs. The airways epithelia are composed of gradually thinning columnar epithelium with thickness of bronchial and bronchiolar epithelium of 3.5 mm and 0.5-1 mm, respectively.[24] In contrary, the alveoli epithelium is only single-cell thick and provides the distance of even less than 400 nm from the alveolar lumen to the blood stream. The accessible large surface area of the alveoli and the intimate air-blood contact in this region makes this zone a suitable site for gaseous exchange as well as for the absorption of inhaled aerosols

including drug delivery nanovectors or nanomedicines.[32] The pulmonary drug delivery system is based on the principle of aerosolization. Aerosols containing uniformly sized particle organized with drug loaded vehicles, may provide uniform dose delivery and drug release kinetics.[33]

The location and extent of drug carrier deposition and the efficiency of the drug loaded nanovehicle after inhalation is strongly influenced by three main factors viz., size and geometry of the DDS, anatomy of the upper and lower airways with the alveolar structure and finally the ventilatory parameters. Ventilatory parameters include breath pattern (i.e. breath-holding and presence of expiratory flow limitation), flow rates and tidal volume, determining the airflow velocity and the residence time in the respiratory tract.[34] Depending upon the size of the drug delivery vector, there are again three principal mechanisms that decide its deposition and distribution in the lungs viz., i) Inertial impaction, ii) Gravitational sedimentation and iii) Brownian diffusion (Table 2).[35] Deposition generally refers to the mean probability of a particle being deposited in the respiratory tract upon settling on airway surfaces. For the lung deposit, particle size is characterized by their mass median aerodynamic diameter (D_a), which is the diameter of the spherical particle having density of 1 gm/cm^3 having same settling velocity (under gravity through air) as the particle of interest. It can be given by the relation:[36]

$$D_a = \sqrt{\frac{\rho}{\rho_a}} D_g$$

Where ρ is the mass density of the particle, ρ_a is the unit density and D_g is the geometric diameter. Considering the aerodynamic diameter of the drug carrier, the inertial impaction usually occurs during the passage of the large sized particles (> 5 μm) through the oropharynx, trachea and other large sized airways. However, sedimentation by the gravitational forces is more prone for the particles having the size range of about 1-5 μm and that too in the smaller airways and the respiratory bronchioles. Particle sedimentation is also found to be dependent on the process of breath-holding (Table 2). Brownian motion by diffusion is the primary mode of particle distribution for small-sized nanoscaled drug carriers (≅ 500 nm). [24, 32-33]

Table 2 Size, site and mechanism of aerosol distribution during pulmonary administration

Size of Inhaled Aerosol Particles	Site of Particle Deposition	Mechanism of Deposition
5-9 µm (Slow Inhalation)	Large Airways including oropharynx, trachea and bronchi	Inertial Impaction
3-6 µm (Fast Inhalation)	Large Airways including trachea and bronchi	Inertial Impaction
1-5 µm	Smaller Airways	Gravitational Sedimentation
≤ 0.5 µm	Alveoli	Brownian Diffusion

A widely accepted notion states that for efficient lung deposition**, aerodynamic diameter should be in the range of 1-5 µm**.[37-38] Small sized particles (<1 µm) are likely to get absorbed quickly from the airways and this pose a risk of systemic toxicity. Moreover, 80 % of the administered particles with sizes of < 1 µm are exhaled out without being deposited because of its low inertia.[39] In contrast, very large particles are cleared out by the mucociliary clearance mechanism.[40] Recent studies suggest that particles with density less than 0.4 g/ml and geometric diameter greater than 5 µm favor efficient deposition in the lungs.[41] Thus, in order to successfully arrive at the deeper lung tissues, the inhaled particles should be small enough to avoid deposition at the upper airways by sedimentation or impaction and at the same time it should be large enough to avoid exhalation. Hence, an optimal particle size in the range of 1- 5 µm is required to achieve efficient pulmonary drug delivery. Hirota et al. have studied the distribution and deposition of respirable PLGA microspheres with incorporated anti-tuberculosis drugs (Coumarin-6 and Rifampicin), with diameter of 2.67±2.18 µm (for Coumarin-6) and 2.35±1.96 µm (for Rifampicin), in small animal models. Results indicate maximum accumulation of microspheres in the tracheal and primary bronchi region.[42] PLGA microspheres of ~ 3 µm diameter were suggested as the best suitable and optimal sizes for phagocytic uptake by the alveolar macrophages.[43]

Being the part of respiratory tract, drug carrying vectors again got absorbed adopting different biological routes depending upon their sizes. In the upper conducting region, drug loaded nanomedicines starts depositing into the mucous layer (~ 5μm deep; composed of electrolytes, proteins, glycoproteins and cell debris) that lines the airways or the surfactant layer (10-20 nm thick; 9:1 wt % of phospholipids and specific proteins) covering the alveolar region. [44] Nature of the drug delivery vehicle do not play any role in deciding the extent of submerging of guest nanocarriers into the lining fluids after their deposition, but it is the size of the nanovector that serves as the deciding factor. Stuart et al. have studied the interaction of lung surfactant film with nanoparticles of two different sizes (187 nm and 230 nm) and indicated that the extent of nanoparticle incorporation into the surfactant layer depends on the dimension of the nanoparticles, particularly its size.[45] Results of the study reveal stronger interaction of smaller nanoparticles with the surfactant monomolecular film compared to their larger counterparts. Smaller is the size of the nanoparticles, more will be the absorption of these nanovehicles into the surfactant layer. After inclusion into the lung lining fluid, there are separate biokinetics for lung absorption and non-absorptive clearance.[46] Most of the small sized and highly soluble hydrophobic molecules undergo rapid absorption through lung epithelial membrane by passive diffusion.[47] And the kinetics of passive diffusion in the alveoli is much faster than in the smaller airways since most of the pulmonary absorption occurs through the alveolar capillaries of the alveolar region. A smaller portion of the inhaled nanoparticles got absorbed from the tracheobronchial airways.[34] On the contrary, low molecular weight hydrophilic molecules will be absorbed by active transport process depending on the lung regional expression and the functionality of the receptors or the transporters. Recently, Bitonti et al have reported on the absorption of large sized immunoglobulin (IgG) molecules in the upper airways by receptor mediated transcytosis of IgG.[48]

