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NANO SCIENCE IN DRUG DELIVERY TO LUNGS

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ABSTRACT

The Pulmonary route has been conventionally used to treat diseases of the respiratory tract and also non-respiratory tract. The significant research work from the last two decades have exposed that in addition to treating local diseases, a wide range of systemic diseases can be treated by delivering drugs to the lungs. In general inhalable formulations of various drugs have been developed to treat the systemic diseases via the lungs. But the problem with those inhalable formulations is they need repeated doses of drug to control the disease condition, since the inhaled drug cleared rapidly. Therefore new technologies have been investigated, where inhaled particles are capable of controlled release of drug from the lungs. In those nanotechnology based drug delivery systems are being developed as a tremendous field. Nano refers to particles size range of 1-1000nm. An important feature of these technologies is the large geometric size of the particles than normal aerosol solutions, which makes it difficult for the lung macrophages to clear these particles. Therefore it results in longer residence times for the particles in the lungs after delivering the drug to the lungs. The present review discusses about the anatomy and structure of lungs, various conventional formulations for pulmonary delivery, and the various colloidal carriers like liposomes, dendrimers, nanoparticles, which involves the delivering of drugs to lungs.

Key words: targeted drug delivery, pulmonary drug delivery, nanotechnology, colloidal particles.

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INTRODUCTION

In modern medicine, drug inhalation has primarily been used as a modality for treating local respiratory diseases and over 500 million people now carry the classical metred dose inhaler with them on a daily basis[1]. The lung is an attractive target for drug delivery due to noninvasive means to provide not only local lung effects but possibly high systemic bioavailability, avoidance of first-pass metabolism, more rapid onset of therapeutic action, and the availability of a huge surface area[2]. Over the last 20 years the research focus within the field of respiratory drug delivery has broadened to include a wider range of potential applications for inhalation by delivering drugs not just onto the airway but across it. Aerosol therapy using particulate drug carrier systems is becoming a popular method to deliver therapeutic or diagnostic compounds either locally or systemically as shown by the development of inhalable insulin. In recent years colloidal drug delivery systems and especially nanoparticles have received great attention, because they can cause retention of the particles in the lungs accompanied with a prolonged drug release if large porous nanoparticle matrices are used[3].

Anatomy of lungs[4]:

The lungs are the essential organs of respiration; they are two in number, placed one on either side within the thorax, and separated from each other by the heart and other contents of the mediastinum. Anatomy and physiology of pulmonary system represented in Figure 1.

