ISSN–2230-7346
Journal of Global Trends in Pharmaceutical Sciences

REVIEW ON LIPOSOMAL IN-SITU GEL AS A NOVEL APPROACH FOR NASAL DRUG DELIVERY SYSTEM

Nishant B. Awandekar, Swati V. Dhawas*, Rita D. Tekade, Milind J. Umekar

Department of Pharmaceutical Quality Assurance Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur - 441002, Maharashtra (India).

***Corresponding author:** swatidhawas03@gmail.com

ARTICLE INFO

Key Words
Nasal drug delivery system, liposomes, *in-situ* gel..

Access this article online
Website: https://www.jgtps.com/
Quick Response Code:

ABSTRACT

Nasal mucosa has been regarded as one of the possible non-invasive routes for the delivery of therapeutic compounds since it offers many advantages for target delivery and a wide range of therapeutic compounds can be delivered intranasally for topical, systemic and CNS intervention. This is due in large part to the avoidance of first-pass hepatic metabolism, high vascularization, large surface area, high permeability, rapid onset of action, low enzymatic degradation. The absorption of drugs can be improved by using enhancers or increasing the drug residence time in the nasal cavity. Sustained and controlled delivery of drugs has become the norm, and research has been conducted to achieve improved efficacy, efficiency and protection of drug products. The liposomes are small artificial vesicles of spherical shape that can serve different functions besides the drug, enzymatic inhibitors, and enhancers of nasal absorption, mucoadhesive polymers to improve stability, membrane permeation, and retention time in the nasal cavity. Therefore the polymeric in situ method has gained considerable interest in developing a controlled release mechanism. Until administration this method is a liquid aqueous solution, and a gel under physiological conditions. In this review, we have tried to discuss the background of nasal drug delivery with biological and pharmaceutical consideration with special reference to in situ gel system

INTRODUCTION

Nasal Route of drug delivery system: Nasal drug delivery system has emerged as a significant area in pharmaceutical research. The nasal mucosa is considered a promising site for the systemic delivery of peptides and proteins, which are not readily delivered through other routes than injection.This route therefore serves as an excellent non-invasive option that can increase patient compliance and allow extended self-medication to be used for any chronic disease. Nasal sprays are locally active medications such as cold or allergy medication Decongestants. Anti-migraine medications, nicotine replacement, and hormone therapy are Examples of the clinically active medicines available as nasal sprays. The bioavailability of a drug and its therapeutic effectiveness are often influenced by the route selected for administration. For a medication to achieve its maximum efficacy a drug should be administered easily and it should be capable of being absorbed efficiently so that enhanced bioavailability can be accomplished. The nasal route could be mainly important for drugs where the pathway from the nose to brain provide a faster and more therapeutic effect. Nasal mucosa has been considered as a potential administration route to realize faster

and enhanced level of drug absorption because it's permeable to more compounds than alimentary canal to lack of pancreatic and gastric enzymatic activity, pH of nasal mucosa and fewer dilution of gastrointestinal contents.[1]

Features of the Nasal Route: Systemic nasal absorption of drug is new alternative to parenteral drug delivery system, as it offers numerous advantages.

1. The nasal mucosa absorption of drug is rapid via highly vascularised mucosa, so the bioavailability of small drug molecules is good.
2. Onset of action is rapid, improved bioavailability; side effects are reduced due to low dose, non- invasive and easy for administration.
3. Bypass the blood-brain-barrier, drug enters directly into systemic circulation and CNS is possible.
4. Avoid first pass eradication through GIT.
5. The plasma concentration verses time profiles as well as rate and extent of absorption is equivalent with parenteral administration.
6. Patient convenience and compliance is improved. Hence, self-administration is possible, convenient route for the patient on long term therapy.[2]

Limitation of Nasal Drug Delivery System: [3-4]

1. There is risk of irretrievable damage of the cilia on the nasal mucosa and local side effects, both from the drug substances and from the excipients added to the dosage form
2. The histological toxicity of absorption enhancers used in nasal drug delivery system is not clearly established, the compound used as absorption enhancers may disrupt.
3. Relatively inconvenient to patients associated to oral delivery systems as there is a possibility of nasal condition like nasal irritation, nasal atrophic rhinitis can reduce the ability of nasal absorption.
4. Nasal cavity provides smaller absorption surface area when compared to GIT, Due to enzymatic degradation result as a low bioavailability and low residence time.

