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Review Article

Hypothetical Formulation to Propel Pico-molecular Medicinal Dust: Application to Total Elevation of Therapeutic Efficiency Compare to Nano Entity

Rakesh Das[1, *], Subhendu Chatterjee[2]

[1]Department of Pharmaceutical Technology, Bioequivalence Study Center, Jadavpur University, Kolkata, India
[2]Department of Biotechnology, IIT Karagpur, Kharagpur, WB, India

Email address:

drakesh.jupharmtech@hotmail.com (R. Das)
[*]Corresponding author

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Abstract: Ongoing through all the applications of nano medicines through various sources, it has been understand that preparation of polymeric nanoparticle, liposomes, Dendrimers, Solid Lipid Nanoparticle (SLN) and polymeric micelles is useful for Drug delivery system. Also, helpful to repairs the DNA and treatment of many diseases by increase rate of toxin elimination. The nano medicines in various way initiate the proper biotransformation in livers and also give rise to effective pharmacodynamics profiles. It has been discovered that many nano molecules can be converted into picomolecular medicinal dust (pMMD) entities on lowering the molecular weight, reducing the bond length and shortening the molecular length. This (pMMD) is basically useful in respiratory system treatment, Skin targeted penetration and ophthalmic disorders ramification to ensure hypothetical probability to facilitate Pico-molecular dust involvement as medicinal propeller. Because, it acquires the finest position to receptors less than nano receptors, nano enzymes, nano amino acids chain/polymers, nano pores, nano-microelements, DNA and other nano bio-molecules etc., where nano molecular modules are not effectives. The pico dust will acquires its position into the more specified pico-receptors where nano molecules cannot penetrate or lodge. Pico medicine spray could be implicated superficially over the skin surface at high pressure. So, that it get penetrate upto the subcutaneous and intradermal skin layers with 100% inoculation easily. In ophthalmic preparation, the pico-molecular drugs spray will help to open the drainage area stimulating the receptor on the iris edge corner for dilation of path openings and constriction of circular muscles of eye to create pressure for fluid ejaculation.

Keywords: Nano-Molecular Medicines, Pico-Molecular Medicinal Dust, High Pressure Propeller, Respiratory Treatment, Skin and Ophthalmic Remedies

1. Introduction

Nanoparticles are basically solid colloidal particles, ranging between 1 to 1000 nm, existing of numerous macromolecules in which the therapeutic drugs can be adsorbed, entrapped superficially covalently attached. The diverted plus-point covered by solid nanoparticles in drug development can be tag to their physical stability and the chance of developing the formulating materials to assist controlled release characteristics.

Many techniques are implemented for the measurement of the particle size of nanoparticular systems such as PCS (also known as dynamic light scattering), laser diffraction (LD) and the Coulter counter method. However the easiest and most useful techniques are PCS and LD [1, 2]. Table-1, a number of synthetic and natural polymers which is utilized in the

preparation of nanoparticles for drug delivery [3-9].

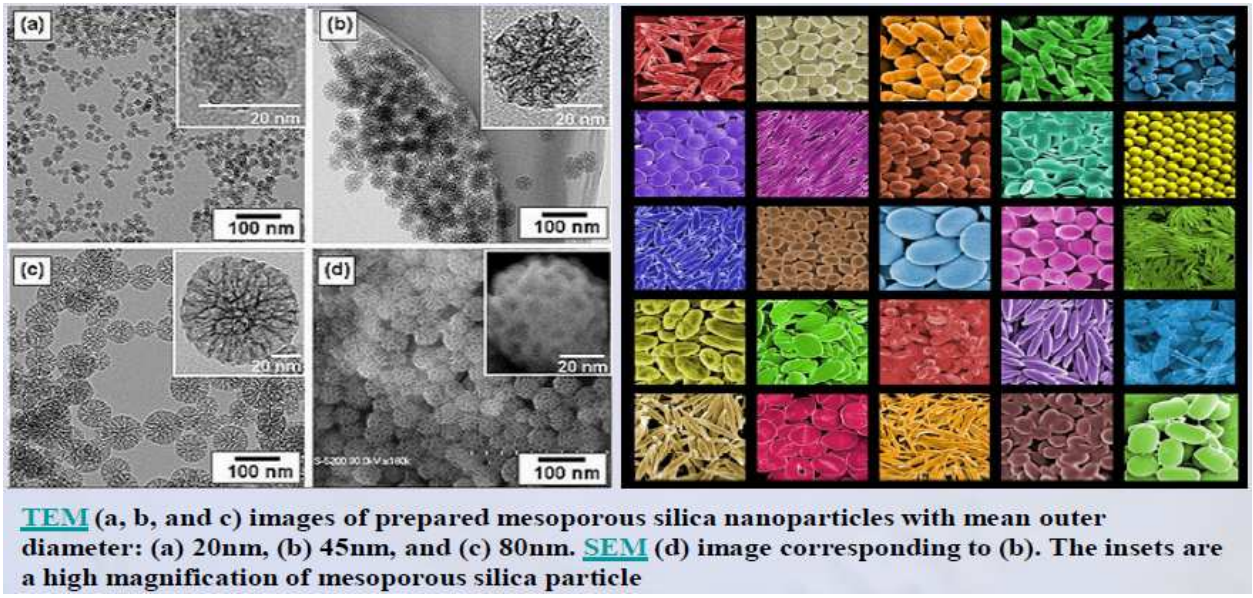

Figure 1. *Transmission and electron micrographs of silica nanoparticles.*

2. Literature Survey

It has been response that the cellular uptake of nanoparticles is size-dependent, with smaller particles being carrierd up more easily than larger particles [10]. Nanoparticles with dimensions ranges 250 nm-3 μm can be started within cells *in vitro via* phagocytosis and micro pinocytosis. Nanoparticles less than 200 nm, on the other hand, are more likely to involve other cellular uptake routes, such as clathrin- or caveolin-mediated endocytosis, independent endocytosis mechanisms, or passive transport. *In vitro* and *in vivo* studies have shown that the interactions of nanoparticles with cells are correlated with particle size, shape, and surface characteristics [11-18].