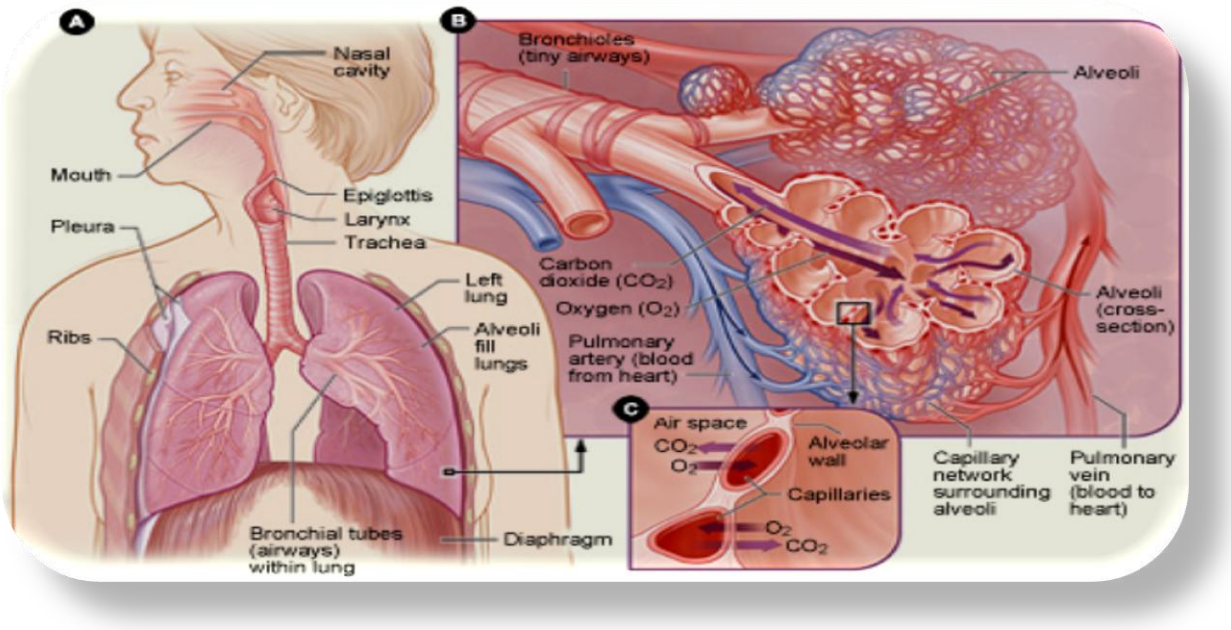

Figure 1: Anatomy and physiology of pulmonary system[5].

At birth the lungs are pinkish white in color; in adult life the color is a dark slaty gray, mottled in patches; and as age advances, this mottling assumes a black color. The coloring matter consists of granules of a carbonaceous substance deposited in the areolar tissue near the surface of the organ. It increases in quantity as age advances, and is more abundant in males than in females. As a rule, the posterior border of the lung is darker than the anterior. The right lung usually weighs about 625 gm., the left 567 gm., but much variation is met with according to the amount of blood or serous fluid they may contain. Each lung is conical in shape, and presents for examination **a**n apex: apex pulmonisa base: basis pulmonis

Three borders:

Inferior border:	Margo inferior
Posterior border:	Margo posterior
Anterior border:	Margo anterior

Two surfaces:

Costal surface:	Facies costalis
Mediastinal surface:	Facies mediastinalis

Structure of lung[4]:

The lungs are composed of an external serous coat, a subserous areolar tissue and the pulmonary substance or parenchyma. The serous coat is the pulmonary pleura it is thin, transparent, and invests the entire organ as far as the root. The subserous areolar tissue contains a large proportion of elastic fibers; it invests the entire surface of the lung, and extends inward between the lobules. The parenchyma is composed of secondary lobules which, although closely connected together by an interlobular areolar tissue, are quite distinct from one another, and may be teased as under without much difficulty in the fetus. The secondary lobules vary in size; those on the surface are large, of pyramidal form, the base turned toward the surface; those in the interior smaller, and of various forms. Each secondary lobule is composed of several primary lobules, the anatomical units of the lung. The primary lobule consists of an alveolar duct, the air spaces connected with it and their blood vessels, lymphatics and nerves. The intrapulmonary bronchi divide and subdivide throughout the entire organ, the smallest subdivisions constituting the lobular bronchioles.

The larger divisions consist of:

(1) An outer coat of fibrous tissue in which are found at intervals irregular plates of hyaline cartilage, most developed at the points of division;

(2) Internal to the fibrous coat, a layer of circularly disposed smooth muscle fibers, the bronchial muscle; and

(3) Most internally, the mucous membrane, lined by columnar ciliated epithelium resting on a basement membrane.

The corium of the mucous membrane contains numerous elastic fibers running longitudinally, and a certain amount of lymphoid tissue; it also contains the ducts of mucous glands, the acini of which lie in the fibrous coat. Thelobular bronchioles differ from the larger tubes in containing no cartilage and in the fact that the ciliated epithelial cells are cubical in shape. The lobular bronchioles are about 0.2 mm. in diameter.

Each bronchiole divides into two or more respiratory bronchioles, with scattered alveoli, and each of these again divides into several alveolar ducts, with a greater number of alveoli connected with them. Each alveolar duct is connected with a variable number of irregularly spherical spaces, which also possess alveoli, the atria. With each atrium a variable number of alveolar sacs are connected which bear on all parts of their circumference alveoli or air sacs. (Miller).