Nasal Anatomy and Physiology: Nasal cavity has a crucial protective function in that it filters, warms and humidifies the inhaled air before it reaches the lower airways. Any inhaled particles or microorganisms are trapped by the hair within the nasal vestibule or by the mucus layer covering the tract. The nasal mucosa provide metabolic capacity that will help convert endogenous materials into compounds that are more easily eliminated. A midline septum divides the human nasal cavity into two non-connected parts. Each part consists of three regions. Firstly, the vestibule consisting of the region just inside the nostrils with an area of about 0.6cm^2. Secondly, the olfactory region, which is situated in the roof of the nasal cavity and only covers about 10% of the total nasal area of 150cm^2.The respiratory area includes the three nasal turbinate's that extend from the lateral wall of each half of the nasal cavity, the superior, the middle and the inferior. The presence of these turbinate's induces a turbulent airflow through the nasal passages that ensures better communication between the inhaled air and the mucous surface, eventually transforming into a pseudo stratified columnar epithelium that covers the respiratory epithelium. The respiratory epithelial cells are covered by microvillus and therefore major part of these cells is also covered with cilia. These cilia, which are long thin projections, of each cilium reaches into the mucus layer and carry this forward followed by a slow return beat, where the cilium is bent and moves within the sol layer that lies beneath the mucus layer. The mucus flow rate is in the order of 5mm per min and hence the mucus layer is renewed every 15-20 min.[5-6]

Nasal Blood Flow: The nasal mucosa is highly vascular. The surface of epithelium is supplied with a dense network of erectile cavernous tissue, which is particularly well developed over the turbinate's and septum. The vascular bed provides a rich surface for drug absorption. Constriction of blood vessels would decrease blood flow and blood content in the nasal

mucosa, whereas vasodilatation would yield the opposite response.[7]In normal and pathological conditions, the penetration of the drug through the sinus mucosa is partially determined by the blood flow in the area. The capillary flow in the nasal mucosa was reported to be about 0.5 ml/g/min. The general factors that affect the nasal blood flow include emotion, fear, frustration, humiliation, anxiety, and changes in environmental temperature, hyperventilation, and exercise. Nasal mucosal blood vessels are surrounded by adrenergic nerves, in which alpha receptors show a functional predominance.

Nasal pH: The normal pH of the nasal secretion in the adult ranges approximately from 5.5 to 6.5, whereas in infants and young children it ranges from 5.0 to 6.7. The course of nasal pH is often altered by the influence of cold and warmth. Cold air produces a drift towards alkalinity, whereas heat yields a drift towards acidity. The pH of nasal secretions also varies with sleep, rest, and therefore the ingestion of food, emotion, and infection.[8]

Barriers to nasal drug delivery: A large number of aspects influence therapeutic efficacy also toxicity of nasally administered drug product.

Low bioavailability: Polar drugs has low bioavailability, generally low about 10% for low relative molecular mass drugs and not contain above 1% like peptides such as calcitonin and insulin. The greatest significant factor limiting the nasal absorption of polar drugs and particularly large relative molecular mass polar drugs such as peptides and proteins is that the low membrane permeability. Larger peptides and proteins are capable to pass the nasal membrane using an endocytic transport process but only in low amounts.[9]

Mucociliary clearance: The drugs administered by nasal route are subject to fast clearance from the nasal cavity due to mucociliary clearance;as a result it leads to decreased transport of drugs across the nasal mucosa. It is been revealed that both liquid and powder formulations, which are not bioadhesive, the half-life for clearance is of the order of 15 - 30 min. The utilization of bio adhesive excipients within the formulations is an approach to overcome the rapid mucociliary clearance. The clearance can be reduced by depositing the formulation within the anterior and fewer ciliated part of the cavity thus resulting in improved absorption. [10-11]

Enzymatic degradation: Another contributing, but often less considered factor to the low bioavailability of peptides and proteins across the nasal mucosa is that the possibility of an enzymatic degradation of the molecule in the lumen of the cavity or during passage through the epithelial barrier. Both these sites contain exopeptidases like as mono and diamino peptidases which will cleave peptides at their N and C termini and endopeptidases like serine and cysteine, which mayattack internal peptide bonds. The use of enzyme inhibitors and/or saturation of enzymes could also be the approaches to overcome this barrier.[12]

Liposomes: Nasal formulations containing liposomes, microspheres or nanoparticles are the results of many research efforts. These systems can contain, besides the drug, enzymatic inhibitors, nasal absorption enhancers and/or mucoadhesive polymers so as to enhance stability, membrane permeation or/and retention time within the nasal cavity.It is small artificial vesicles of spherical shape which can beformed from cholesterol and natural non- toxic phospholipids. From the sizeand hydrophilic and hydrophobic character, liposomes are capable systems for drug delivery. Liposomes are extensively used as carriers of numerous molecules in cosmetic and pharmaceutical industries.[13]Liposomes are capable of trapping both hydrophobic and hydrophilic materials, preventing decomposition of the trapped varieties and releasing the trapped at destinations. Because of their biocompatibility, biodegradability, low toxicity and the ability to capture both hydrophobic and hydrophilic drugs and facilitate site-specific drug distribution, liposomes have evolved both as a testing tool and as a commercial drug delivery system.