The prospective of macrophages for rapid blue-print and clearance of foreign particles has provided a rational approach to macrophage-specific targeting with nanoparticles. Antimicrobial agent (s) delivery of Nanoparticle-medium into pathogen-containing intracellular vacuoles in macrophages could be useful and help to removing cellular reservoirs [19]. A simple one-step procedure to obtain CS-TPP and concomitant complexion with sodium alginate was implicated, to prepare trans mucosal formulations for the absorption of insulin [20]. Developed PLGA nanoparticles intended for the transdermal application of encapsulated glucosamine, which is a highly hydrophilic and poor permeable drug. The nanoparticles were prepared by self-assembly of PLGA–glucosamine which was facilitated by probe sonication followed by reversible locking. The authors hypothesized that the nanoparticle's flexibility was due to its structure (hydrophobic PLGA assembly on the outer surface and hydrophilic glucosamine in the inner core). This flexibility helps the nanoparticles to permeate through the skin lipid membrane and release the drug in a sustained manner [21].

Various pharmaceutical nanotechnology such as Nano pharmaceuticals like polymeric nanoparticles, magnetic nanoparticles, liposomes, carbon nanotubes, quantum dots, dendrimers, metallic nanoparticles, polymeric nanoparticles, etc. have brought a change in the total medical service system. With the aid of nanopharmaceuticals, Pharmaceutical nanotechnology could have intensely influence on disease prophylaxis to provide better action on the molecular basis of disease. Some recently found health risk evidences limits their utilization in pharmaceutical industry. Some concerning issues like safety, bioethical issues, toxicity hazards, physiological and pharmaceutical challenges get to be ratified by the scientists.

Table 1. *Various characteristics and brief applications of Nano systems [22].*

Types of Nanosystems	Size (nm)	Characteristics	Applications
Carbon nanotubes	0.5–3 diameter and 20–1000 length	Third allotropic crystalline form of carbon sheets either single layer (single walled nanotube, SWNT) or multiple layer (multi-walled nanotube, MWNT). These crystals have remarkable strength and unique electrical properties (conducting, semi conducting, or insulating)	Functionalization enhanced solubility, penetration to cell cytoplasm and to nucleus, as carrier for gene delivery, peptide delivery
Dendrimer	<10	Highly branched, nearly mono disperse polymer system produced by controlled polymerization; three main parts core, branch and surface	Long circulatory, controlled delivery of bioactives, targeted delivery of bioactives to macrophages, liver targeting
Liposome	50–100	Phospholipid vesicles, bio- compatible, versatile, good entrapment efficiency, offer easy	Long circulatory, offer passive and active delivery of gene, protein, peptide and various other

Types of Nanosystems	Size (nm)	Characteristics	Applications
Metallic nanoparticles	<100	Gold and silver colloids, very small size resulting in high surface area available for functionalization, stable	Drug and gene delivery, highly sensitive diagnostic assays, thermal ablation and radiotherapy enhancement
Nanocrystals Quantum dots	2–9.5	Semi conducting material synthesized with II-VI and III-V column element; Size between 10 and 100 Å; Bright fluorescence, narrow emission, Broad UV excitation and high photo stability	Long term multiple color imaging of liver cell; DNA hybridization, immunoassay; receptor mediated endocytosis; labeling of breast cancer marker HeR 2 surface of cancer cells
Polymeric micelles	10–100 nm	Block amphiphilic copolymer micelles, high drug entrapment, payload, biostability	Long circulatory, target specifi c active and passive drug delivery, diagnostic value
Polymeric nanoparticles	10–1000	Biodegradable, biocompatible, offer complete drug protection	Excellent carrier for controlled and sustained delivery of drugs. Stealth and surface modified nanoparticles can be used for active and passive delivery of bioactives

Table 2. *Various characterization tools and methods for nanoparticles [23].*

Parameter	Characterization method
Carrier-drug interaction	Diffential scanning calorimetry
Charge determination	Laser Doppler Anemometry Zeta potentiometer
Chemical analysis of surface	Static secondary ion mass spectrometry Sorptometer
Drug stability	Bioassay of drug extacted from Nanoparticles Chemical analysis of drug
Nanoparticle dispersion stability	Critical flocculation temperature (CFT)
Particle size and distribution	Atomic force microscopy Laser defractometry Photon correlation spectroscopy (PCS) Scanning electron microscopy Transmission electron microscopy
Release profile	In vitro release characteristics under physiologic and sink conditions
Surface hydrophobicity	Rose Bengal (dye) binding Water contact angle measurement X-ray photoelectron spectroscopy

Table 3. *Various applications of nanotechnology in the different field. [24].*

Applied field	Application
Agriculture	Atomic force, microscopic and scanning tunnelling microscope
Chemical and Cosmetics	Nanoscale chemicals and compounds, paints, coatings etc.
Electronics	Semiconductors chips, memory storage, photonica, optoelectronics
Environment and Energy	Water and air purifi cation fi lters, fuel cells, Photovoltaic
Food Sciences	Processing, nutracetical food, nanocapsules
Materials	Nanoparticles, carbon nanotubes, biopolymers, points, coatings
Military and Energy	Biosensors, weapons, sensory enhancement
Nanomedicines	Nano drugs, Medical devices, Tissue Engineering
Scientifi c Tools	Atomic force, microscopic and scanning tunnelling microscope

Novel drug delivery systems plays a important role in targeted drug delivery compared to conventional dosage forms due to its advantages in site specificity and stability. The main objective in designing Novel drug delivery system (nanoparticles) is to change or modify particle size of the drug, its surface characteristics by conveying pharmacologically active drug molecules to its specific site action with minimal dose and reduced dosing frequency. Thus, Nanoparticles became very popular drug delivery system as it increases the stability and protects drug molecular degradation [25].