CONVENTIONAL FORMULATIONS:

AEROSOLS[6]:

Aerosol preparations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium. The drug particles delivery by aerosols is deposited in the airways by: gravitational sedimentation, inertial impaction, and diffusion. Most of the larger drug particles are deposited by gravitational sedimentation and inertial impaction in the airways, while for the smaller particles get their way into the peripheral region of the lungs by diffusion mechanism.

The aerosol administration further complicated by the hygroscopic properties of most therapeutic aerosols that allow the particle size to change drastically during the drug transport in the highly humid atmosphere of the respiratory tract. Other factors, which directly influence the aerosol deposition by above three mechanisms, are aerodynamic size distribution of the aerosol particles, and the density of the aerosol particles.

There are three commonly used clinical aerosols: jet or ultrasonic nebulizers, metered–dose inhaler (MDI), and dry-powder inhaler (DPI). The metered–dose inhalers are most frequently used aerosol delivery system. The dry-powder-inhalers are designed to deliver drug/excipients powder to the lungs[7].

Advantages:

More uniform distribution of drug with greater extent of penetration into the peripheral or the alveolar region of the lung.

Disadvantage:

This costs more and also faced with difficulty in measuring the exact dose inside the lungs.

Intratracheal inhalation[8,9]:

This technique delivers a small amount of solution into the lungs by syringe. This route provides a rapid and quantifiable method of drug delivery to the lungs. The drug deposition is localized and uneven and only small absorptive area is used for the absorption from deposition.

Insufflation:

This method administers drug's powder formulation by syringe or any other similar device into the lungs.

Disadvantage: Non-uniform distribution of drugs.

Targeting strategies for drug delivery to lungs:

Although the intranasal route is efficient for topic, systemic and CNS delivery of a wide range of drugs, it cannot be applied for many others due to their low nasal bioavailability. Briefly, bioavailability of nasally administered drugs is particularly restricted by low drug solubility, rapid enzymatic degradation in nasal cavity, poor membrane penetration and rapid mucociliary clearance (MCC). Factors which affect the nasal drug absorption and practical strategies to overcome them are represented in Figure2.

