

Mucoadhesive Nanoparticles: A Roadmap to Encounter the Challenge of Rapid Nasal Mucociliary Clearance

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ABSTRACT

The modulation of mucoadhesion at the nanoscale is a very challenging task before the formulation scientists. Mucoadhesive nanoparticles are endowed with distinct properties such as increased residence, intimate contact of mucoadhesive dosage form at the mucosal surface and reproducible drug absorption. Large surface area, porous endothelial membrane, high total blood flow, ready accessibility, rapid onset of action, low enzyme level compared to gastrointestinal tract and avoidance of hepatic first pass metabolism are few of the major reasons for preferred drug delivery across the nasal mucosal membrane. There is a limited systematic summarized literature is available which could outline the potential of mucoadhesive nanoparticles for intranasal administration and present review could be an excellent platform to fulfill the voids. The authors put very enthusiastic opinion that the nasal mucoadhesive nanocarriers would meet the criteria set by regulatory authorities and soon such formulations would be available to accomplish the healing desires of the community, provided a successful execution of extensive clinical research with encouraging outcomes.

Key words: Nanomedicine, Nanoparticles, Mucoadhesion, Intranasal, Drug delivery.

INTRODUCTION

Nanotechnology is a multidisciplinary field where *Nano* refers to the scale of objects measured in nanometers (nm, which is 10^{-9} of a meter). The dimensions of nanoparticles (NPs) are similar to biomolecules, such as proteins (1–20 nm), DNA (~diameter 2 nm), virus (~20 nm), cell surface receptors (~10 nm) and hemoglobin (~5 nm). Therefore, scientists with diverse backgrounds have clutched their attention to work with and understand properties of materials on a nano scale.¹ Nanomedicine comes along one of the most important disciplines of nanotechnology and according to National Institute of Health (NIH), the term *nanomedicine*

refers to highly specific medical intervention at the molecular scale for diagnosis, prevention and treatment of various diseases. Broadly, nanomedicines include nanopharmaceuticals, nanodiagnostics, nanotherapeutics and nanobiomaterials.²⁻⁴

Last 20 years have witnessed an outburst in research on the development of novel drug delivery systems. Among them, the multiparticulate drug delivery systems have broad prospects in the pharmaceutical field, due to their superior outcomes *viz.* greater therapeutic efficacy and reduced dosing frequency.^{5,6} At the University of North Carolina, a chemistry Professor

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Joseph De Simone once said about NPs that *You want to deliver it where you want it, when you want it, without wasting it.*⁷ A very first report was published on the designing a specified drug delivery system to achieve selective targeting of drugs and was originated from the perception of Paul Ehrlich, who proposed a hypothesis of *magic bullet concept*.⁸

Drug delivery *via* nasal route has been practiced since ancient times for the treatment of local nasal disorders. Now, it has been recognized as a safe (being non-invasive) way to accomplish faster and higher levels of drug absorption. Large surface area, porous endothelial membrane, high total blood flow, ready accessibility, rapid onset of action, low enzyme level, avoidance of hepatic first pass metabolism and patient-friendly delivery using nasal administration devices are few of the major reasons for frequent intranasal drug delivery.⁹⁻¹²

Mucoadhesion (introduced in early 1980s) can be defined as the state in which two materials adhere to each other for extended periods of time with the help of interfacial forces and when one of these materials is biological in nature, the phenomenon is said to be *bioadhesion*.¹³ Longer and Robinson (1986) defined the term bioadhesion as the “attachment of a synthetic or natural macromolecule to mucus and/or epithelial surface”.^{14,15} Mucoadhesion is gaining much attention today in formulation development of some mucoadhesive multiparticulate (micro or nano) drug delivery systems. Unlike single unit dosage forms, mucoadhesive multiparticulate dosage forms show some important merits *viz.* uniform distribution at the target site, more reproducible drug absorption and compact local irritation.^{16,17} To the best of authors’ knowledge, there is no single review available illustrating the information on mucoadhesive nanocarriers for intranasal administration and present review could be a nice piece of paper for the researchers’ engaged in developing the novel nanoparticulate dosage forms with mucoadhesion potential at the nasal mucosal surface. Looking at literature, the authors are confident about the future outcomes of the abundantly investigated mucoadhesive nanocarrier platforms particularly for intranasal administrations.