Polymeric nano particulate delivery systems enable enhanced penetration of drugs through membranes (e. g. mucosal, epithelial and endothelial). Their size permits delivery via intravenous injection. The nanoscale of these particulate systems also minimizes the irritant reactions at the injection site. They exhibit greater stability with longer shelf storage lives. They can be tailored to elicit the desired kinetics, uptake and response from the body. Polymeric nanoparticles (NPs), therefore, have prime applications as Drug Delivery System [DDS]. A major limitation of NPs as DDS is drug loss during processing. A major proportion of drug may remain un-entrapped and free, and is thereby wasted or would entail specialized recovery methods.

2.1. Preparation of Polymerics Nanoparticles for Drug Delivery

Nanoparticles could be prepared by using simple techniques. Following one or more techniques would be used for the preparation of Nano- particulate DDS.

1. Solvent precipitation technique
2. Solvent evaporation technique using:

– Water immiscible organic solvent
– Water miscible organic solvent

By the:

– Homogenization technique
– Double emulsion technique

1. Desolvation of polymer by chemical reaction
2. Desolvation of polymer by salt addition
3. Phase separation
4. Spray drying. [26-32]

2.2. Nano-Structure Delivery Systems

2.2.1. Liposomes

Liposomes itself is a microscopic vehicles composed of a

bilayer phospholipid that could encapsulating the active drug. Whether the drug is encapsulated in the core or in the bilayer of the liposome is dependent on the characteristics of the drug and the encapsulation process. In general, water-soluble drugs are encapsulated within the central aqueous core, whereas lipid-soluble drugs are incorporated directly into the lipid membrane. The liposomes which consists spherical particles that encapsulate both hydrophilic and lipophilic materials. It can have one, several or multiple concentric membranes [33].

Liposomes can change both the tissue distribution pattern and the rate of clearance of the drug by making the drug depend on the pharmacokinetic characteristics of the carrier [34-36]. Drug loading can be achieved either passively through drug is encapsulated during liposome formation or actively through after liposome formation. Hydrophobic drugs, such as amphotericin taxol or annamycin, can be directly incorporated into liposomes during vesicle formation, and the extent of uptake and retention is governed by drug-lipid interactions. Hydrophobic drugs has importance on various formulation strategies to improve their dissolution and bioavailability. Lipid based formulations such as emulsions, liposomes and solid lipid nanoparticles have been prosperous, in selected cases, for resolving the poor solubility errors of hydrophobic drugs [37]. Many approaches have been activates to achieve targetable properties, including non-covalent association of cell specific antibodies with liposomes, coating of liposomes with heat aggregated immunoglobulin's M (IgM), covalent attachment of poly and monoclonal antibodies to the liposomes, glycoprotein bearing liposomes and natural and synthetic glycolipid containing liposomes [38]. Passive encapsulation of water-soluble drugs depends on the capacity of liposomes to trap aqueous buffer containing a dissolved drug during vesicle formation.