For the nanovectors which are absolutely insoluble in the mucus and the lining fluids, there are different post-defense mechanism available in the body, including mucociliary escalator transport, phagocytosis by macrophages and endocytosis, for removal of deposited nanoparticles and maintainance of the lung mucosal surface.[49] The mucociliary escalator dominates the clearance of comparatively larger particles from the upper

airways by action of the ciliated epithelial cells pushing the mucus along with the particles that deposited on the airway walls to the larynx, where they are swallowed to the gastro-intestinal tract or excreted through the mouth.[50] These deposited structures may also get removed by coughing within 1–2 days of time period.[24] Macrophage phagocytosis and endocytosis are the main mode of clearance for slowly dissolving and insoluble nanoparticles from the alveolar region.[51] There are around 500 million alveoli present in the lungs which are consistently examined on the air-side surface by 12–14 alveolar macrophages in the lung lining fluid.[29] And the particle size has to play a very important role here in deciding the uptake of deposited particles by alveolar macrophages. Particles of 1–3 μm in diameter are far better taken up than those of 6 μm by macrophages (with cell diameter of 15–22 μm).[52] Particles of less than 0.26 μm might escape from phagocytosis.[53] These small sized nanoparticles will further interact with the non-phagocytic cells of the epithelium and initiates the endocytic events which are regulated by clathrin-coated pits and caveolae.[54] Caveolae are the indentations of the plasma membrane lined with caveolin-1, and are predominantly expressed by lung capillaries and Type I alveolar cells. Particles of several nanometers in radii may be transported within caveolae from lung to blood.[55] Inspiratory expansion and expiratory contraction of lung alveoli may lead to the opening and closing of the caveolae. These openings measure between 40 and 100 nm in size and are thought to be involved in the transport of macromolecules, such as proteins, across the alveolar-capillary barrier.[56] These processes of phagocytosis by macrophages and/or endocytosis by the epithelial and the endothelial cells will results in the extra-pulmonary nanovector translocation to various sites depending upon its size, chemical composition, particle size, surface characteristics, labeling materials and experimental models reported in the different studies.[57] Rapid and excessive translocation of ^{13}C labelled nanoparticles with diameter of 26 nm is reported in the liver within 1 day after administration via pulmonary route in rat model.[58] Kreyling et al. have estimated the biodistribution of 1% iridium nanoparticles 10-20 nm diameter) after inhalation and the maximum nanoparticle accumulation was observed in the liver, spleen, kidneys, brain and heart, by these researchers.[59] Following 3 months of exposure to ultrafine (~20 nm) and fine (~200 nm) titanium dioxide (TiO_2)

particles by inhalation in rats, the ultrafine particles were cleared significantly more slowly, and showed more translocation to interstitial sites and to regional lymph nodes compared to the fine TiO_2 particles (Oberdorster et al., 1994).[60] Particles between 20 and 50 nm in diameter might enter the central nervous system and cells. In addition, alveolar macrophages on the surface of the lungs were unable to recognize particles of less than 70 nm as being "foreign", thus allowing them to gain access to the pulmonary interstitium, and further to the capillary blood flow.[61] Fig. 1 reveals pulmonary distribution of drug loaded carriers in lungs with respect to their size.

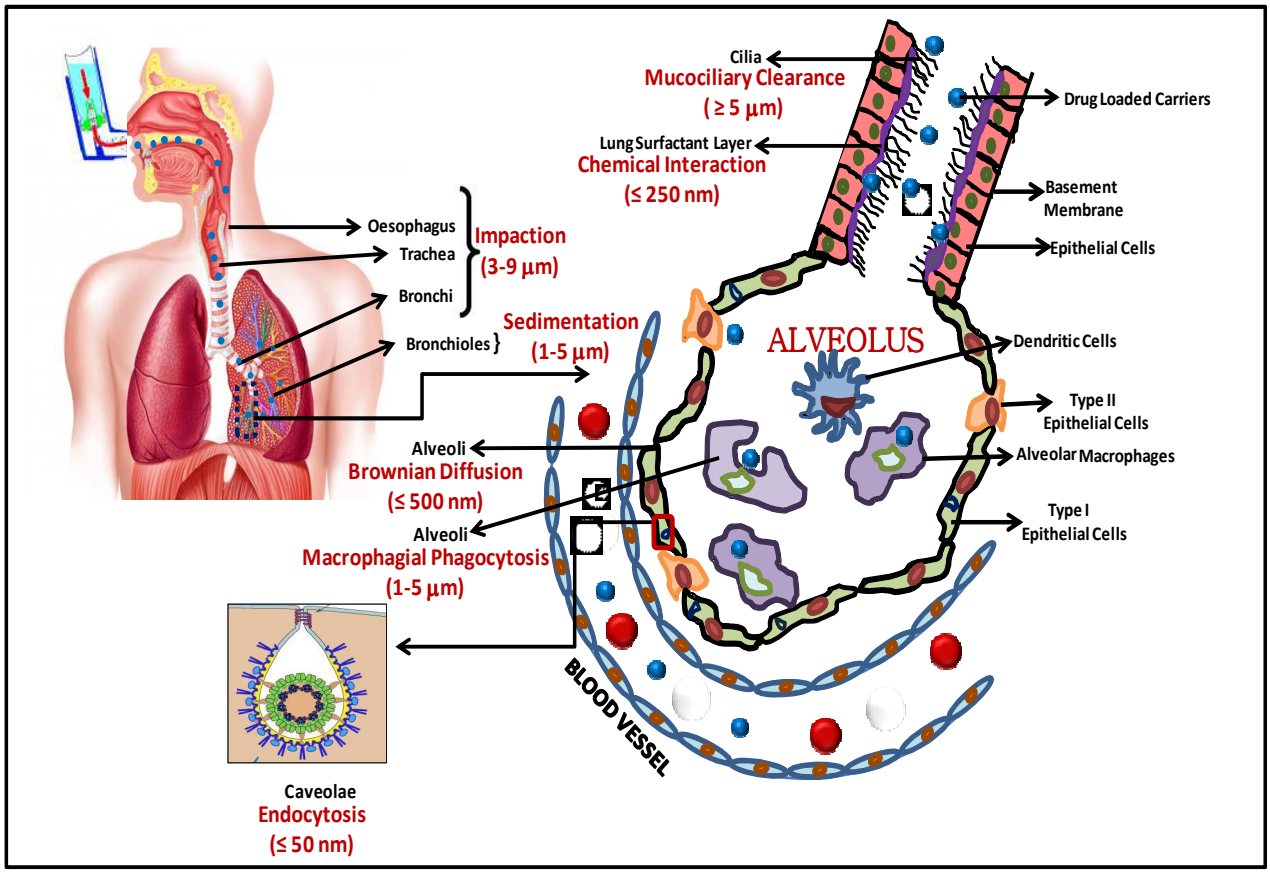


Fig. 1 Schematic revealing different routes for pulmonary drug carrier distribution, their clearance and absorption with their size dependence and preferences.

NebuPent (Drug: Pentamidine isothionate, Size: **1-2 µm**, Treatment for pneumocystis carinii pneumonia), **Virazole** (Drug: Ribavirin, Size: **< 1 µm**, RSV lower respiratory tract infection), **Tobramycin Inhalation Solution** (TOBI ®, Drug: Tobramycin, Size: **0.5-10 µm**, first inhaled antibiotic given by nebulizer), Amphotericin B Inhalation Powder

(ABIP, Size: **1-5 µm**, inhaled antifungal product), **Ventavis** (Drug: Iloprost, Size: **1-3 µm**, Inhaled treatment for pulmonary arterial hypertension), **Resmycin™** (Drug: Doxorubicin.HCl, Size: **< 2 µm**, Inhalation solution for lung cancer therapeutics) are some of the FDA approved inhaled formulations and vaccines administered via pulmonary route. And all these medicines falls in the narrow size range of 1-10 µm.