Nanotechnology in Drug Delivery

It all started way back in December 29, 1959, with a talk delivered by Dr. Richard Feynman (1918-1988), a physicist, wherein he presented the ideas and concepts behind nanoscience and nanotechnology in his presentation titled ‘*There’s a Plenty of Room at the Bottom*’ at an international forum in the meeting of American Physical Society at the California Institute of Technology.¹⁸⁻²⁰

Over the last thirty years, nanomedicines have matured from proof-of-concept demonstrations in the lab into commercial products used in the clinic that are improving patient care as well as contributing to economic growth. The global market of nanomedicines was valued by the BCC Research firm (www.bccresearch.com) at \$209 billion in 2014 and is anticipated to expand to \$412 billion by 2019. The market share of nanomedicines represented 15% of the total pharmaceutical market in 2014 and is predicted to increase to 22% in 2019.^{21,22}

As evidenced by the significant nanopharmaceutical market, the application of nanotechnology in the field of medicine has the potential to improve the treatment of many diseases. Several nanomedicines have been approved by the US Food and Drug’s Administration (FDA) and European Medicines Agency (EMA) for a variety of therapeutic indications.²⁰⁻²³

In history, nanocarriers were developed to encapsulate small molecules that suffer from low solubility, poor pharmacokinetic profile and high off-target toxicity. Lipid vesicles, later called liposomes, were among the first nanopharmaceuticals described in the 1960s. In 1980, targeting to specific regions of the body was demonstrated with pH-sensitive liposomes. In 1987, the first long-circulating liposomes or stealth liposomes were described, introducing the concept of PEGylation. In 1995, doxorubicin (DOX) loaded PEGylated liposomes (named DOXIL in the USA and Caelyx in other countries) were approved for the treatment of AIDS-associated Kaposi’s sarcoma.²²

Concept of mucoadhesion

In the early 80’s, Professor Joseph R. Robinson (1939-2006), a pharmacy researcher in the school of pharmacy at the university of Wisconsin (Madison, USA) pioneered the concept of mucoadhesion as a new strategy to prolong the residence time of variety of drug molecules on the mucosal surface of eye.²⁴ This phenomenon has potential to optimize the controlled drug delivery in both ways *viz.* localized drug delivery (by spatial placement of drug-formulation within GI tract) and systemic drug delivery (by keeping the formulation in intimate contact with the tissues or cells at the absorption site).²⁵

Mucoadhesion phenomenon has shown numerous path-breaking advantages including (i) prolonged residence time enhances absorption, which results in an increase in the therapeutic efficacy of the drug, (ii) enormous blood supply and good blood flow rate causes rapid absorption of the drug, (iii) prevention of hepatic first-pass metabolism results in increase in drug bioavailability, (iv) avoidance of drug degradation due to acidic

environment in the GI tract, (v) ease of drug administration, thereby improved patient compliance and (vi) faster onset of action due to mucosal surface.^{14,25,26}

Mucoadhesion means simply an attachment of the drug-loaded carrier to the biological membrane. It is a complex phenomenon which involves several stages like wetting, adsorption and interpenetration of the polymer chains. A schematic diagram illustrating the mechanism of mucoadhesion is presented in Figure 1.²⁷⁻²⁹ The mucoadhesion takes place in two stages: (a) Contact stage: Intimate contact between a mucoadhesive NP formulation and a membrane (wetting or swelling phenomenon) and (b) Interactive stage (consolidation stage): Penetration of the mucoadhesive NPs into the tissue or into the surface of the mucous membrane.²⁹ Numerous theories have been proposed to explain the above-mentioned mechanism of mucoadhesion. These theories of mucoadhesion along with their mechanism and key attributes are briefly summarized in Table 1.²⁹

A mucoadhesive polymer is added to the pharmaceutical formulation in order to promote the adhesion of the formulation on the mucosal surface. An ideal mucoadhesive polymer must swell in the aqueous biological environment at the site of absorption, must interact with mucus or its components for adequate adhesion, must allow controlled release of active therapeutic when swelled and it must be excreted unaltered or be degraded to inactive or nontoxic oligomer.^{29,30} The classification of mucoadhesive polymers suitable for drug delivery applications is given in Figure 2.

Intranasal drug delivery

Traditionally, nasal route has been explored for delivery of drugs for the treatment of local nasal disorders. But, since the last few decades, nasal route has attracted wide

attention as a reliable, safe (being noninvasive) and convenient route to accomplish faster and higher levels of drug absorption. The crucial reasons behind interest in nasal route are listed in introduction section of this manuscript.³¹⁻³⁵

Anatomy and physiology of nose

Structurally, the nose is divided into two nasal cavities via a midline septum. The nasal cavity is about 12 cm long, the volume of each nasal cavity is 13 mL and has a total surface area of ~150 cm².⁹ Each cavity consists of three different regions namely: the vestibule (0.6 cm²), the olfactory region (2-10 cm²) and the respiratory region (130 cm²). The respiratory region contains three nasal turbinates, the superior, the middle and the inferior turbinate. These turbinates project from lateral wall of each half of nasal cavity and produces turbulent