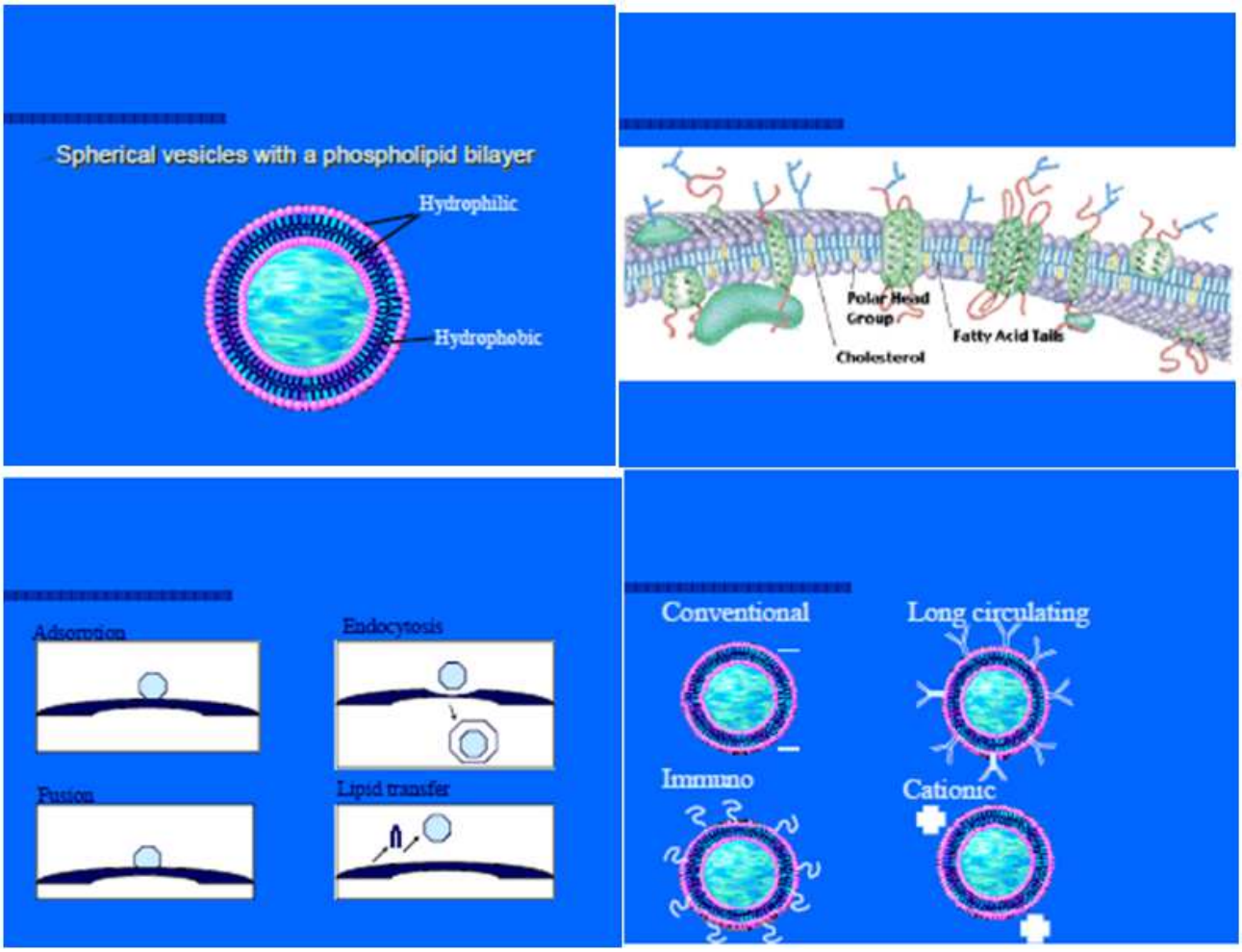

Figure 2. *Involvement of lysosome in drug delivery system.*

2.2.2. Dendrimers

A dendrimer is a polymeric molecule composed of multiple branched monomers that emanate radially from a central core, reminiscent of a tree, whence dendrimers derive their name. When the core of a dendrimer is removed, a number of identical fragments called Dendron's remain, the number of dendrons depending on the multiplicity of the central core (2, 3, 4 or more) [39]. Dendrimer surfaces may be functionally confirmed to enhance or resist *trans*-cellular, epithelial or vascular bio-penetrability. Total interior void space within the dendrimer is capable for encapsulation (i. e., interior isolation) of small-molecule drugs, metals or signalling groups [40-41]. Drug molecules can be incorporated into dendrimers via either

complexation or encapsulation. Dendrimers are being evaluated for both drug and gene delivery, as carriers for penicillin and for use in anticancer therapy [42-44]. Some of the commonly encountered types of dendrimers in biological applications are based on polyamidoamines, polyamines, polyamides (polypeptides), poly (aryl ethers), polyesters, carbohydrates and DNA.

2.2.3. Solid Lipid Nanoparticle (SLN)

Solid lipid nanoparticles are carrier systems for cosmetic ingredients mostly and pharmaceutical drugs which combines the advantages of either, liposomes and solid polymeric nanoparticles. SLN consists of a matrix made from solid lipids which stands rigid in aqueous dispersion by surfactants or polymers, and the dispersion can be relocate to a dry product by spray-drying or lyophilization. Solid lipid nanoparticles can conjugate physical integrity of particle shape as well as the chemical and physical stabilization of fragile ingredients [28]. Solid lipid nanoparticles (SLN) are nanostructures made from solid lipids for example, glyceryl behenate (Compritol), stearic triglyceride (tristearin), cetyl palmitate and glycerol tripalmitate (tripalmitin) with a size range of 50 and 1,000 nm [45].

2.2.4. Polymeric Micelles

Polymeric micelles are particulate self-assemblies in aqueous media that are composed of linear amphiphilic macromolecules possessing both hydrophilic and hydrophobic 'blocks' (AB-type) on a single strand (each copolymer strand is amphiphilic). The particle sizes range between 10–100 nm, making them considerably smaller than phospholipid vehicles (liposomes) [46].

Researchers have developed numerous varied formulations of amphiphilic polymeric preparations for stabilizing membrane proteins. These approaches include hydrophobized low molecular weight poly (acrylic acid) derivatives (amphipods) that successfully stabilized bacteriorhodopsin, the bacterial photosynthetic reaction center, and cytochrome b5, hydrophobically modified natural polymers [47, 48].

Nanoparticles and other colloidal drug delivery systems modify the kinetics, body distribution and drug release of an associated drug. Other effects are tissue or cell specific targeting of drugs and the reduction of unwanted side effects by a controlled release. Micelles in which the most commonly used amphiphilic block copolymer is "Pluronic" a ternary copolymer of poly (ethylene glycol) and poly (propylene oxide). Multifunctional micelles can be prepared throught conjugation of targeting ligands (e. g., folic acid, RGD peptide, antibodies, RNA a tamer and carbohydrates like glucose, lactose, etc.) to their shell aiming to induce specific targeting and uptake by the cells. Liposomes are forms of vehicle that consist either of many, few or just one phospholipid bilayers. Polar drugs can be encapsulated in the liposome core, whereas amphiphilic and lipophilic molecules can be solubilized within the phospholipid bilayer. Dendrimers consist of a central core, branching units and terminal functional groups. Nanoparticles (inclu-ding nano spheres and nanocapsules) are stable, solid, organic or inorganic particles, with sizes in the range of 10-1000 nm. Nanoparticles tend to be accumulated in tumors, Inflammatory and infectious sites by virtue of the enhanced permeability and retention (EPR) effect on the vasculature [49].

2.3. Drugs for Inhalation

Various drugs are investigated for local or systemic pulmonary delivery. 2 These include small molecules, protein/ peptide drug and genes (Table 1). In case of small molecule drugs, many studies were focused on local application for the treatment of chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). However, pulmonary protein /peptide delivery offers great potential for both local targeting for the treatment of respiratory diseases and systemic targeting for the treatment of diabetes mellitus or thrombosis. Gene delivery to the lungs are mainly focused on the localized delivery of drugs to the site of disease, the lungs and airways, including lung cancer, genetic disorders affecting the airways (cystic fibrosis, alpha-1-antitrypsin deficiency), no obstructive lung diseases (asthma), and vaccination.