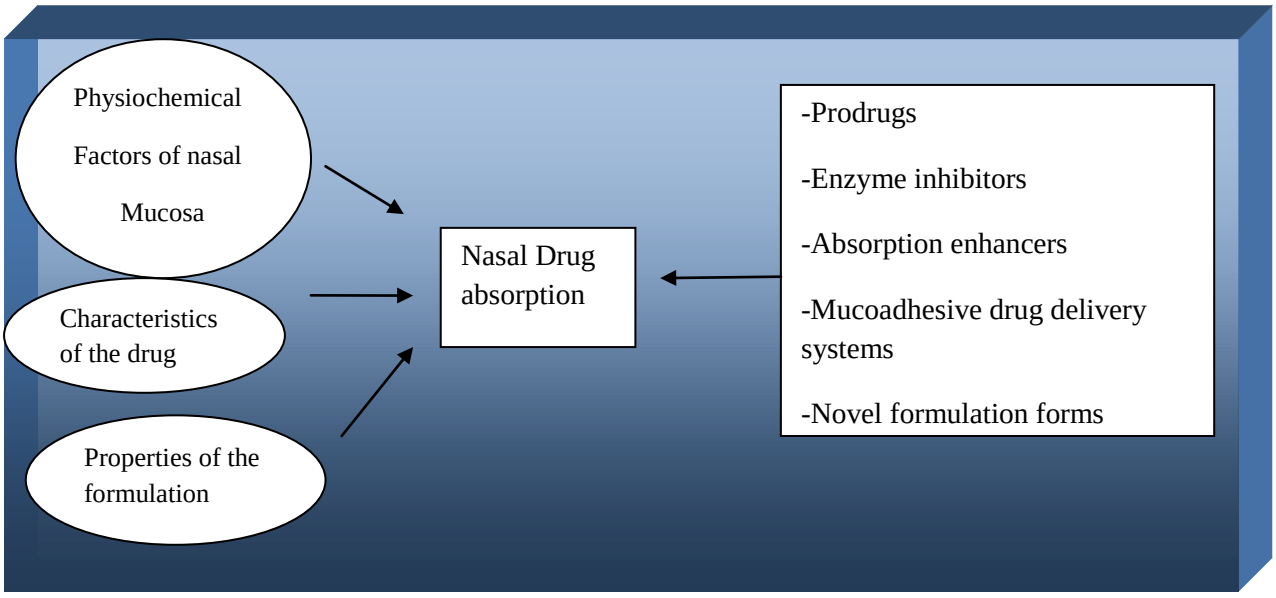

Figure 2. Factors which affect the nasal drug absorption and practical strategies to overcome them[10].

NANOTECHNOLOGY:

Pulmonary delivery is also important and is effected in a variety of ways - via aerosols, metered dose inhaler systems (MDIs), powders (dry powder inhalers, DPIs) and solutions (nebulizers), all of which may contain nanostructures such as liposomes, dendrimers and nanoparticles.

Parenteral routes (intravenous, intramuscular, subcutaneous) are very important. The only nanosystems presently in the market (liposomes) are administered intravenously. Nanoscale drug carriers have a great potential for improving the delivery of drugs through nasal and sublingual routes, both of which avoid first-pass metabolism; and for difficult-access ocular, brain and intra-articular cavities. In addition, there is the possibility of improving the occular bioavailability of drugs if administered in a colloidal drug carrier. For example polymer -stabilized nanoreactor with the encapsulated enzyme represented in Figure 3.

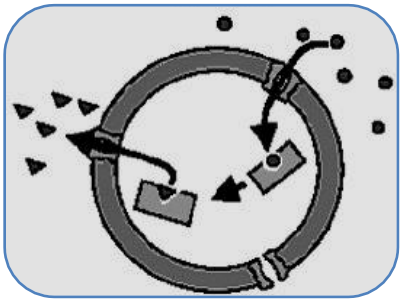

Figure 3. A polymer-stabilized nanoreactor with the encapsulated enzyme.[11]

Liposomal pulmonary delivery[2,12,13]:

Liposomes are important carriers for the delivery of medicinal agent to the targeted organ because these vesicles are prepared from the compounds that are endogenous to the lungs Drug encapsulation technique in liposomes represented in Figure 4.

The first marketed pharmaceutical liposomal formulation is synthetic lung surfactant Alveofact. This is used for the treatment of Respiratory Distress Syndrome by pulomonary instillation route. Nebulizers are used for the delivery of liposomes in the liquid state. Problems such as drug stability and leakage from device are occurred when nebulizers are used for delivery of liposomes in liquid state. We can overcome such problems by developing liposomal dry powder formulations. Cationic liposomes are used for pulmonary gene delivery, because cationic liposomes have the advantage of self assembly with DNA material through cationic-anionic electrostatic interaction. Liposomes conjugated with cell-penetrating peptides are recognized as potential nanocarrier systems for intracellular delivery of macromolecules to the lung.

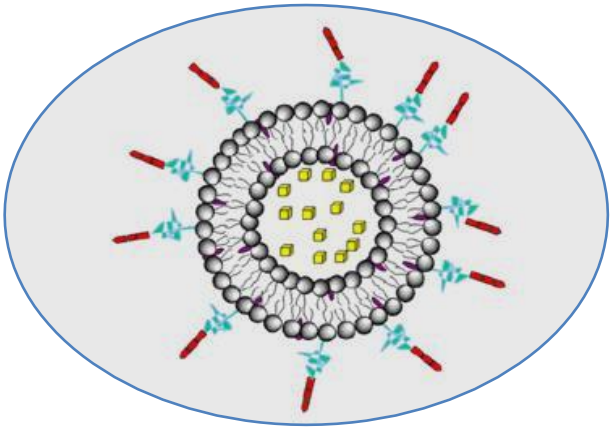

Figure 4. Drug encapsulation in liposomes.[11]

Dendrimer-based pulmonary delivery[14-16]:

Dendrimers are globular repeatedly branched macromolecules that exhibit controlled patterns of branching with multiple arms extending from a central core represented in Figure 5. They are used in drug delivery and imaging at a size typically ranging from 10 to 100 nm in diameter. Encapsulation of therapeutic agents, particularly peptide therapeutics, in dendrimers has been shown to improve their pharmacokinetic and pharmacodynamic properties.