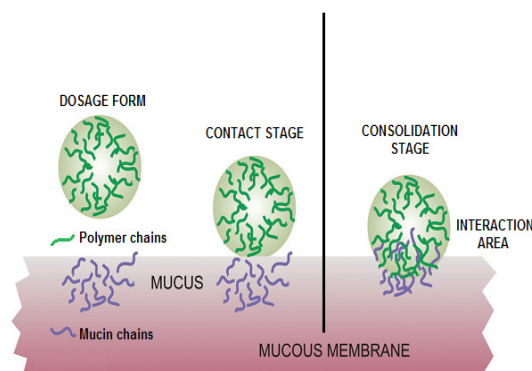


Figure 1: Mechanism of mucoadhesion.

The mucoadhesion takes place in two stages. (A) Contact stage: Intimate contact between a mucoadhesive formulation and a membrane (wetting or swelling phenomenon). (B) Interactive stage: Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration). [Modified after 29].

Table 1: Various theories of mucoadhesion.²⁹

Theory	Mechanism and key attributes
Wetting theory	<ul style="list-style-type: none"> ✓ Is primarily applied to liquid or low viscosity mucoadhesive systems ✓ Affinity of the liquid to the mucosal surface inversely dependent on contact angle
Adsorption theory	<ul style="list-style-type: none"> ✓ Adhesive interaction among substrate surface depends upon the intermolecular forces such as hydrogen bond, van der Waals' forces, etc. ✓ Interaction across the interface occurs as a result of strong covalent bonding
Diffusion interlocking theory	<ul style="list-style-type: none"> ✓ This theory proposes the time-dependent diffusion of mucoadhesive polymer chains into the glycoprotein chain network of the mucus layer
Electronic theory	<ul style="list-style-type: none"> ✓ Electron transfer among surfaces resulting in attractive forces ✓ Bonding occurs due to electron transfer between polymeric system and the mucus membrane epithelium
Fracture theory	<ul style="list-style-type: none"> ✓ This theory relates the force required for polymer detachment from the mucus to the strength of their adhesive bond
Mechanical theory	<ul style="list-style-type: none"> ✓ This theory considers adhesion due to the filling of irregularities on a rough surface by a mucoadhesive liquid ✓ Such irregularity increases the interfacial area available for interactions

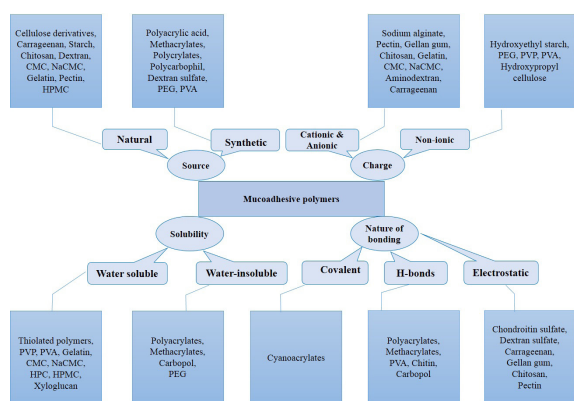


Figure 2: Classification of mucoadhesive polymers [Modified after [25]]

Table 2: Composition of mucus. ¹¹	
Component	Percentage
Water	~ 95 %
Glycoproteins (Sialomucin, fucomucin, sulfomucin)	2 %
Salts (polyelectrolytes)	1 %
Proteins (Albumin, immunoglobulin) and Enzymes (Lactoferrins, lysozymes)	1 %
Lipids, cells, bacteria, cellular debris	<1 %

airflow through nasal passages, which ensures a better contact between inhaled air and mucosal surface.^{9,11}

Functionally, the main functions of the nose are olfaction, regulation of humidity and temperature of inhaled air and removal of large particulates including microorganisms from the inhaled air. The nasal cavity plays an important protective role to filter, warm and humidify the inhaled air before it reaches the lower airways. It provides supply and conditioning of air to lungs.³⁶⁻³⁸

Mucociliary clearance mechanism

Any inhaled particle or microorganisms are trapped by the hairs of nasal vestibule or by mucus layer covering respiratory area of nasal cavity. Mucociliary clearance mechanism of mucus layer gradually carries such particulates to back of the throat, down the esophagus and further into gastrointestinal tract. Nasal mucosa also has metabolic capability of converting endogenous materials into compounds that are eliminated more readily.^{37,38}