Summarizing this, the size of the drug delivery vehicle not only affects its pulmonary distribution but also its metabolism, clearance, and absorption. Regarding drug carrier distribution, particles with sizes in the range of 5-9 µm have more probability to stay in the upper airways region including oropharynx, trachea and bronchi. Particles with dimensions of 1-5 µm and ≤ 0.5 µm have more chances to deposit in the smaller airways (bronchi and bronchioles) and terminal alveoli, respectively. Regarding their clearance efficiency, vehicles having size less than 1 µm have more tendencies to be exhaled out due to low inertia and those having more than 5 µm can be sweeped out easily due to mucocilliary mechanism. In view of the effect of size on the metabolism and absorption of drug loaded carriers, small sized (>250 nm) hydrophobic particles shows rapid absorption through lung epithelial membrane by passive transport and similar sized hydrophilic particles undergoes active transport via endocytosis. However, larger particles (> 1 µm) undergoes their absorption and translocation by receptor mediated transcytosis, macrophagial phagocytosis etc. Also, particles with sizes range of 1-3 µm are reported best suitable for macrophagial uptake.

3. Effect of Size of Drug Delivery Carriers on Intravenous Administration: Special Emphasis on Cancer Therapeutics and Lung-Targeted Intravenous Drug Delivery

Intravenous administration is a very important and most adopted drug delivery route, particularly, if the target organ is far away from the administration site. Like other therapeutic administration modes, size of the drug delivery vehicle is a very important parameter in deciding the drug targeting, biodistribution, drug clearance and consequently the desired therapeutic action during intravenous administration. During this journey through the vascular bed and before reaching the target site, drug carrier

undergoes biodistribution steps depending upon its size. For example, the nanoparticles of < 20-30 nm size can be easily cleared from the blood via renal clearance; while nanoparticles with dimensions of 30-150 nm are more prone to accumulate in the bone marrow, heart, kidney and stomach. And the nanoparticles of >150 nm size are generally found in the liver and spleen. Larger nanoparticles can be easily taken up by the mononuclear phagocyte system. Thus, the drug delivery carriers can easily escape from the blood circulation to different body organs/parts through the openings available at their endothelial barrier, also known as fenestrations. To pass this continuous and intact endothelial barrier, the particle size/carrier size should be < 150 nm under normal conditions. However, under different pathological conditions the vasculature and the fenestration size undergo changes e.g., in cancerous tissues rapid growth and multiplication of cells demands more blood supply that leads to the development of neovasculature characterized by discontinuous endothelium with large fenestration of 200-780 nm. Table 3 summarizes the fenestration size of various vital organs in animals.

Table 3 Different fenestration sizes in the vasculature of different body organs

Organ and the Animal Model	Fenestration Size	Reference
Organ: Kidney **Animal Model:** Rat or Guinea Pig	20-30 nm	[62]Caliceti et al., 2003
Organ: Liver **Animal Model:** Mice	150 nm	[63]Takakura et al., 1998
Organ: Spleen **Animal Model:** Mice	150 nm	[63]Takakura et al., 1998
Organ: Lung **Animal Model:** Dog	1-400 nm	[64]Conhaim et al., 1988
Organ: Bone Marrow **Animal Model:** Rat or Guinea Pig	85-150 nm	[65]Moghimi et al., 1995
Organ: Skeletal, Cardiac and Smooth Muscles **Animal Model:** Mice	≤ 6 nm	[66]Seymour et al., 1992
Organ: Skin, Subcutaneous and Mucous Membrane	≤ 6 nm	[66]Seymour et al., 1992

Animal Model: Mice		
Organ: Blood-Brain Barrier **Animal Model:** *In-vitro* model	No Fenestration	[67]Cucullo et al., 2002
Organ: Tumor in ear and brain **Animal Model:** Mice	200-380 nm	[68]Jain et al., 1994
Organ: Tumor in brain **Animal Model:** Mice	100-380 nm	[69]Arfors et al., 1979

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Joliano et al. have reported the direct relation between the rate of clearance of encapsulated liposomal vesicles from bloodstream and their particle size.[70] Attempts have been made to evaluate the carrier endocytosis, trafficking and eventually intracellular fate within the endothelial cells (lining the vascular lumen) with respect to the size (0.1-10 μm) and shape (Spheres versus Elliptical Disks) of the intracellular adhesion molecule-1 (ICAM-1) targeted polymer carriers via intravenous administration. These size-dependant studies reveal that the endothelial cells internalized anti-ICAM-coated polymer carriers with size up to several microns via cell adhesion molecule mediated endocytosis. Further, micron-size carriers have been found to have prolonged residency in prelyposomal compartments, whereas, submicron carriers trafficked to liposomes more readily. Rational design of the carrier geometry might be helpful to optimize the endothelium targeted therapeutics.[71] Koval et al. have examined the uptake and transport of IgG opsonized polystyrene beads of particular dimension, ranging from 0.2 to 3 μm, using mouse bone marrow-derived macrophages. Although, the kinetics of the opsonized beads internalization is determined to be comparable for different size particles, the involved internalization mechanism is demonstrated as size-dependent. The smaller size particles (0.2-0.75 μm) are found to be internalized by clathrin-mediated endocytosis whereas actin-dependent phagocytosis plays an important role in case of larger particles (1-3 μm).[2]

Illum et al. have systematically studied the blood clearance, and subsequent organ deposition profile following intravenous administration of colloidal particles of different size, shape and nature. Small polystyrene microspheres (1.27 μm) have been found to get removed by the retinoendothelial system of the body and thus retained by kupffer cells of

liver and conversely the large polystyrene particles (15.8 μm) got lodged in the capillary beds of the lungs since they have sizes larger than the critical size for passage through the pulmonary vascular bed.[3] Kanke et al. have also reported liver as the primary deposition centre for small spherical polystyrene particles of < 7 μm, while particles of > 7 μm have been filtered mechanically and retained for prolonged periods in the lungs.[72] Size of the DDS also influences its splenic and renal clearance profile. It has been accounted that the particles with size more than 200 nm are more prone to elimination via splenic filtration whereas the particles smaller than 20 nm are susceptible to be cleared through kidney's filtration route. Table 4 shows the indirect proportionality relation between the hydrodynamic diameters (HD) of different globular proteins and their biodistribution, with special emphasis on extent of renal filtration (Modified version of the Table 1 in Reference 73).[73]

Table 4 Biodistribution and Renal Filtration of different globular proteins as a function of hydrodynamic diameter

Protein Molecule	Molecular Weight (KDa)	Hydrodynamic Diameter (nm)	Urine/Blood Filterability (%)	Blood Half-Life (mins)	Whole Body Half-Life (mins)
Insulin	5	3.0	100	9	1.9
Myoglobin	17	3.8	75	9	2.0
ScFv	30	5.3	74	11	1.4
Fab	50	6.0	9	28	4.0
HSA	67	7.3	0.3	110	16.0
IgG	152	11.0	<0.1	330	730

ScFv: Single Chain Variable Fragment; **Fab:** Portion of Antibody; **HAS:** Native Albumin; **IgG**: Immunoglobulin