Since original aerosol technology was developed for small molecule drugs, it is necessary to evolve the reengineering of nano carrier self-assembly systems for macromolecular pulmonary delivery. Examples of drugs for pulmonary nano carrier systems.

2.4. Polymeric Nanoparticulate Pulmonary Delivery

Polymeric nanoparticles are widely studied in drug delivery system for parenteral administration; [50, 51] however their application to the pulmonary routes are also widely recognized.

Table 4. *Examples of drugs for pulmonary delivery using colloidal carrier self-assembly systems.*

Therapeutic areas and drugs	Drug types[a]	Colloidal carrier self-assembly systems and references[b]
Asthma (anti-inflammatory)	S	LP, 2, 3 DN4, 5
Budesonide	G	LP6
Syk antisense oligodeoxynucleotides	S	LP7
Ketotifen	S	DN8
Ibuprofen	G	PN9
Interleukin-4 antisense oligodeoxynucleotides	S	SLN10
Indomethacin, ketoprofen	P	LP, 11–13 PN14
Vasoactive intestinal peptide	S	LP15
Dexamethasone palmitate	S	DN5
Fluticasone		
Pulmonary hypertension		LP, 11–13

Therapeutic areas and drugs	Drug types[a]	Colloidal carrier self-assembly systems and references[b]
Vasoactive intestinal peptidec	P	PN14
Vascular endothelial growth factor (VEGF) gene	G	LP16
Nuclear factor B decoy oligodeoxynucleotides	G	NP17
Nifedipine	S	DN18
Cystic fibrosis		
Amiloride hydrochloride	S	LP19
Secretory leukocyte protease inhibitor	P	LP20
Infections		
Tobramycin	S	LP, 21, 22 DN23
R ifampicin	S	LP, 24–27 PN, 28–31 SLN32
Isoniazid, pyrazinamide	S	PN, 28, 29 LP, 27 SLN32
Ciprofloxacin	S	LP33, 34
Amphotericin B	S	LP35, 36
Itraconazole	S	DN37–40
Lung cancers		
Interleukin-2	P	LP41
p53 gene	G	PN42–45
9-nitrocamptothecin	S	LP46
Leuprolide	P	LP47
Doxorubicin Programmed cell death protein 4 (PDCD4)	S	PN48
Antisense oligonucleotide 2'-*O*-methyl-RNA G	P	PN49, 50
Akt1 (protein kinase B) siRNA	G	PN51
6-{[2-(dimethylamino)ethyl]amino}-3-hydroxyl-7H-indeno[2,1-c]	G	PN52, 53
quinolin-7-one dihydrochloride	S	S PN54
Mutative defects in lung		
Chimeric oligonucleotide	G	PN55
Immune modulators		
Cyclosporine A	P	LP, 56 DN57, 58
Tacrolimus	S	LP59
Vaccination		
HLA-A*0201-restricted T-cell epitopes from *Mycobacterium tuberculosis*	G	PN60
V 1Jns plasmid encoding antigen 85B from *M. tuberculosis*	G	SE61
Reactive oxygen species mediated diseases		LP62–64
Superoxide dismutase	P	
Parathyroid disease		PN65
E lcatonin	P	
Diabetes		PN, 66 LP, 67, 68 SLN69
Insulin	P	
Thrombosis		DD70, 71
Low molecular weight heparin	P	PN72
Urokinase	p	

Notes: a S, small molecules; P, protein/peptide; G, gene; b DN, drug nanoparticle; PN, polymeric nanoparticle; LP, liposome; SLP, solid lipid nanoparticle; DD, dendrimer; SE, submicron emulsion; c Can be used for treatment of pulmonary hypertension as well as asthma.

2.5. Solid Lipid Nanoparticles in Pulmonary Delivery

Solid lipid nanoparticles (SLNs) are made from solid lipids (ie, lipids solid at room temperature), surfactant (s) and water. Since the beginning of 1990s, the SLNs have been focused on an alternative to polymeric nanoparticles. The advantages of drug release from SLNs in the lung are control of the release profile, achievement of a prolonged release and having a faster *in vivo* degradation compared to particles made from PLA or PLGA. In addition, SLNs proved to possess a higher tolerability in the lungs compared to particles made from some polymeric materials.

Table 5. *Various polymers for colloidal pulmonary drug delivery systems [52].*

Polymers	Drugs and references	Size
Alginate		
Sodium alginate	Rifampicin, isoniazid, pyrazinamide29	235.5 nm
Chitosan		
Chitosan	Plasmid DNA	91–164 nm
	Small interfering	40–600 nm
Chitosan/tripolyphosphate	Insulin	300–388 nm
Trisaccharide-substituted chitosan	Plasmid DNA80	77–90 nm
Urocanic acid–modified chitosan	Programmed cell death protein	NA
Gelatin		
Gelatin type A	Fuoresceinamine	277.8 nm
Gelatin type B	Sulforhodamine 101 acid chloride	242±14 nm