About 15-20 % of respiratory cells are covered with a layer of mobile cilia (2-4 μm long, hair-like structures), which helps in propulsion of mucus towards the pharynx. Cilia are sensitive to temperature (optimally working at 35-40°C) and their natural beat frequency drops below these temperatures.⁹

The composition of mucus is presented in Table 2. The goblet cell and the submucosal glands secrete about 20-40 ml mucus per day, in human beings. The pH of the mucus varies from 5.5-6.5 in adults whereas 5-7 in infants.³⁹⁻⁴¹ The mucus layer protects the underlying tissues from various environmental factors and the metabolic effects of enzymes. The mucus layer and hairs in the anterior nose filter 80% of particles larger than 12.5 μm out from the inhaled air stream.⁴²

The mucociliary clearance mechanism (MCC) is a very efficient defense mechanism in humans protecting the lungs against inhaled particulates, droplets and microorganisms. Mucus is present in two layers on epithelium in order to propagate mucociliary clearance. A 2-4 μ thick viscous mucus blanket called as ‘gel layer’ (Figure 3c), which floats on the 3-5 μ thick serous fluid layer called as ‘sol layer’ (Figure 3d). The viscous gel layer is moved along by the hook shaped cilia termini during energy dependent effective stroke phase of ciliary motion (Figure 3a). Cilia are up to 7 μ in length when fully extended but can fold to half this length during recovery stroke (return beat). During recovery stroke, the hook terminus disengage from gel layer and moves immersed in the sol layer in opposite direction to the movement of gel layer (Figure 3b). The cilia beat with a frequency of 1000 strokes per min. These coordinated strokes of cilia result in movement of mucus in one direction only (Figure 3e) from anterior to posterior part of nasal cavity up to the nasopharynx. Therefore, particles applied on nasal respiratory mucosa will be transported on the mucus to the back of throat. The mucus flow rate is 5 mm/min (with a range of 0.5–23.6 mm/min) and hence mucus layer is renewed every 15-20 min. In humans, mucociliary flow can be measured by means of gamma scintigraphy or saccharine clearance test.^{9,37-40}

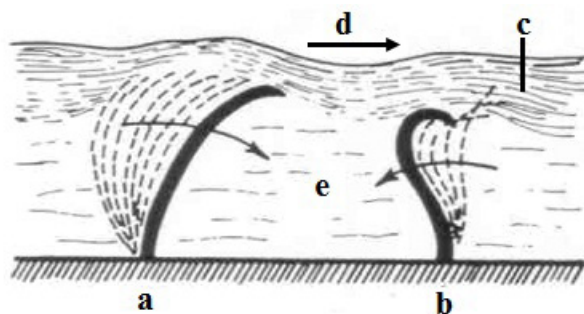


Figure 3: The relationship between ciliary motion and mucus layer composition that allows mucociliary clearance (a) Effective stroke, (b) Recovery stroke, (c) Gel layer, (d) Direction of gel layer movement and (e) Sol layer.

[Adapted from 9 with kind permission of the copyright holder, Elsevier, Amsterdam].

Nasal mucociliary clearance limits the residence time of intranasally administered formulation, thereby decreasing the extent of nasal drug absorption. Mucociliary clearance can be modulated by using specific components of the formulation viz. viscosity enhancers and mucoadhesive polymers.³⁹

Mucoadhesive nanoparticles for intranasal administration

This section deals with the various mucoadhesive NPs developed so far for intranasal administration. These

nanocarriers are prepared by either of the following three ways viz. i) by using mucoadhesive polymers, ii) by modifying the nanocarrier formulation with mucoadhesive polymers or iii) by incorporating the nanocarrier formulation into the mucoadhesive polymer-based gel. The authors have categorized the nasal mucoadhesive nanocarrier formulations into three categories viz. lipid-based, polymer-based and protein-based nanocarriers for readers' convenience. The details of respective categories of NPs are detailed in Table 3.

Table 3: List of selected mucoadhesive nanoparticles investigated for intranasal drug delivery.