Hydrodynamic diameter of nanoparticle is a critical parameter during the development of potential diagnostic and therapeutic agents. It can be calculated using the power law given below

$$HD = A \times MW^{B} + C \times MW^{D}$$

where A = -0.000 00 0002614, B = 3.326, C = 0.9482, D = 0.5001

The mammalian vasculature has the average pore size of ~5 nm and hence DDS with size approaching this value shows rapid equilibration between the agents injected intravenously and the extracellular space.[73] But above this value, transport across the endothelium is extremely slow. For non-biodegradable nanoparticles, other routes for the nanoparticle elimination are through liver, into bile or into the feces. Liver has been specifically appointed to take-up and eliminate nanoparticles with HD in the range of 10-20 nm. But to bypass this removal step via retinoendothelial system, the therapeutic agents are coated with specialized materials such as PEG. The extraction of the nanoparticles into the bile is an extremely slow and inefficient step and can be ignored. The particles having the dimension of < 10 nm has the ability to leave the systemic circulation through permeable vascular epithelium of the lymph nodes. These small-sized particles also have the capability of elimination by following the sinus endothelium route of the bone marrow.[74] Choi et al. have reported a very interesting study on the intravenous administration of quantum dots (having ZnS shell and CdSe as the core material) of different hydrodynamic diameters (4.36 nm, 4.99 nm, 6.70 nm and 8.65 nm) into the rat body and then to estimate its blood clearance, biodistribution and body clearance parameters as a function of their size.[73] The blood concentration studies carried out at different time intervals shows the following trend i.e. 8.36>6.70>4.99>4.36, revealing that the larger nanoparticles have more tendency to remain in the blood stream and thus having more blood half-life and this trend was reversed during the urine elimination studies. After 4h intravenous injection, quantum dots with an HD of 8.36 nm showed its distribution trend as Liver (Maximum concentration) > Kidney > Spleen ≈ Intestine > Feces (Least Concentration). On the other hand, the trend was reversed in case of QDs with HD of 4.36 nm. **Minchin** et al. have recently investigated the effect of size and charge of Gold-dendrimer nanoparticles with respect to its bio-distribution in mice. A progressive decrease in NP concentration in kidney with enhancement in particle diameter from 5 nm to 22 nm was reported by these authors, whereas, lungs, liver and spleen showed continuous accumulation of the nanoparticles with their size increment. These results clearly reveal the fact that without having any targeting molecule attached;

these nanoparticles can selectively enter into specific organs solely on the basis of their charge and size.[75]

Undeniably intravenous drug delivery is one of the most efficient, rapid and common route of administering drugs in most of the health problems but this mode of drug delivery has gained special attention and thus explored tremendously in the field of cancer therapeutics. Considering the high impact research on cancer nanomedicines and significant effect of the size of drug delivery carriers on the therapeutic performance of chemotherapeutic drugs, we have reviewed the effect of size of the drug delivery nanocarriers, administered by intravenous route, on cancer therapeutics in our upcoming subsection (3.1). Moreover, since we have already discussed the effect of size on the pulmonary administration in our previous section in detail, we are also covering here the effect of the dimension of the drug carrier on lung-targeted drug delivery by intravenous route (subsection 3.2).

3.1 Effect of Size of Drug Delivery Vehicles on Cancer Therapeutics

Cancer drugs have great potential within the therapeutic market mainly because cancer is the second leading cause of death worldwide after cardiovascular diseases. Approximately 12.5 million new cases of cancer are being diagnosed worldwide each year and considerable research is in progress for drug delivery for cancer. Cancer drug delivery is no longer simply wrapping up cancer drugs in new formulations for different routes of delivery. The focus is on targeted cancer therapy. Targeted drug delivery limits side effects, necessitates fewer dosages and facilitates the honing in on cancerous tissues while leaving healthy areas of the body untouched. According to the technical market research report i.e., cancer therapies: technologies and global markets (HLC027B) from BCC research, the global market for cancer therapies was worth $47.3 billion in 2008.[76] This was estimated to increase to over $110.6 billion by 2013 with a compound annual growth rate (CAGR) of 12.6%. Among the four main types of cancer therapies (chemotherapy, hormone therapy, target therapy and immunotherapy), target therapy segment has the largest share of the market.

Advanced cancer therapeutics requires the development of drug delivery carriers with highly specified targeting and enhanced drug bioavailability/loading without much chemotherapeutic side effects. DDS accumulate in solid tumors through EPR effect, characterized by leaky blood vessels and impaired lymphatic drainage in tumor tissues.[22] Size of the DDS plays a crucial role while targeting drugs to cancer cells within the tumors. Anthracyclines are the class of drugs, derived from *Streptomyces Peucetius* var. *Caesius*, which are commonly used to treat a range of cancers including breast cancer, lung cancer, stomach cancer, some leukemias, Hodgkin's lymphoma etc.[77-78] However, Anthracyclines, including doxorubicin and daunorubicin, are notorious for causing cardiotoxicity and neutropenia. Particle sizes of around 100 nm are too big to exit the healthy blood vessels and they can easily escape through the leaky and hastily built tumor feeding vasculature. Therefore to downsize the cytotoxic effects and aiming for small sized particles, several liposomal and particulate drug formulations have been designed and investigated as efficient drug delivery nanovector for cancer therapeutics.

Compared to the conventional drugs, encapsulation of Anthracyclines within liposomes significantly alters their pharmacokinetic profiles and promotes selectively high drug concentrations in tumors.[79] Conventional liposomes used for drug delivery purpose typically have the size dimension of <300 nm, composed of naturally occurring or synthetic phospholipids, and are reported to be easily internalized by the mononuclear phagocyte system (MPS) cells. They are found to have enormous potential to protect other body tissues from the dose-dependent toxic effects of these drugs.[80] MyocetTM is one such liposome-encapsulated doxorubicin drug, introduced by Elan pharmaceuticals, USA, as a multiple vial kit composed of liposomes of the size ranging 150-250 nm, lyophilized doxorubicin, and citric acid buffer. These individual components are mixed at point of care and results in highly efficient loading of the therapeutic agent within the liposomes. Nevertheless, Myocet^{TM} does not affect the drug circulation time but is found to reduce the chances of cardiotoxicity and neutropenia.[81]

Similarly, Doxil® (Also known as Caelyx in Europe) is a novel ~85 nm "Stealth" liposomal formulation of doxorubicin where liposomes contains surface-grafted segments of the hydrophilic polymer polyethylene glycol (PEG) (Fig. 2).[82] The smaller size of

these nanocarriers equilibrates the drug carrying capacity and circulation time and allows their extravasation through the endothelial defects/gaps in the microvasculature of tumor.[83] Thus, these sterically stabilized PEGylated liposomes display reduced interactions with plasma proteins and mononuclear phagocytes, and consequently display greatly prolonged circulation time. Doxil® has been reported to have one-third of the congestive heart failure incidences compared to conventional doxorubicin, resulting in "a quantum jump in quality of life".[84] It is considered to be the most efficient liposomal drug delivery formulation which has achieved the most prolonged circulation till date, with a terminal half-life of 55 hours in humans with enhanced bioavailability of drug in the cancer cells. DaunoXome® is another nano-sized daunorubicin containing liposomal formulation with markedly prolonged circulation and enhanced tumor accumulation, designed by Gilead Sciences, Inc., Forest City, CA, USA, resultant of series of modifications to liposome structure helps retarding the uptake by mononuclear phagocytes. Its liposomal composition includes lipid bilayer of distearoylphosphatidylcholine and cholesterol in 2:1 molar ratio. This liposomal daunorubicin provides extended circulation due to its smaller size (~45 nm) and rigid bilayer, and is highly efficient against Kaposi's sarcoma and other tumors.[85]