Benefits of drug loading in liposomes: For drug delivery, liposomes can be formulated as a suspension, as an aerosol or in a semi solid form such as a gel, cream or drug powder.Liposomes increase therapeutic and

efficacy value of the drug.Liposomes increase stability of the drug. Liposomes are flexible, non-toxic, biocompatible, and totally biodegradable, Liposomes are non – immunogenic for systemic and non-systemic administrations.Liposomes reduce the toxicity of the excipients. Liposomes has Site avoidance effect.Liposomes protect to reduce the exposure of sensitive tissues to toxic drugs.

Classification of liposomes: [14] the liposomes can vary in size from very small (0.025 micrometer) to large (2.5 micrometer) vesicles. Moreover liposomes may have one or more bilayer.Based on their size and number of bilayer, liposomes can be classified into one or more categories.

Oligo Lamellar Vesicles: these are made of 2 to 10 bilayers of lipids surrounding a large internal volume.

Multilamellar Vesicles: multilayer vesicles liposomes are made from series of concentric bilayers of lipids enfolding a small internal volume.

Unilamellar Vesicles: these are made from single bilayer of lipids.

Small Unilamellar Vesicles: these liposomes ranging fromsize 20 to 40 nm.

Medium Unilamellar Vesicles: these liposomes ranging from size 40 to 80 nm.

Nasal gel: Nasal gel is the gel which is available in the solution form and when sprayed in the nose gets converted to gel under different stimuli.Gel is semisolid form between the liquid and solid which comprise of physically cross linked networks of long polymer molecules with liquid molecules trapped within a three dimensional polymeric network swollen by a solvent.[15]

Nasal *In-Situ* gel: Nasal In-situ gel is the typeof drug delivery system were the preparation of the drug in a solution form before administration in body, but it converts into gel form after administration.[16]An in-situ gel is formed of polymer materials that contain a solution or semi solid state that responds to the external stimuli at the administration site.

It is a new dosage form which has been applied as nasal drug delivery in recent times. Nasal in situ gels are introduced as low viscosity solutions into the nasal cavity and upon contact with the nasal mucosa, or nasal composition the polymer changes conformation producing a gel, so it cannot only prolong the contact time between the drug and therefore the absorptive sites within the nasal cavity, but also release drug slowly and continuously. Hence it leads into the very useful for those drugs used chronically.

Advantages of *In-Situ* Nasal Gel Drug Delivery: [17-20] In situ gel Increased residence time of drug in nasal cavity.Decreased frequency of drug administration.Rapid absorption and onset of effect.Avoids gastrointestinal tract degradation. Required low dose for therapeutic effect of drug.Minimized local and systemic side effects.Improved bioavailability of drug.

Approaches of *In Situ* gel drug delivery:here are three generally defined mechanisms used for triggering the in- situ gel formation of biomaterials: Physiological stimuli (e.g.temperature and pH)Physical changes in biomaterials (e.g.solvent exchange and swelling)Chemical reactions (e.g.enzymatic, chemical and photo-initiated polymerization)**In-situ formation based on physiological stimuli:Thermally triggered systems**:The use of biomaterials from sol-gel is produced by increase in temperature is an attractive way to approach in-situ formation. The ideal critical temperature range for such system is ambient and physiologic temperature, such that clinical manipulations is facilitated and no external source of heat other than that of body is required for the trigger gelation.[21]Temperature sensitive hydrogels are classified into three main categories:Negatively thermosensitive gels, Positively thermosensitive gels, Thermally reversible gels. Negative temperaturesensitive hydrogels have a lower critical solution temperature (LCST) and contract upon heating above the LCST. Polymers with low critical temperature (LCST) transition between sufficient and physiologic temperature is used for this purpose. Pluronics are triblock co-polymer that are fluid at low temperature, but forms thermo reversible gel

when heated as a consequences of an in-situ gelation.[22] The most commonly used thermoreversible gels are those prepared from poly (ethylene oxide) b-poly (propylene oxide) b-poly (ethylene oxide) (Pluronics, Tetronics, Poloxamer). Polymer solution is a free flowing liquid at ambient temperature and gels at body temperature.

pH Triggered Systems: This type of in-situ gel based on physiologic stimuli is formation of gel made by pH changes. All the pH–sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH. The polymers with a large number of ionisable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, and decreases if polymer contains weakly basic drugs.[23]The most anionic pH-sensitive polymers are based on PAA (Carbopol, Carbomers) or its derivatives. Drug formulated in liquid solutions have several restrictions, including limited bioavailability and propensity to be easily removed by tear fluid.