Therapeutic payload	Mucoadhesive polymer	Nannocarrier formulation	Therapeutic applications	Reference
LIPID-BASED NASAL MUCOADHESIVE NANOCARRIERS				
BACE1 siRNA	Chitosan	SLNs	Alzheimer's disease	43
Carbamazepine	Pluronic F-127 (gel)	SLNs	Epileptic seizures and trigeminal neuralgia	44
Ondansetron HCl	Delonix regia gum	NLCs	Chemotherapy-induced nausea and vomiting	45
Ropinirole HCl	HPMC K15M	PLNs	Parkinson's disease	46
Insulin	Chitosan	Liposomes	NM	47
Acyclovir	PVP (gel)	Liposomes	HSV infections	48
DNA	Glycol chitosan	Liposomes	Viral-specific immunization	49
OIL-BASED NASAL MUCOADHESIVE NANOCARRIERS				
Zolmitriptan	Polycarbophil	MEs	Migraine	50
Sumatriptan	Polycarbophil	MEs	Migraine	51
Clonazepam	Polycarbophil	MEs	Myoclonic seizures	52
Tacrine	Carbopol 934 P	MEs	Alzheimer's disease	53
Diazepam, Lorazepam and Alprazolam	Polycarbophil	MEs	Insomnia	54
Risperidone	Chitosan	NEs	Psychotic disorders	55
Risperidone	Chitosan	NEs	Psychotic disorders	56
Zaleplon	Carbopol 934 (gel)	NEs	Insomnia	57
Curcumin	Chitosan	NEs	Cancer	58
Ropinirole	Chitosan	NEs	Parkinson's disease	59
POLYMER-BASED NASAL MUCOADHESIVE NANOCARRIERS				
Rivastigmine	Chitosan	Chitosan NPs	Alzheimer's disease	60
Ropinirole HCl	Chitosan	Chitosan NPs	Parkinson's disease	61
Bromocriptine	Chitosan	Chitosan NPs	Parkinson's disease	62
Tetanus toxoid (TT)	Chitosan	Chitosan NPs	Immunization against TT antigen	63
Ovalbumin	N,N,N-trimethyl chitosan (TMC)	TMC NPs	NM	64
Leucine-enkephalin	TMC	TMC NPs	Acute and chronic pain	65
Ropinirole HCl	TMC	TMC NPs	Parkinson's disease	66
Ropinirole HCl	TMC	TMC-DS PECs	Parkinson's disease	67
Insulin	Starch	Starch NPs	Hyperglycemia /Diabetes	68
HBsAg	Chitosan, Glycol chitosan	PLGA NPs	Hepatitis B	69
Chlorpromazine	Chitosan	PLGA NPs	Schizophrenia	70
Venlafaxine	Alginate	Alginate NPs	Depression	71
PROTEIN-BASED NASAL MUCOADHESIVE NANOCARRIERS				
Tacrine	HP-β-CD, SBE-β-CD	Albumin NPs	Alzheimer's disease	72

Lipid-based nasal mucoadhesive nanocarriers

Solid lipid nanoparticles (SLNs)

The solid lipid-based nanoparticles (SLNs) have been reported to enhance the absorption of intranasally administered drug molecules through modification of the surface of SLNs using mucoadhesive polymer (chitosan)⁴³ or by incorporating the preformed SLNs into Pluronic-based gel.⁴⁴ Recently, Rassu *et al.* (2017) proposed a nasal drug delivery system based on mucoadhesive SLNs to exploit both the olfactory and trigeminal nerve pathways in order to promote the transport of siRNA into the central nervous system (CNS). A modified solvent emulsification evaporation method based on a w/o/w double-emulsion technique was employed to prepare SLNs and further surface-modified using chitosan in order to obtain an efficient and optimal nose-to-brain transport of BACE1 siRNA, potentially useful in the treatment of Alzheimer's disease.⁴³

Nanostructured lipid carriers (NLCs)

Nanostructured lipid carriers (NLCs), comprising a mixture of solid and liquid lipids, has been utilized for the effective delivery of variety of drug molecules. However, there are but a single report demonstrating the nose to brain drug delivery using surface engineered NLCs. In an investigation by Devkar *et al.* (2014), ondansetron hydrochloride (OND) loaded NLCs were prepared by using high pressure homogenization technique and further surface modified using *Delonix regia* gum, a naturally occurring mucoadhesive polymer. The increase in particle size and shifting of zeta potential values towards positive side indicated the surface modification of the NLCs by the mucoadhesive polymer. The mucoadhesive strength imparted to the NLCs resulted in increased residence time of the formulation on the nasal mucosal membrane ensuring rapid and high nasal absorption of OND. The higher values of drug targeting efficiencies confirmed the efficiency of OND-loaded NLCs in nose to brain drug delivery.⁴⁵

Polymer-lipid hybrid nanoparticles (PLNs)