Scientific focus is also on investigating and designing the polymeric nanocarriers as a new advancement in the area of nanomedicines and as an efficient drug delivery vehicle. BIND-014 is a cancer drug formulation comprising of 100 nm polymeric nanospheres loaded with Dacetaxel (Drug used to treat solid tumors). Like Doxil, this drug carrying polymeric nanovehicle also rely on its size to leave the tumor vasculature.[84, 86] In BIND-014, the drug carrying polymeric core has been engineered to control the drug release and the outer layer has been composed of polyethylene glycol and specific biomarkers to evade the nanocarrier from the body immune system and to make it highly specific to the tumor cells at the same time. ABI-007 is another novel bioformulation that incorporates the albumin particle technology in the field of nanomedicines and provides a novel medication to breast cancer. ABI-007, also known as Abraxane, consists of 130 nm-sized, biologically interactive albumin-bound pacitaxel particles which have been administered as a colloidal suspension into the body.[12] These nano-sized drug carriers allow the safer

infusion of significantly higher doses of pacitaxel than used with the standard pacitaxel therapy with shorter infusion schedules (30 min ν 3 h) and no pre-medication.[87] Further by taking the advantages of their small size, the nanostructured ABI-007 colloidal particles are reportedly been able to penetrate and reach even in the deeper regions of the solid tumors.

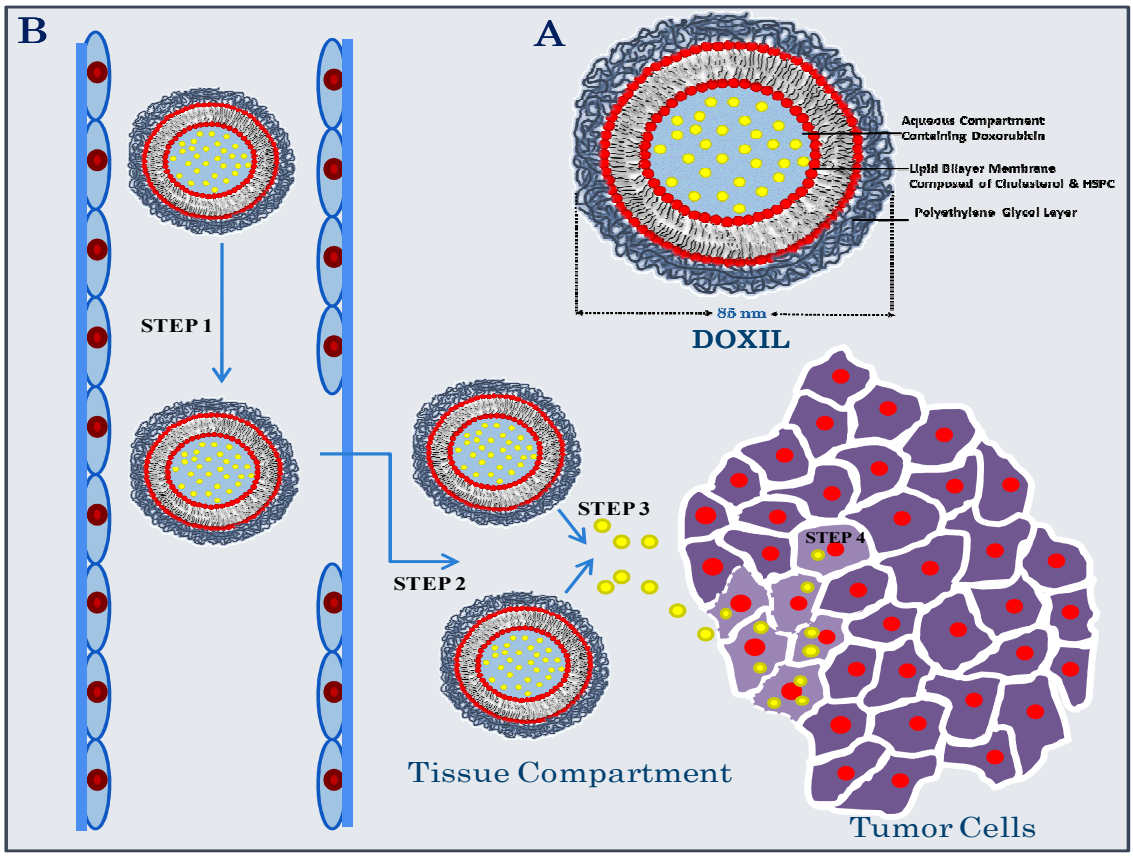

Fig. 2 A) Illustration for chemical structure of DOXIL liposome. **B)** Schematic showing the proposed mechanism of DOXIL transport to the tumor cells. **STEP 1:** Circulation of the doxorubicin containing liposomes in the blood circulation with half life of approximately 55 hours (for humans) after injection without releasing the drug. **STEP 2:** Extravasation of ~85 nm sized liposomal nanovehicles into the tissue compartment through the leaky tumor vasculature. **STEP 3:** Release of the free doxorubicin from the liposome which is believed to be due to the physical and chemical breakdown of the liposomal membrane in the intestinal fluid because of low pH, presence of oxidizing agents and enzymes or via the uptake by macrophages. **STEP 4:** Penetration of the free drug into the tumor cells, its binding with the nucleic acid followed by the killing of the tumor cells.

Thus, all these chemotherapeutic nanomedicines [DOXIL (~85 nm), BIND-014 (100 nm), ABI-007 (130 nm)] having size around 100 nm are reported to reveal remarkably significant antitumor activity but only in highly vascularized tumors such as Kaposi's sarcoma and breast cancer. Reason being, although the size of around 100 nm of DDS is sufficient enough to seep out from the main bloodstream to tumor blood vessels and to treat the permeable tumors but is too large to penetrate deep into the abnormal tissue foliage of hypovascular and solid impermeable pancreatic tumors. Cabral et al. have recently investigated and compared the accumulation and effectiveness of drug loaded polymer micelles with diameters of 30 nm, 50 nm, 70 nm and 100 nm in both highly and poorly permeable tumors.[88] Studies revealed that all the nano-sized polymer micelles (ranging 30-100 nm) are equally competent and able to penetrate the highly permeable tumors. However, for poorly permeable tumors, only smallest micelles of 30 nm dimensions have proven themselves to be the winner of all and succeeded in reaching deep inside the poorly permeable pancreatic tissue to achieve the desired antitumor effect. Nishayama et al. have also attempted to target highly hypopermeable Lewis lung cancinoma cells by employing small sized (28 nm) cisplatin-incorporated polymeric micelles.[89] Cisplatin is a platinum based drug which has been most commonly involved in pancreatic chemotherapy. These micelles have been found to show remarkably prolonged blood circulation with effective accumulation in solid tumors. Interestingly, in spite of their small size these nanocarriers reveal reduced detrimental accumulation in the vital organs compared to free drug, declaring its promising specificity and efficiency as a drug nanocarrier. Recently, "Nanocarrier", a company entreprenered by Kazunori Kataoka, a material scientist from the university of Tokyo (Japan) developed a 30 nm polymer DDS to transport Cisplatin.[90] Free Cisplatin administration in the body usually cause severe renal toxicity and requires the patient to drink large amounts of water during treatment. However, this newly designed polymeric formulation allow the drug to accumulate more in the pancreatic tumor region instead of being in the kidneys "due to the small carrier size" and helps to get rid of this excruciating therapy with enhanced survival time.