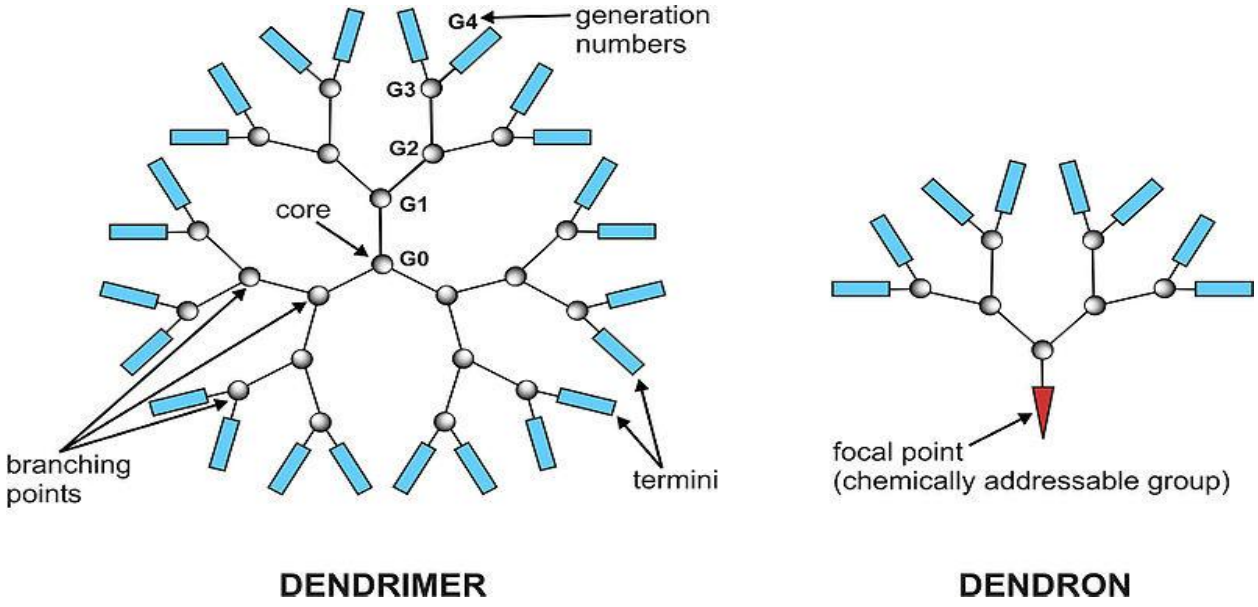

Figure 5. Illustration of dendrimer[14].

The use of dendrimers has proved to be superior to that of linear polymers in some applications since the dendritic nature can allow attachment of drug molecules and targeting groups to the end chains. However, the shortfall of this system is in the synthesis of the dendrimers, due to their complex architecture. They can be designed to be water soluble when the end group is a hydrophillic group. It is also possible to design them with internal hydrophobicity thus allowing

encapsulation of hydrophobic drugs in the interior. Dendrimers have demonstrated great potential in the delivery of anticancer therapeutic agents, when they have a polycationic surface, which can form multiple interactions with a number of target receptors. The polycationic surface is, however, also the main disadvantage in therapeutic delivery applications, due to their toxic effect on cell membranes.

Nanocarrier systems for pulmonary drug delivery:

Nanoparticles as drug carriers, which includes nanospheres and nanocapsules of size 10-200nm and they can be formed from both biodegradable polymers and non-biodegradable polymers. They are able to adsorb and/or encapsulate a drug, thus protecting it against chemical and enzymatic degradation.

Nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a unique polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed.