In 2013, our group (Pardeshi *et al.* 2013b) reported the fabrication and evaluation of novel surface modified polymer-lipid hybrid nanoparticles (PLN) as robust carriers for intranasal delivery of ropinirole hydrochloride (ROPI HCl), an anti-parkinsonian agent. Sustained release, avoidance of hepatic first pass metabolism and improved therapeutic efficacy, through enhanced retention of formulation in nasal cavity are the major objectives of the proposed PLN formulation. PLN were fabricated by emulsification-solvent diffusion technique. We employed

trimyristine as a solid lipid and HPMC K15M as a mucoadhesive polymer. In conclusions, the PLN was found to be safe and robust nanocarrier for the intranasal delivery of hydrophilic ROPI HCl, especially in treatment of Parkinson's disease.⁴⁶

Liposomes

The nasal route of administration holds a great promise in the systemic delivery of small molecules, peptides like insulin and genetic immunization (DNA vaccination) due to particular organization of the nasal mucosa.⁴⁷⁻⁴⁹ The nasal mucosae is the first site of contact with inhaled macromolecules and the nasal associated lymphoid tissue (NALT) at the base of the nasal cavity (Waldeyer's ring in humans) is important in the defense of mucosal surfaces. Additionally, the nasal epithelium is leaky and there are underlying blood vessels, cervical lymph nodes and lymphoid cells to which the macromolecule may have direct access if it can be adequately transported across the epithelium. Hence, nasal mucosal immunization offers significant advantages in terms delivery, safety and efficacy, in comparison to traditional systemic delivery of vaccines.⁴⁹

Khatri *et al.* (2008) investigated the potential utility of glycol chitosan-coated liposomes carrying plasmid DNA as nasal vaccine delivery vehicle, in mice, for producing viral specific humoral mucosal and cellular immune response. Liposomes were prepared by dehydration-rehydration method and subsequently coated with glycol chitosan by simple incubation method. Upon intranasal administration, glycol chitosan-coated liposomes elicited humoral mucosal and cellular immune responses that were significant as compared to naked DNA justifying the potential advantage of mucosal vaccination in the production of local antibodies at the sites where pathogens enters the body.⁴⁹

Microemulsions (MEs) and nanoemulsions (NEs)

The only scientifically important difference among microemulsions (MEs) and nanoemulsions (NEs) is that the MEs are the equilibrium systems which are thermodynamically stable while the NEs are non-equilibrium systems which are kinetically stable. Diverse studies have been reported on the development of MEs and NEs for brain targeting after intranasal administration.⁵⁰⁻⁵⁹

Porecha *et al.* (2009) prepared the mucoadhesive MEs loaded with diazepam, Lorazepam and alprazolam and proposed for the treatment of insomnia. MEs were prepared by titration method. The fabricated MEs were evaluated for sleep induction studies in male albino rats to assess their role in effective relief of insomnia

patients. It was observed, from their findings, that the intranasal mucoadhesive MEs had shown the fastest onset of sleep (< 9 min) and longest duration of sleep as well in rats.⁵⁴

Sood *et al.* (2014) fabricated the curcumin-loaded chitosan-coated mucoadhesive NEs using spontaneous nanoemulsification method and intended for intranasal administration. The alteration of the zeta potential values indicated the successful coating of chitosan on the NE globules. The developed formulation was found to be non-toxic and safe for intranasal administration as demonstrated by the *in vitro* cytotoxicity (on SK-N-SH cells, a human neuroblastoma cell lines) and nasal ciliotoxicity studies. In addition, the nasal mucoadhesive NEs had shown enhanced flux and permeability coefficient across sheep nasal mucosal membrane compared to uncoated NEs and bulk drug solution, indicating the suitability of mucoadhesive NEs for intranasal delivery of poorly soluble curcumin.⁵⁸

Polymer-based nasal mucoadhesive nanocarriers

There is a numerous literature available demonstrating the findings on the polymer-based mucoadhesive nanocarriers developed so far for intranasal administration. The prime objective being to enhance the retention time of nanocarrier formulations on the nasal mucosa, in order to improve the nasal mucosal absorption and permeability characteristics. These nanocarriers are extensively investigated for the delivery of variety of therapeutic agents *viz.* small drug molecules, proteins, peptides, vaccines and other macromolecules. The polymer-based mucoadhesive nanocarriers are mainly made of either mucoadhesive polymers like chitosan,⁶⁰⁻⁶³ TMC,⁶⁴⁻⁶⁷ or made from non-mucoadhesive polymers like starch,⁶⁸ PLGA,^{69,70} alginate,⁷¹ etc. but further surface-modified with mucoadhesive polymers.