Polymers	Drugs and references	Size
PEGylated gelatin Plasmid	Plasmid DNA	100–500 nm
	Insulin	254.7 nm
Polyalkylcyanoacrylate	Doxorubicin	173±43 nm
	Ciprofloxacin	156–259 nm
PLGA		
PLGA	Rifampicin, isoniazid, pyrazinamide	570–680 nm
PEG-PLGA	Nuclear factor *κ*B decoy oligodeoxynucleotide	44 nm
Chitosan-modified PLGA	Elcatonin	650 nm
Chitosan/PLGA Antisense oligonucleotide 2-*O*-methyl-RNA	Antisense oligonucleotide 2-*O*-methyl-RNA	135–175 nm
Poly [vinyl 3-(diethylamino) propylcarbamate-co-vinyl acetate-covinyl alcohol]-*graft*-PLGA	5 (6)-carboxyfluorescein	195.3±7.1 nm
Proticle		
Protamine-oligonucleotide	Vasoactive intestinal peptide	
PEI		
PEI Chimeric oligonucleotide55	Chimeric oligonucleotide	30–100 nm
Plasmid	Plasmid DNA	50–100 nm
PEI-*alt*-PEG Small interfering	Small interfering RNA	NA
Glucosylated PEI Programmed cell death protein	Programmed cell death protein 4	NA
Galactose-PEG-PEI Plasmid	Plasmid DNA	105–210 nm
Cell-penetrating peptides-PEG-PEI Plasmid DNA	Plasmid DNA	113–296 nm
Poly-L-lysine		
PEGylated poly-l-lysine Plasmid DNA	Plasmid DNA	211±29 nm
Dendrimer		
G9 PAMAM Plasmid	Plasmid DNA	NA
G2/G3 PAMAM Low molecular weight heparin	Low molecular weight heparin	NA
Pegylated G3 PAMAM Low molecular weight heparin	Low molecular weight heparin	17.1±3.3 nm

The basic theory of nano-technology applied in medicine and the preparation of nano-drugs are still incomplete, especially the safety of nano- medicines has many problems remain to be explored in depth. Therefore, the research in the field of nano-technology applied in medicine has a great deal of work needs to be done, but the superior capability that nano-drugs owns indicates a very wide range of applications in the clinical disease treatment [53].

The development of several nano carrier systems (liposomal, solid-lipid nanoparticles, polymeric nanoparticles) offers various potential advantages for respiratory drug delivery with reduced and undesirable side-effects. The application of several nano-carriers for drug delivery particularly in chronic lung diseases. Use of different experimental models currently available (*in vitro* and/ *in vivo*) to study the risk assessment of nano-carriers. Although nano-medicine based studies suggests that drug delivery systems for systemic and/or local treatment of diseases are promising, yet further research is warranted to elucidate long-term toxicity, deposition and clearance of nanoparticle especially following repeated administration [54].

Table 6. *Summarizes the chemical properties and function of some widely used nano-carriers used to develop nano-medicines for specific respiratory disorders.*

Nano Carrier	Properties	Functions	Application for respiratory Disorder
Polymeric	Composed of Biodegradable or Biocompatible materials such as poly lactic acid, alginic acid, gelatin and Chitosan	Presence of biocompatible component result in prolonged release of drug	This nano carriers are used in several pulmonary drugs such as asthma, tuberculosis, pulmonary hypertension etc.
Liposomes	Delivered in liquid and dry powder form. Cationic Liposome is also used for gene delivery.	Increase the cellular uptake of drug due to presence of several cells penetrating peptide.	Respiratory distress syndrome.
Solid Lipid Nanoprticles	These nano carriers re composed of solid lipid,, surfactant and water. Solid lipid nano carriers are more accepted for drug delivery due to its less or almost no cytotoxic effect than polymer based carrier.	More tolerable to lungs and major advantages of solid lipid nano particles are the control release of drugs with rapid in vivo degradation.	Mainly used for lung cancer and vaccine Delivery
Submicron emulsions	The stable sub-micron emulsions are promising carriers for DNA vaccines to the lung compare to the commercially available liposomes.	The emulsion system re able to transfect pulmonary epithelium cells which directly activate dendritic cells, resulting in stimulation of antigen specific T-cells.	The sub-micron emulsions re used as promising crrier for DNA vaccines (e.g. Mycobacterium Tuberculosis) for the pulmonary mucosal vaccination

Subclone sensitive cell phenotypic pharmacology of ligands at the b2-adrenergic receptor (b2-AR) stably expressed in HEK-293 cells. The parental cell line transfected with green fluorescent protein (GFP)-tagged b2-AR. Four stable subclones were established and used to profile a library of sixty-nine AR ligands. Dynamic mass redistribution (DMR) profiling resulted in a pharmacological activity map suggesting that HEK293 endogenously expresses functional Gi-coupled a2-AR and Gs-coupled b2-AR, and the label-free cell phenotypic activity of AR ligands are sub clone dependent.

Pathway deconvolution revealed that the DMR of epinephrine is originated mostly from the remodeling of actin microfilaments and adhesion complexes, to less extent from the microtubule networks and receptor trafficking, and certain agonists displayed different efficacy towards the cAMP-Epac pathway. We demonstrate that receptor signaling and ligand pharmacology is sensitive to the receptor expression level, and the organization of the receptor and its signaling circuitry.