There are various types of nanoparticles have been developed. They are

- Polymeric nanoparticulate pulmonary delivery:
- Solid lipid nanoparticles in pulmonary delivery:
- Bioadhesive nanoparticles:
- Coated nanoparticles(synthetic polymer-based nanoparticles).

In recent years, biodegradable polymeric nanoparticles have attracted considerable attention as potential drug delivery devices in view of their applications in the controlled release of drugs, in targeting particular organs / tissues, as carriers of DNA in gene therapy, and in their ability to deliver proteins, peptides and genes through the peroral route. Nanoparticles can be administered via different routes of administration such as parenteral, oral, intraocular, transdermal or pulmonary inhalation[17].

CHARACTERIZATION OF NANOPARTICLES:

Characterization of nanoparticles can be done by using a variety of different techniques, after synthesizing nanoparticles. Here various manufacturing methods have been included for synthesis of nanoparticles, they are Emulsion polymerization, Interfacial polymerization, Desolvation evaporation, Solvent deposition.

Common techniques for characterization of nanoparticles are [2,6]:

- Electron microscopy (TEM, SEM),
- Atomic force microscopy (AFM),

- Dynamic light scattering (DLS),
- X-ray photoelectron spectroscopy (XPS),
- Powder X-ray diffraction (XRD),
- Fourier transform infrared spectroscopy (FTIR),
- Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF),
- Ultraviolet-visible spectroscopy,
- Dual polarization interferometry,
- Nuclear magnetic resonance (NMR).

Polymeric nanoparticles for pulmonary delivery[2,18,19]:

Polymeric nanoparticles are widely studied in drug delivery system for parenteral administration. The polymeric nanoparticles carry the drug molecules to protect the drugs from degradation and release the drug at controlled rate. Polymeric nanoparticles which are used therapeutically are composed of biodegradable or biocompatabile materials like poly lactic acid, poly lactic-co-glycolic acid, alginic acid, chitosan and gelatin. Various polymers for pulmonary drug delivery using nanocarrier systems are shown in below Table 1.

Table 1:Various polymers for pulmonary drug delivery using nanocarrier systems

Polymers	Drugs	Size
Alginates		
Sodium alginate	Rifampicin	235.5mm
Chitosan		
Chitosan	Plasmid DNA	91-164mm
Chitosan	Insulin	300-388mm
Gelatin		
Gelatin type A	Fuoresceinamine	277.8mm
Gelatin type B	Sulforhodamine	242±14nm
PEGylated gelatin	Plasmid DNA	100-500nm

Because of biocompatibility, surface modification capability and sustained release properties polymeric nanoparticles are widely studied using most of the pulmonary drugs.

Solid lipid nanoparticles in pulmonary delivery[13,20]:

Solid lipid nanoparticles are mixture of solid lipids, surfactants and water. These solid lipid nanoparticles are considered as the alternative to polymeric nanoparticles. The advantages of solid lipid nanoparticles for the release of drug in lungs are controlled release and achieve prolonged drug release and faster degradation in vivo. Drug properties and Liposome association are mentioned in Table 2

Table 2: Drug properties and Liposome association:

Nature	Drug properties	Liposome association:
Hydrophilic	Retained in aqueous interior may be difficult to get high loading	Slowly released over several hours – several days
Hydrophobic	Inserted into hydrophobic interior of the lipososme bilayer can disrupt lipososmes at high concentrations	Excellent retention
Intermediate	Rapidly partition between lipid bilayer and aqueous phase	Rapid release from lipososmes but p^H manipulation or formation of molecular complexes can result in good retention

It is feasible that aqueous suspension and sometimes dry powder formulations of solid lipid nanoparticles can be used for pulmonary inhalation aerosol administration of drugs using nebulizers and dry powder inhalers.

Bioadhesive nanoparticles:

The major disadvantage of conventional aerosol formulation is the absence of prolonged duration of action which is due to the very low residence time of drug in respiratory tract. Nanoparticles formulated with bioadhesive agents show a unique property of adhering to the mucosal surface very conveniently. These drug loaded bioadhesive agents show prolonging the residence time of drug in the respiratory tract by increasing lung deposition and decreasing the nasal mucociliary clearance of the drug[17].