Concluding the above discussion regarding chemotherapeutic delivery vehicles, nanomedicines are the established nanocarriers for delivering the drug at the malignant tissue region. The upper size range has been optimized to **300 nm**, which is enough to come out from the leaky blood vessels and punctured lymphatic drainage at the tumor tissue site. And these nanocarriers can be easily internalized by the mononuclear phagocyte system (MPS) cells and thus protect the other body tissues from the dose-dependent toxic effects of these drugs. The large sized nanocarriers appear to stay near the tumor vasculature instead of diffusing throughout the tumor matrix. To enhance the bioavailability and accumulation of the drug into the tumor cells, nanovehicles of the size of **50-150 nm** have been proven to be excessively effective. Nanomedicines with this size range e.g. Doxil®, BIND-014 and ABI-007 (Table 5) have already been successful in reaching the clinics and revealing enormously remarkable results. A few other nanocarriers like NK105 and CALAA-01 are also under clinical trials. Undoubtedly, these nanomedicines have established themselves as the leaders in cancer therapeutics but their efficacy is limited to treat the permeable tumors but is still large enough to penetrate deep into the abnormal tissue foliage of hypovascular and solid impermeable tumors e.g. pancreatic tumors etc. To reach the deep vasculature of these hypopermeable tumors, it is necessary to reduce the size of the nanocarriers further to < 50 nm. Daunoxome® (45 nm) has already been approved by FDA to target the AIDS-related Kaposi's sarcoma and many such smaller sized drugs are under advanced clinical trials. Thus, capitalizing the EPR effect and to efficiently escape from the physiological barriers, many studies advocate the optimal nanoparticle size range of approximately 10–250 nm.[91] Table 5 show different FDA approved nanomedicines (including their size and formulation) and other nanoscale drug carriers under clinical trials for cancer therapy.

Table 5 Different nanomedicines for cancer therapeutics.

Nanomedicines	Drug Formulation	Size	Present Status	Description
Doxil®	PEGylated Doxorubicin containing Liposomes.	~85 nm	First FDA approved nanomedicine	Targets Ovarian Cancer, AIDS-related Kaposi's Sarcoma and Multiple Myeloma with Bortezomib

Myocet™	Doxorubicin containing Liposomes	150-250nm	Approved in Europe and Canada for treatment of metastatic breast cancer in combination with Cyclophosphamide, but is not yet approved by the FDA for use in the United States	Targets Metablastic Breast Cancer. Taken up by the Mononuclear phagocyte cells due to comparatively large size.
Daunoxome® [92]	Daunorubicin containing Liposomes	~ 45 nm	FDA approved Daunoxome as first-line therapy for Kaposi's sarcoma but still under Clinical Trial for Breast Cancer Therapy	Targets AIDS-related Kaposi's sarcoma and other blood cancers
BIND-014	PEGylated Dacetaxel containing Polymeric spheres	100 nm	Under Phase I Clinical Trials	Targets solid or metastatic prostate cancer cells by binding to prostate-specific membrane antigen
ABI-007	Albumin bound Pacitaxel particle	130 nm	Under Phase III Clinical Trials; Recently approved by FDA	For pre-treated metastatic breast cancer patients
NK105 [93]	Polymeric nanocarrier containing paclitaxel	85 nm	Under Phase II Clinical Trials for Stomach Cancer and Phase III Clinical Trial for Breast Cancer	Progression-free survival in patients with metastatic or recurrent breast cancer
Nanoplatin (NC-6004)	PEGylated polymer nanocarrier containing cisplatin	30 nm	Under Phase I/II Clinical Trials	For advanced or metastatic pancreatic cancer aiming for reduced kidney toxicity
Oxaliplatin [94] (NC4016)	PEGylated polymer micelles containing DACH-Pt	~ 30 nm	Under Phase I Clinical Trials	Platinum-based chemotherapy drug used in the treatment of Colorectal cancers
CALAA-01 [95]	Cyclodextrin based polymeric nanocarrier containing gene-silencing RNA	> 100 nm	Under Phase I Clinical Trials	Holds RNA that silences a gene in solid tumours needed for DNA synthesis and replication
CRLX101 [96]	pH-Sensitive cyclodextrin based polymeric nanocarrier releases camptothecin in the acidic environment of cancer cells	25-50 nm	Under Phase II Clinical Trials	Separate studies testing CRLX101 in advanced non-small cell lung cancer and in ovarian cancer

3.2 Effect of Size of Drug Delivery Vehicles on Lung-Targeted Intravenous Administration

Lung targeted drug delivery systems (LT-DDS) are the DDS that can deliver the required medicine effectively to the lung to increase predominant drug concentration within a target zone and reduce drug distribution in other organs or tissues. This aims to increase the drug efficacy, minimize drug originated systemic toxic effects and improve patient compliance and convenience and thus an ideal strategy for the treatment of lung diseases. LT-DDS mainly consists of dry powder formulations, nebulized suspensions or inhaled solutions administered via pulmonary route; and liposomes, nanoparticles or microparticles via intravenous administration.[97] Lung targeting via pulmonary route in context to size of DDS has already discussed in detail in section 2. So here we attempted to provide a brief overview about the effect of size of the drug carrier on lung targeted drug delivery via intravenous administration. Certainly pulmonary administration have attracted enormous scientific attention for delivering drugs, however this also has its own limitations. The main disadvantages are that most of the drugs have to be administered at least three to four times daily in aerosol form due to their short duration of resultant clinical effects, rapid absorption of some drugs from the lung epithelium results in undesirable side effects, such as bronchodilators and corticosteroids. Furthermore, to some extent, pulmonary delivery is not capable of delivering drugs effortlessly to disease locations in the lungs via inhalation due to blocking of airways from inflammation or mucus plugs, which leads to more deposition in the conducting airways rather than periphery. Therefore, recently interest is more focused on designing LT-DDS that can be administrated via intravenous route.