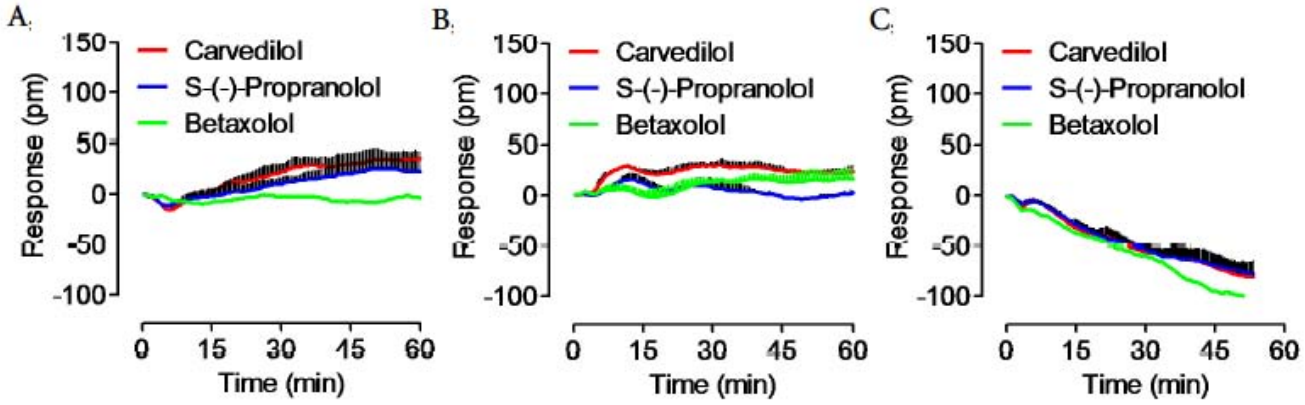

Figure 3. *The DMR of three antagonists, betaxolol, carvedilol, and S-(-)- propranolol, each at 10 mM, in untreated subclone A (A), Epac1 RNAi-treated subclone A (B), or untreated subclone D (C).*

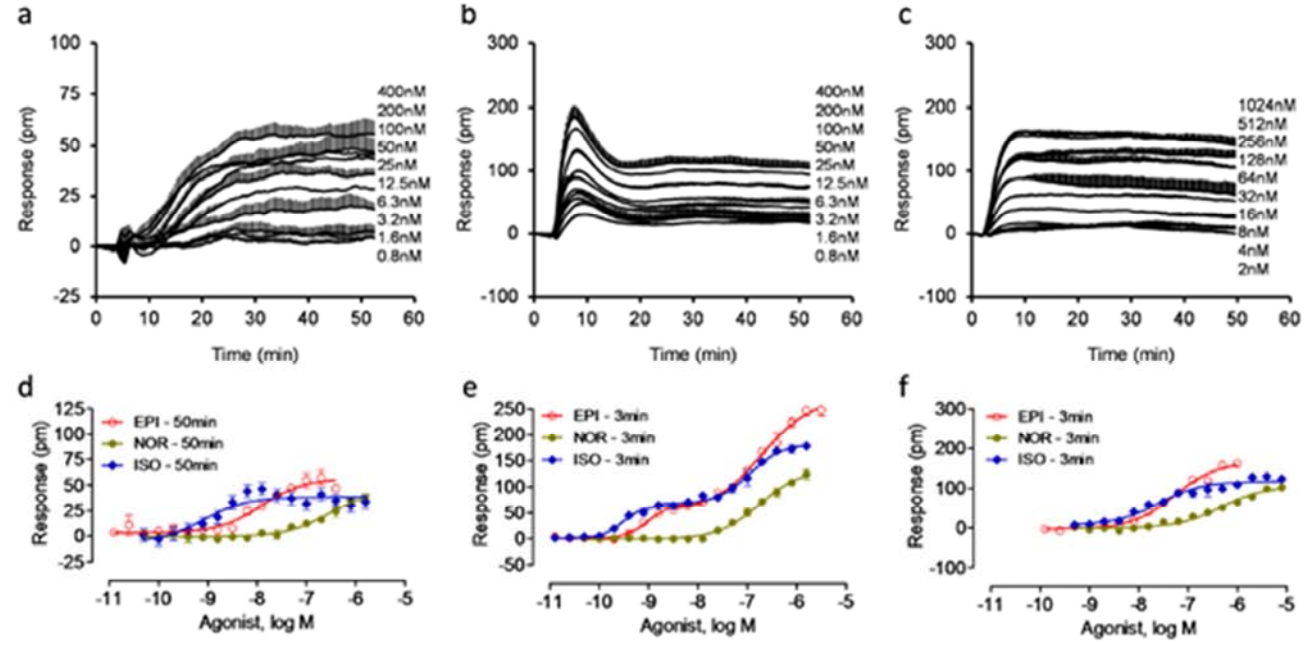

Figure 4. *The DMR dose responses of epinephrine in three different cell lines, (a-c). Real time DMR dose responses of epinephrine in the parenteral EK293 (a), sub-clone A (b), sub-clone D (c). (d-f) The DMR amplitudes at 50 min as a function of agonist doses in the parental HEK 293 (d), SUBCLONE A (e), and sub-clone D (f), EPI: epinephrine; NOR, norepinephrine; ISO, isoproterenol, Data represents Mean ± s. d. (n=4) for all.*

2.6. Polymers for Gene Delivery

At the research level, many synthetic DNA particles have been produce for transfection in cell cultures and in animal studies. However, several authors (70) are of the opinion that, certain issues must be addressed in the development of DNA particles with cationic polymers. These are

(i) potential toxicity of cationic polymers especially when administered at high concentrations; (ii) instability of particles on storage; (iii) instability of DNA particle size and particle size distribution leading to undesirable particle aggregation; (iv) poor transfection efficiency; (v) poor stability in blood circulation; and (vi) high cost of scaling up the process to achieve reproducible product quality.