Applications of nanoparticles in pulmonary drug delivery:

Delivery of nanoparticles using dry powder carriers[21,22]:

Because of presence of large alveolar surface area, the low thickness of the epithelial barrier and an extensive vascularisation make the pulmonary route an ideal route for administration of active ingredients. Since nanoparticles are in a size range which is not suitable for deep lung delivery, the major challenge for pulmonary delivery of nanoparticles is to find a proper carrier system. Several researchers have prepared carrier systems for nanoparticles to improve the delivery of nanoparticles to the alveolar area. Applications of pulmonary delivery of nanoparticles using dry powder carriers are mentioned in Table 3.

Delivery of nanoparticle suspensions using nebulisation[23]:

Another method for the delivery of nanoparticles was spraying or nebulization of a nanoparticle suspension using a nebulizer. In a study Dailey et al., introduced a novel surfactant free biodegradable nanoparticle system for aerosol therapy. They formulated nanoparticle suspension

Table 3: Applications of pulmonary delivery of nanoparticles using dry powder carriers[2]:

Nanoparticle type	Nanoparticle size (nm)	Carrier particle	Carrier particle size (µm)	Active Ingredient	Method for the preparation of carrier
Hydroxypropylmethyl cellulose phthalate (HPMCP)	51.6	Lactose	0.6–9.3	Pranlukast	Spray drying and freeze drying
Gelatin and iso-butyl cyanoacrylate	173, 242	Lactose	2.50–2.60	-	Spray drying
Iso-butyl cyanoacrylate	244	Effervescent carrier powder	2.17	Ciprofloxacin	Spray drying

from branched polyester, diethylaminopropyl amine-poly (vinyl alcohol)-grafted-poly (lactide-co-glycolide) (DEAPA-PVAL-g-PLGA), as well as with increasing amounts of carboxy methyl cellulose. They showed that this new polymer has high encapsulation efficiency for drug molecules by utilizing electrostatic interactions.

Table 4: Applications of pulmonary delivery of nanoparticles using nebulisation [2]:

Nanoparticle type	Nanoparticle size (nm)	Nebulization device	Active ingredient	In vivo models
DEAPA-PVAL-g-PLGA	76.2–213.6	Pari® LC Star and Optineb®	-	-
Solid lipid nanoparticles (SLN)	200	Ultrasonic nebulizer	99mTc	Rat
Surface modified PLGAc with chitosan	650	Ultrasonic nebulizer	Calcitonin	Guinea pig
Itraconazole nanocrystals	300-800	Aeroneb Pro micropump nebulizer	Itraconazole	Mice

Toxicity of inhaled nanoparticles:

- ✓ **Toxicity of inhaled ultrafine particles[24]:**

Most of the toxicological data is based on our knowledge from nanoparticles inhaled during daily life such as carbon black, diesel particulates, silica and titanium oxide nanoparticles, which are considered ultrafine particles (b100 nm in diameter). It has been shown that the toxicity of nanoparticles increases with decreasing particle size. Ultrafine carbon black particles are known to produce greater pulmonary toxicity in rats when compared to large-sized carbon black particle.

- ✓ **Toxicity of polymeric nanoparticles used in drug delivery[25]:**

Forbes and Ehrhardt suggest different cell culture models which might be used to assess pulmonary drug delivery systems. They report that A549 (alveolar) and BEAS-2B (airways) cell

lines have been used to study the nano-toxicological aspects of inhaled environmental pollutants. These two cell lines which do not form functional tight junctions are considered suitable for toxicology studies of inhaled nanoparticles. Standard toxicity assays such as cellular metabolic activity, membrane integrity and the release of pro-inflammatory and inflammatory mediators can be performed with these cells after nanoparticles uptake.