Recently, our group (Kulkarni *et al.* 2016) fabricated the new self-assembled polyelectrolyte nanocomplex based on two mucoadhesive polymers *viz.* N,N,N-trimethyl chitosan (TMC) and dextran sulfate (DS), the nanocomplex formulation being referred to as TMC-DS PECs. The PECs were prepared by using ionic interactions between charged functional groups of both the participating mucoadhesive polymers at different pH conditions (pH 5, 8, 10 and 12) and proposed for the intranasal delivery of ROPI HCl. It has been observed, from the permeation experiments, that the PECs prepared at pH 10 shows high permeability of ROPI HCl across sheep nasal mucosa *via* paracellular route of drug transport (that takes place between the adjacent epithelial cells through hydrophilic pores and the tight junctions between the cells). Again, the *in vitro* muco-

adhesion potential of prepared PECs was assessed by mucus glycoprotein assay. The mucin binding efficiency (MBE) of TMC-DS PEC prepared at pH 10 found to be rated as good mucoadhesive strength, based on a rating criteria for mucin adsorption on a mucoadhesion-scale from poor (MBE < 50 %) to excellent (MBE > 75 %). The high mucoadhesive strength is due to a highly specific, concentration-dependent adsorption with strong electrostatic interactions between positively charged trimethyl amino groups of TMC and negatively charged sialic and sulfonic acid moieties in mucin. It was proposed that the higher adsorption of mucin on PEC particles would result in better penetration of PEC particles in mucosal layer. At alkaline pH conditions (pH 10), the participant polymer chains (TMC and DS) are sufficiently close to form more stable PECs. Authors concluded that the further *in vivo* brain pharmacokinetics, scintigraphic/microscopical imaging and stability studies need to be addressed appropriately in order to validate the biofate of TMCDS PECs as novel nose to brain drug delivery carriers and further, their scale-up.⁶⁷

Protein-based nasal mucoadhesive nanocarriers

The only report on protein-based nasal mucoadhesive nanocarriers for drug delivery application is given by Luppi *et al.* (2011). In their investigations, the researchers employed coacervation method for the preparation of bovine serum albumin (BSA) NPs. The nanoparticles were loaded with tacrine, the first acetylcholinesterase inhibitor licensed for the treatment of Alzheimer's disease. The effect of three difference cyclodextrins *viz.* beta cyclodextrin (β -CD), hydroxypropyl beta cyclodextrin (HP- β -CD) and sulphobutylether beta cyclodextrin (SBE- β -CD) on the lading efficiency, mucoadhesion potential, drug release and permeation characteristics of tacrine was examined. From the results, it has been observed the inclusion of different CDs into the albumin NPs has modulated the permeability of tacrine, more specifically the albumin NPs carrying HP- β -CD had shown maximum permeability across the nasal mucosa.⁷²

Regulatory aspects and clinical status

Interest in the use of mucoadhesive polymers in the formulation of nanopharmaceuticals is not new however, it still does not appear in much marketed products. Despite of the long list of nanopharmaceuticals approved by FDA (Food and Drug Administration) for use in clinic by numerous routes of administration but mucoadhesive nanopharmaceuticals delivered *via* intranasal route are still under investigation into the laboratories. The lack of sufficient safety data and valid outcomes, very few of the mucoadhesive NP formula-

tions have found a way to the commercial market. In addition, there are but few patents on the mucoadhesive NPs for intranasal administration.⁷³⁻⁷⁶ However, none of them have translated to the clinical phase, even after being investigated extensively in the laboratory. For instance, about 22 clinical trials are going-on on the nanopharmaceuticals by various routes of administration and the excellent preclinical outcomes have energized the researchers for the further clinical advancements, but the researchers are still waiting for the encouraging results in human subjects.

Into the future

At present, the nasal mucoadhesive nanoparticulate formulation have proved their wide applicability in various fields. On laboratory scale, the excellent research outcomes have been reported with significant early preclinical success, alarming the pharmaceutical industries to take over the challenge of successful commercialization of such formulations. However, it is very important to make a note on the crucial aspect that the selection of ideal mucoadhesive polymer, ideal nanocarrier formulation and the ideal drug candidate for a particular mucoadhesive nanocarrier formulation is a task of extreme significance in order to develop a safe and stable dosage form successfully. Again, the toxicity experiments on the polymer- or lipid-based nanocarriers carrying therapeutic payloads must be performed so as to provide additional evidences on the risks associated with the development of such nanocarrier formulations.

To look into the future, the upcoming developments in the mucoadhesive nanocarrier formulations for intranasal administration need to be extensively explored with respect to increasing performance, improving the absorption or permeability characteristics and reducing the toxicity issues.