Polymeric microparticles including microspheres and microcapsules are among the most explored drug carriers for lung targeted drug delivery by intravenous means. And as per the existing literature and research, the particles sizing in the range of 7-28 μm have more tendency to accumulate/deposit in the lungs by mechanical filtration through capillary bed of the lung after intravenous administration.[98-99] Hao et al. have prepared and demonstrated the efficiency of ceftiofur-loaded gelatin microspheres having mean diameter of 21.26 μm as lung targeted DDS. The organ distribution pattern studies have

shown the highest accumulation of drug in the lungs than any other organ (liver, spleen, stomach etc.) with the lung targeting efficiency (T_e) enhancement by the factor of 300.[100] With the objective to design lung targeted drug carriers, Yang et al. have prepared erythromycin loaded gelatin microspheres with the mean particle size of 15.62 μm. The drug distribution studies again reveal significantly enhanced accumulation of the microparticles in the lungs than the other tissues including liver, kidney, heart, spleen, plasma etc.[101] In another report by Tang et al., enrofloxacin loaded lung targeting microspheres have been prepared chemically by emulsifying with gelatin and liquid paraffin. The microspheres designed are observed to have the mean diameter of 11.7 μm with 92.8% of them were in the range of 7-30 μm. After a single dose injection into dog, compared to conventional drug, the half-life of distribution phase has reduced by 77.78%, the half-life of elimination phase has lengthened from 5.15 to 33.86 h; and the clearance of drug concentration in the lung have reduced from 0.603 to 0.267 L h^{-1} kg^{-1}. Also the relative intake rate (R_e) and T_e of the lung have been 2.48 and 4.27, respectively, which are much greater than that of other tissues.[102] In another study, Sree et al. have developed the lung targeting albumin loaded ofloxacin microspheres (ALOME) composed of ofloxacin and albumin prepared by water in oil emulsion method. The ALOME drug carriers, having average particle size of 11.32 μm, showed maximum drug concentration in the lung i.e., 1048 μg/g at 10 min, which was significantly more than that in any other tissues and blood.[33, 103]

With the aim to design pactitaxel (Chemotherapeutic drug) based novel drug delivery vehicles, Yan and Pei et al. have prepared sustained release microspheres of paclitaxel using poly(1actic-co-glycolic acid) (PLGA) as the biodegradable materials by the emulsion evaporation technologies. The mean diameter of the microspheres was 9.65 mm with over 87.2% of the microspheres ranging from 5 to 15 μm. They determined the drug concentration in lung, heart, liver, spleen and kidney of mice at 0.25, 1, 24 and 72 h after intravenous administration of paclitaxel microspheres and with injectable formulation as control. The result showed that in comparison to the injective solution, the drug concentration in the lung increased as much as about 30 times in the case of the microspheres. Furthermore, growth rate inhibition of subcutaneously implanted tumor

with paclitaxel microspheres and injection was 83.1% and 62.8%, respectively. These results suggested that the microsphere carriers could target delivery of paclitaxel to the lung and increase antitumor efficiency.[104] Using one of the most potent anticancer drug i.e., Cisplatin, Huo et al. have fabricated lung targeting drug delivery PLGA microspheres with a diameter of 12.8 mm with 98% of the microspheres being in the range of 5–30 mm.[98] The drug distribution results with Cisplatin-loaded PLGA microsphere formulation showed a notable higher concentration of drug in the lung (212 mg/g, 15min) than those in other tissues and blood, while the drug concentration in the lung was only 1.37 mg/g after 15 mins administration of Cisplatin injection in rabbits. In another work, Ying et al. have prepared PLGA microcapsules containing carboplatin (Platinum based antitumor drug) with a mean diameter of 14.25 ± 3.52 μm and studied their tissue distribution in mice after intravenous single dose administration. The results showed drug concentration of carboplatin microcapsules in the lungs were increased by a factor of 1.76 in comparison with carboplatin solution as the control.[105] In another report, Lu et al. have developed carboplatin gelatin microspheres having an average particle size of 13.20 μm with 98% of the microspheres being in the range of 5.0–28.6 μm. The results demonstrated that the T_e of the lung increased to 9.4 times in comparison with spleen and 90.5 times compared with liver in the case of carboplatin microspheres. The result of pharmacodynamic study based on mouse model of S-180 lung cancer suggested that the microcapsulated carrier improved the antitumor effect of carboplatin.[99] In 2011, Guo and his coworkers have investigated the feasibility of targeted delivery of protionamide (Anti-Tuberculosis drug) to the lung through the intravenous administration of PLGA microspheres having a mean diameter of 9.86 ± 1.38 μm with over 81.53% of the microspheres ranging from 7 to15 μm. Compared with the aqueous formulation, the drug concentration in the lung of mice for microsphere group increased by a factor of greater than two at 6 h and maintained for a long period.[106] Very Recently in 2014, Wang et al. have introduced Docetaxel loaded, glutaraldehyde cross-linked microspheres having uniform size of 9.6±0.8μm as LT-DDS.[107] The microspheres were found to release the drug to a maximum extent in the target tissue (lungs). Table 6 shows different microparticles designed for lung targeted drug delivery via intravenous administration.

Table 6 Summary of various microparticles studied for lung targeted drug delivery by intravenous administration.

MP Type	Active Ingredient	Particle size (µm)	Lung Targeting Effect	Animal Model Used	Reference
Albumin	Ofloxacin	11.32	Lung drug Concentration at 10 mins MS formulation = 1048 µg/g Control Formulation = 432µg/g	Mice	[103]Sree et al., 2009
Gelatin	Enrofloxacin	11.7	Re: 2.48, Te: 4.27, Ce: 4.27	Dog	[102]Tang et al., 2007
PLGA	Paclitaxel	9.65	Drug concentration shows 30 times increase in the lungs using MP formulation compared to injective drug solution in 15 mins.	Mice	[104]Yan and Pei, 2006
PLGA	Protionamide	9.86± 1.38	Drug concentration shows 1 fold enhancement in the lungs using MP formulation compared to aqueous formulation at 6 h and maintained for long duration.	Mice	[106]Guo et al., 2011
PLGA	Cisplatin	12.8	Lung drug Concentration at 15 mins MS formulation = 212 µg/g Control Formulation = 1.37µg/g	Rabbit	[98]Huo et al., 2005
PLGA	Carboplatin	14.25± 3.52	Compared to Control Formulation Re: 3.41, Te: 2.82-5.58, Ce: 1.76	Mice	[105]Ying et al., 2007
Gelatin	Ceftiofur	21.26	Te of lung increased by the factor of 300 compared with blood and stomach, and 27.5 and 15.95 for liver and spleen	Mice	[100]Hao et al., 2011
Gelatin	Erythromycin	15.62	Drug targeting Index of MS formulation is 6.65 compared to erythromycin solution.	Rabbit	[100]Hao et al, 2011
Gelatin	Carboplatin	13.20	Ce: 4.1, Te: Increased 9.4 times compared with spleen and 90.5 times compared with liver.	Mice	[99]Lu et al., 2003
Chitosan	Docetaxel	9.6± 0.8	MS are found to release the drug to a maximum extent in the target tissue	Mice	[107]Wang et al., 2014

MP: Microparticles, MS: Microspheres, Re: the relative intake rate, Te: Targeting efficiency, Ce: Ratio of Drug Peak concentration in lungs, PLGA: PLGA: Poly(lactic-co-glycolic acid)