Recent advancements in nano-particulate pulmonary drug delivery:

- **Pulmonary delivery of nanoparticle-encapsulated ATDs[26]:**

The name itself indicates that nanoparticles are in the range nanometer range i.e. 10 to 100nm. Whereas microparticles are in the range of 1 and 1000mm. The main difference between the microparticles and nanoparticles is drug loading i.e. nanoparticle achieve high drug loading, minimize the consumption of polymers, cross permeability barriers and show better therapeutic response. PLG is the most intensively studied nanoparticulate drug carrier. We can prepare PLG nanoparticle by double emulsion or solvent evaporation technique, co-encapsulating rifampicin, isoniazid and pyrazinamide.

- **Nano range polymeric colloidal systems applied for improving TB treatment[26]:**

There are two types of polymers have been developed for the nano-encapsulation of active medicaments. Two types of polymers include synthetic polymers and natural polymers. Synthetic polymers are synthesized by applying different types of polymerization chemistry and these are essentially poly esters and poly acids. Natural polymers are composed of oligomers that are abundant in nature and they include chitosan, alginate and starch.

Future Opportunities and Challenges[11,27,28]:

Nanoparticulate drug delivery systems have still greater potential for many applications, including anti-tumour therapy, gene therapy, and AIDS therapy, radiotherapy, in the delivery of proteins, antibiotics, virostatics, and vaccines are as vesicles to pass the blood - brain barrier.

Nanoparticles provide massive advantages regarding drug targeting, delivery and release and, with their additional potential to combine diagnosis and therapy, emerge as one of the major tools in nanomedicine. The main goals are to improve their stability in the biological environment, to mediate the bio-distribution of active compounds, improve drug loading, targeting, transport, release, and interaction with biological barriers. The cytotoxicity of nanoparticles or their degradation products remains a major problem, and improvements in biocompatibility obviously are a main concern of future research.

There are many technological challenges to be met, in developing the following techniques:

1. Nano-drug delivery systems that deliver large but highly localized quantities of drugs to specific areas to be released in controlled ways;
2. Controllable release profiles, especially for sensitive drugs;
3. Materials for nanoparticles that are biocompatible and biodegradable;
4. Architectures / structures, such as biomimetic polymers, nanotubes;
5. Technologies for self-assembly;
6. Functions (active drug targeting, on-command delivery, intelligent drug release devices/ bioresponsive triggered systems, self-regulated delivery systems, systems interacting with the body, smart delivery);
7. Virus-like systems for intracellular delivery;
8. Nanoparticles to improve devices such as implantable devices/nanochips for nanoparticle release, or multi reservoir drug delivery-chips;
9. Nanoparticles for tissue engineering; e.g. for the delivery of cytokines to control cellular growth and differentiation, and stimulate regeneration; or for coating implants with nanoparticles in biodegradable polymer layers for sustained release;
10. Advanced polymeric carriers for the delivery of therapeutic peptide/proteins (biopharmaceutics),

And also in the development of:

1. Combined therapy and medical imaging, for example, nanoparticles for diagnosis and manipulation during surgery (e.g. thermotherapy with magnetic particles);
2. Universal formulation schemes that can be used as intravenous, intramuscular or peroral drugs
3. Cell and gene targeting systems.
4. User-friendly lab-on-a-chip devices for point-of-care and disease prevention and control at home.
5. Devices for detecting changes in magnetic or physical properties after specific binding of ligands on paramagnetic nanoparticles that can correlate with the amount of ligand.
6. Better disease markers in terms of sensitivity and specificity.

CONCLUSION:

Targeted delivery of drug molecules to organs or special sites is one of the most challenging research areas in pharmaceutical sciences. This field of drug development experiences very low success rates with regards to drugs that enter the market. These shortfalls are due to factors such

as toxicity of the therapeutic compounds, poor solubility leading to lowered bioavailability and thus reduced efficacy. There are number of significant achievements in technologies to express and deliver drugs by pulmonary route. However the issues for drug companies and patients concerning pulmonary delivery revolve around economic evaluations, approvals, administration and managed health care. . As these issues are resolved, pulmonary delivery will be probably regarded as one of the most important drug delivery alternative.

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