CONCLUSION

To be called as a successful drug delivery system, the formulation must offer commercial applicability to the pharmaceutical industries for large scale production. Among all developed novel drug delivery systems, the multiparticulate drug delivery systems have broad prospects in the pharmaceutical field. The most promising outcomes (greater therapeutic efficacy and reduced dosing frequency) received from the nanocarrier formulations have attracted numerous research groups from various disciplines to work over. Among the much vastly investigated drug delivery systems, the mucoadhesive nanoparticulate dosage forms gained much attention today in formulation development due to their inherited

advantages like prolonged residence time, uniform distribution at the target site, rapid and more reproducible drug absorption.

The nasal mucoadhesive nanoparticulate drug delivery systems have already proved their potential in the efficient delivery of pharmaceuticals, on laboratory scale. However, to bring such nanocarrier formulations to the commercial market, extensive clinical research is needed. If the encouraging results are obtained, the day is not so far when we see the nasal mucoadhesive nanoformulations on the pharmacist's shelves.

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Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects performed by any of the authors.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

NPs: Nanoparticles; **IN:** Intranasal; **NIH:** National Institute of Health; **FDA:** Food and Drug Administration; **EMA:** European Medicines Agency; **nm:** Nanometers; **DOX:** Doxorubicin; **PEG:** Polyethylene glycol; **GI:** Gastrointestinal; **Mw:** Molecular weight; **MCC:** Mucociliary clearance mechanism; **SLNs:** Solid lipid nanoparticles; **CNS:** Central nervous system; **NLCs:** Nanostructured lipid carriers; **OND:** Ondansetron hydrochloride; **PLN:** Polymer-lipid hybrid nanoparticles; **ROPI HCl:** Ropinirole hydrochloride; **HPMC:** Hydroxypropyl methyl cellulose; **NALT:** Nasal associated lymphoid tissue; **MEs:** Microemulsions; **NEs:** Nanoemulsions; **TMC:** *N,N,N*-trimethyl chitosan; **DS:** Dextran sulfate; **PEC:** Polyelectrolyte complex; **MBE:** Mucin binding efficiency; **BSA:** Bovine serum albumin; **CD:** Cyclodextrin; **SBE:** Sulfobutylether; **NLC:** Nanostructured lipid carriers; **PLN:** Polymer-lipid hybrid nanoparticles; **CHT:** Chitosan; **HCl:** Hydrochloride; **HSV:** Herpes simplex virus; **PVP:** Poly-N-Vinyl-2-Pyr-

rolidone; **HBsAg**: Hepatitis B surface antigen; **PECs**: Polyelectrolyte complex; **HP- β -CD**: Hydroxypropyl beta cyclodextrin; **SBE- β -CD**: Sulphobutylether beta cyclodextrin; **NM**: Not mentioned.

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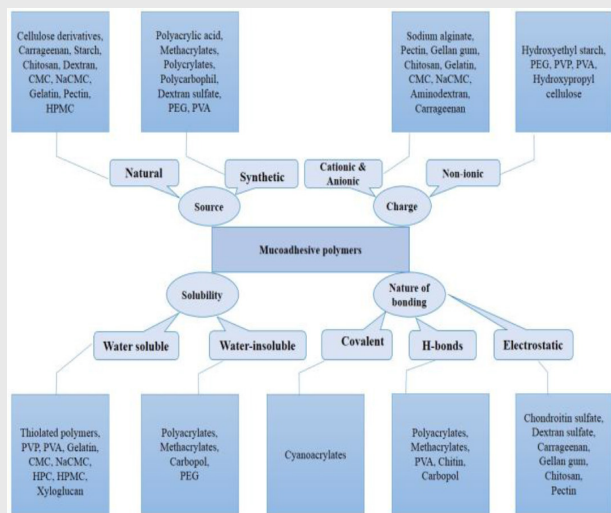
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SUMMARY

- The multiparticulate formulations possess high commercial scalability among all novel drug delivery systems, now-a-days, in pharmaceutical field.
- The most promising outcomes (greater therapeutic efficacy and reduced dosing frequency) received from the nanocarrier formulations have attracted numerous research groups from various disciplines to work over.
- The lack of sufficient safety data and valid outcomes, very few of the mucoadhesive NP formulations have found a way to the commercial marker. In addition, there are but few patents on the mucoadhesive NPs for intranasal administration.
- The nasal mucoadhesive nanoparticulate drug delivery systems have already proved their potential in the efficient delivery of pharmaceuticals, on laboratory scale. However, to bring such nanocarrier formulations to the commercial market, extensive clinical research is needed. If the encouraging results are obtained, the day is not so far when we see the nasal mucoadhesive nanoformulations on the pharmacist's shelves.

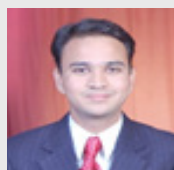
PICTORIAL ABSTRACT



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