In addition to microparticles, liposomes and nanoparticles have also been explored for their applications in intravenous mediated lung targeted drug delivery. Many studies showed that liposomes accumulate mostly in the organs of the RES such as liver, spleen and lung within the first 15–30 min after intravenous administration of the liposomal formulation.[108] In general, the liposomes with particle size of more than 5 µm could be trapped passively by the vascular network of the lung to reach lung targeting effect.[46, 109]

With these size considerations, Cheng et al. have developed dipyridamole (DIP) liposomes having a mean diameter of 4.434 ± 0.252 μm within a span of particle size of 1.103 ± 0.080 and determined drug (Pyrimidopyrimidine) concentration in lung, heart, liver, spleen and kidney of mice at different time intervals after intravenous administration.[110] The results showed that the relative intake rate for the lung was 2.23 in the case of DIP liposomes, which indicated that the exposure of the DIP to the lung was significantly increased by a liposome carrier. The T_e of the lung increased by a factor of 12.07 compared with plasma, 1.98 compared with spleen and 1.49 compared with liver for DIP liposomes. Zhang et al. developed levofloxacin loaded liposomes composed of soybean phosphatides, cholesterol and levofloxacin by the ammonium sulfate gradients method.[109] The results showed that the mean particle size and zeta-potential of levofloxacin liposomes were 7.424±0.689 μm and 13.11±1.08mV, respectively. They studied tissue distribution of levofloxacin in rabbits after intravenous administration. The results suggested that the value of R_e for the lung was 7.02, which was obviously higher compared with other tissues in the case of levofloxacin liposomes. In another work, Jiang et al. have explored multivesicular liposomes loaded with gedopentetate dimeglumine drug , also known as DepoFoam, for its lung targeted drug delivery characteristics.[111] The biodistribution results obtained for this liposomal DepoFoam formulation (average diameter ~ 18 μm) have indicated that drug concentration of the drug in the lung at 30 min after intravenous administration is 325.17±74.52 mg/g compared to the conventional drug which is 6.69±1.82 mg/g, respectively. Thus, it was concluded that the liposomal formulation possess good lung targeted effect.

It has been found that in addition to the size of the liposomes, its disposition and localization is also affected by its surface charge and lipid composition.[112-113] Several investigators have reported that liposomes bearing negative surface charge could accumulate in the lungs to a greater extent than free drug or neutral and positively charged liposomes of similar size.[114-115] Contrary to this, Jonah et al. have found highest uptake of the EDTA drug by the lungs from positively charged liposomes after a single intravenous administration of liposomal preparation.[116] In another study, Wang and coworkers developed the azithromycin liposomes having a mean particle size of 6.582

μm with a zeta-potential of 19.5mV.[117] Azithromycin concentration in heart, liver, spleen, lung and kidney of mice after intravenous administration of liposomal and injectable formulation has been then measured. The results showed that after intravenous injection to mice, the AUC in the lung increased by 7.4 fold in the case of azithromycin 1iposomes in comparison with its solution. Thereby, it is thought that large particles with a positive charge could deliver drug to the lung more easily than other particles. In the recent report by Zhao et al., they have used for the first time the combination of solid dispersion and effervescent techniques to prepare docetaxel liposomes composed of docetaxel/Tween-80/Phosopholipon90H/cholesterol/citric acid at molar ratios of 0.18:0.09:3.78:3.78:91.17 with a diameter of 1011±22 nm. Zeta-potential and entrapment efficiency of the resulted liposomes were -23.7±0.26mV and 90.12±0.36%, respectively.[118-119] In general, for a passive targeting of liposomes to the lungs, the particle size should be above 5 μm to be retained in the alveolar capillaries. Interestingly, when the evaluation of lung targeting effect of docetaxel liposomes in rabbit was studied in this case, it was found that these negatively charged docetaxel liposomes with a diameter of about 1 μm have favorable lung targeting effect, the Re and the Ce (ratio of peak concentration) of the lung were 28.91 and 74.28, respectively. Accepting this fact that for passive targeting to the lungs the size of the DDS should be above ≥ 7 μm, there is not much reports available on lung targeted DDS of nanoparticles via intravenous route of administration except on cancer therapeutics (refer subsection 3.1).

Thus, we can say that since the particles sizing in the range of 7-28 μm have more tendency to accumulate/deposit in the lungs by mechanical filtration after intravenous administration, the particles sizing ≥ 7 μm are most suitable for lung-targeted intravenous drug delivery. However, this particle dimension can vary depending on the carrier surface properties (charge, hydrophobic/hydrophilic, porosity etc.).

Conclusions

In the present review article, attempts have been made to provide comprehensive view about the effect of size of drug delivery vehicle towards biodistribution, specific organ targeting, body clearance kinetic and most importantly its therapeutic efficiency. Key emphasis has been given to compile the relevant literature particularly in the field of

pulmonary and intravenous administration focusing more on cancer therapeutics and lung-targeted drug delivery. For the pulmonary drug administration, drug carriers of the size of 1-5 μm are affirmed to be optimum. Smaller sized delivery vectors are found to pose cytotoxicity and most of them (80 %) got exhaled out without being deposited, conveying any therapeutic effect. On the contrary, larger particles (> 5 μm) are found to be cleared out by strong mucociliary clearance mechanism. For intravenous drug delivery, the size of the drug delivery vehicle depends upon the targeted organ, their respective endothelial fenestration size and on the internalization. For cancer therapeutics, nanomedicines particularly drug entrapped liposomes, polymeric nanoparticles, dendrites are studied by many research groups. The effective size range for the drug deliver carriers targeting tumor cells are reported in the range of 10-250 nm depending upon the type of the targeted tumor cells (Hypopermeable/Hyperpermeable or Hypovascularized/Hypervascularized), tumor location, carrier material composition and surface characteristics. And finally microparticles sizing ≥ 7 μm are the best suited and proven themself as fittest vehicles for lung-targeted intravenous administration as per the present literature. Thus, by this review our attempt is to flash light on a very important physical parameter, related to drug carriers, which has a pivotal role to play in drug therapeutic i.e. SIZE.

Acknowledgements

We acknowledge the financial support received from Singapore Ministry of Health's National Medical Research Council under its Cooperative Basic Research Grant (NMRC/CBRG/0048/2013) and TCR Grant R618/41/2008 (RWB), R1054/69/2013 (RL).

Notes

[a] Anti-Infectives Research Group, Singapore Eye Research Institute, Singapore 168751, Singapore

[b] Center for Nanofibers and Nanotechnology, Nanoscience and Nanotechnology Initiative, Faculty of Engineering, National University of Singapore, Singapore 117576

[c] Duke-NUS SRP Neuroscience and Behavioral Disorders, Singapore 169857, Singapore

[d] Department of Electrical and Computer Engineering, National University of Singapore, Singapore117576, Singapore

[e] Department of Mechanical Engineering, National University of Singapore, Singapore117576

† Seeram Ramakrishna, Center for Nanofibers and Nanotechnology, Department of Mechanical Engineering, National University of Singapore, Singapore-117576; Email: seeram@nus.edu.sg; Contact Number: 065-65162216; Fax: 68725563

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