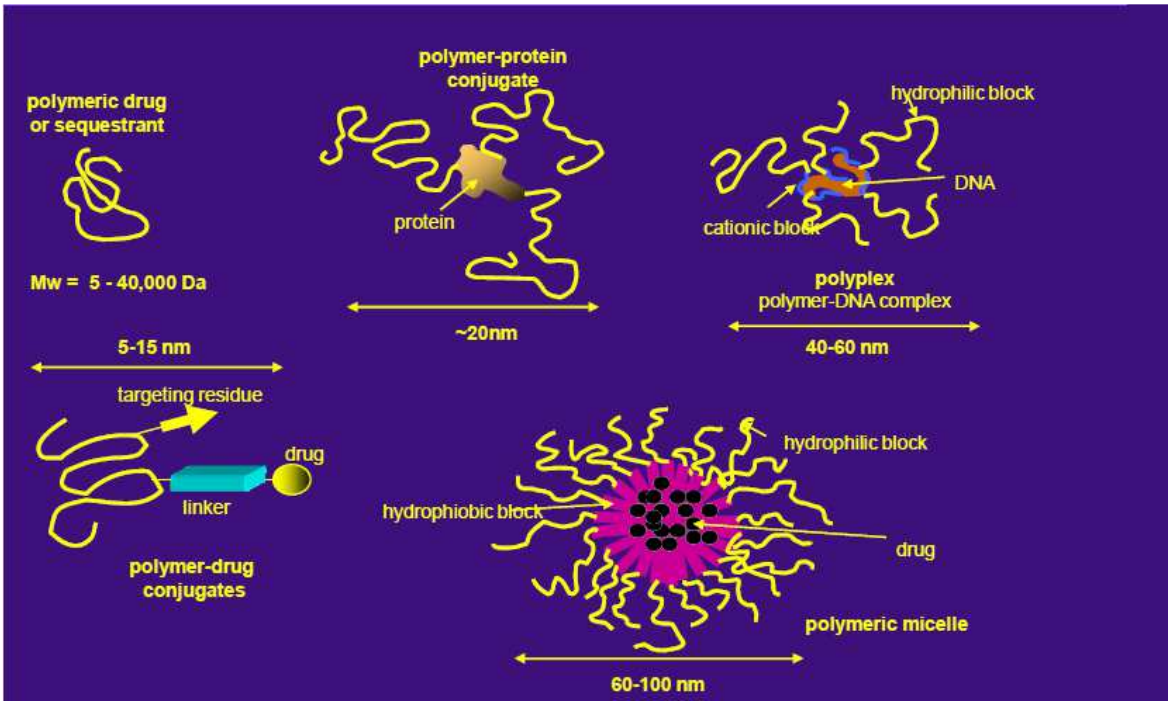

Figure 5. *Polymer-drug-DNA conjugation.*

2.7. Biofunctionalization of Cube-Octameric Silsesquioxanes by Peptides and Miniproteins

A new bioorthogonal cube-octameric silsesquioxane (COSS) scaffold was developed transfer of nano to pico bearing eight aminooxy coupling sites allowing for the conjugation of diverse peptides via oxime ligation. The coupling efficacy depends on the ligand in view of steric hindrance and electrostatic repulsion. For the first time scaffold-based conjugation of cystine-knot miniproteins having a backbone of about thirty amino acids was successfully accomplished without loss of bioactivity. Atomic force microscopy (AFM) provided further knowledge on the size of COSS verifying them as pico- scaffolds growing upon bioconjugation to nano-dimension.

2.8. Hypothetical Probability to Facilitate Pico-Molecular Dust Involvement in Medicinal Propeller

The pico-molecular dust could be promoted parallel to nano molecular application in medicines and may be much better s compared to nano molecular medicines. The basic plus point is that it acquires the finest position to receptors less than nano receptors, nano enzymes, nano amino acids chain/ polymers, nano pores, nano-microelements, DNA and other nano bio-molecules etc.

2.8.1. Respiratory System Involvement

The more beneficent as per our topic is preparation of pico nasal spray to propel the pico dust directly as mist to the respiratory system. The pico dust will acquires its position into the more specified pico-receptors where nano molecules cannot penetrate or lodge. Thus, it's benefited to response all the untouched receptors involving in the respiratory physiological functions. This help to activates the 100% stimulus to the respiratory system and helpful in remedy of bronchitis, Asthma, forceful expiration, antihistaminic activity, anti-allergic and COPD etc.

2.8.2. Skin Remedies

Other than this pico medicine spray could be implicated superficially over the skin surface in high pressure. So, that it get penetrate upto the subcutaneous and intradermal layers with 100% inoculation easily. This types of pico spray application could be beneficial as anti-allergic, pain-killer, anti- fungal, anti-melanin activities, prominent moisturizing of skins. This applications are beneficial to cosmetics and antiseptics as well.

2.8.3. Ophthalmic Treatment

In eye, other than all types of infective diseases ophthalmic occultation and glaucoma are the disorders which always coming under the challenge for medicines, especially under the complications. At that time eye operation or forceful ejaculation is the only major option laid behind for 100% cure. Glaucoma is a group of eye diseases which result in damage to the optic nerve and vision loss due to increase production aqueous humor fluid at intraocular pressure. It happens gradually as per Primary open-angle glaucoma, where the eye does not drain fluid as well as it should (like a clogged drain). Secondly, Angle-closure glaucoma happens when someone's iris is very close to the drainage angle in their eye. The iris can end up blocking the drainage angle. When the drainage angle gets completely blocked, eye pressure rises very quickly. This is called an acute attack**.** It is a true eye emergency, and you should call your ophthalmologist right away or you might go blind. The pico-molecular drugs spray will help to open the drainage area stimulating the receptor on the iris edge corner

for dilation of path openings and constriction of circular muscles of eye to create pressure for fluid ejaculation.

3. Conclusion

Pico particles acquires the finest position to receptors less than nano receptors, nano enzymes, nano amino acids chain/ polymers, nano pores, nano-microelements, DNA and other nano bio-molecules etc in the area of effectiveness. It has been concluded firmly that, Pico dust has advantages specifically on Pico-receptors where nano molecules cannot penetrate or lodge. Pico medicine spray could be implicated superficially over the skin surface at high pressure on the demand of penetration upto the subcutaneous and intradermal skin layers with 100% inoculation easily. In ophthalmic preparation, the pico-molecular drugs spray will help to open the drainage area stimulating the receptor on the iris edge corner for dilation of path openings and constriction of circular muscles of eye to create pressure for fluid ejaculation.

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