In-situ formation based on physical mechanism:

Swelling: There can also be in-situ forming as material absorbs water from the natural atmosphere and grows to fill ideal space.

Diffusion: This method requires the penetration of solvent from a polymer solution into the surrounding tissue and leads to the polymer matrix being precipitated or solidified.

In-situ formation based on chemical reactions: Chemical reactions resulting in in-situ gelation can include precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and processes undertaken photographically.

Ionic cross linking: In the presence of diverse ions, polymers can undergo phase transition. Any of the polysaccharides come into the range of those susceptible to ions.

Gellan Gum, commonly known as Gelrite, is an ionic polysaccharide which in the presence of mono and divalent cations, started to form gel in-situ, including Ca2 +, Mg2 +, K+ and Na+.

Enzymatic cross-linking: In situ formation catalysed by natural enzymes has not been extensively investigated yet appears to have certain advantages over chemical and photochemical approaches. For example, under physiological conditions, an enzymatic process operates effectively, without the need for potentially harmful chemicals such as monomers and initiators.Intelligent stimulus-responsive delivery systems were investigated using hydrogels which release insulin. The modification of the enzyme quantity also provides a handy mechanism for controlling the rate of gel formation which allows the mixture to be injected before gel formation.

Photo-Polymerization: Photo-polymerisation is widely used for biomaterial formation in situ. A monomer or reactive macromer and initiator agent can be injected into a tissue site and electromagnetic radiation treatment used to create a gel can be used.Acrylate or related polymerizable functional groups are usually used on the individual monomers and macromers as the polymerizable groups because they undergo rapid photo-polymerization in the presence of sufficient photoinitiators. Ultraviolet and visible wavelengths usually of long duration are used. Short wavelength ultraviolet is not used often because it has limited penetration of tissue and biologically harmful. [24]

Polymers Used In In-Situ Gel Drug Delivery System: For achieving better drug product effectiveness, reliability selection of appropriate polymer for the formulation is very essential. Materials that show sol to gel transition in aqueous solution are used in in-situ gelation. Some examples of polymers which are capable of in-situ gelation such as Poloxamer, Pluronics, various co-polymers such as PEO-PLLA and PEG-PLGA-PEG. Pectin, Gelrite, Cellulose acetophalate latex, Gellan gum, Alginate, Matrigel, Carbopol, and Chitin. The gel formation is induced by temperature change in case of Poloxamer, Cellulose, Acetophalate latex and in Carbopol gelation is induced by pH change.[25]

Application of intranasal in situ gel delivery: Intranasal delivery is a simple, cost-effective, easy, and non-invasive delivery system for targeting the brain. Throughthis system, various molecules, such as peptides, proteins,vaccines, analgesics, antidepressants, and antimalarial,antiepileptic, antimigraine, antiemetic, and anticonvulsantdrugs etc., are successfully administered to the target site.[26-27]

CONCLUSION:

Nasal drug delivery is an innovative vehicle and exciting alternative drug administration route for local, systemic, and central nervous system intervention that opens up fresh possibilities for drug distribution locally and systemically. It has benefits in terms of minimizing systemic exposure and therefore side effects and preventing metabolism from the first step. But the intranasal route also has several drawbacks that need to be addressed in order to develop a successful nasal drug. The most important factors influencing nasal absorption are physiological conditions, physicochemical properties of the drug and the formulation. The nasal mucosa provides in-situ gelling mechanism for controlled-release drug delivery. In-situ gels also provide a variety of other benefits, such as prolonged or sustained release of drug. For the past few decades, extraordinary and novel research has been identified in the literature on the temperature-sensitive, pH-induced and ion-induced gel-forming formulations. Using good biodegradable, biocompatible and water-soluble polymers to formulate in-situ nasal gels will make them as drug delivery systems better suited and excellent. Therefore extensive research is required to make this distribution route more effective and popular

Acknowledgement: The author wishes to thank Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Maharashtra, India, for providing guidance and support for this study.

REFERENCES:

1. Hussain A, Hamadi S, Kagoshima M, Iseki K, Dittert L. Does Increasing the Lipophilicity of Peptides Enhance their Nasal Absorption JPharm Sci.80: 1180-1181 (1991).
2. Frazen U, Vermehren P, Jensen H, Ostergaard J. Physiochemical Characterization of a PEGylated Liposomal Drug Formulation using Capillary Electrophoresis. Electrophoresis.32: 1-11 (2011).
3. Gopinath, P. G., Gopinath, G., Anand Kumar, T.C. Target site of intranasally sprayed substances and their transport across the nasal mucosa:A new insight into the intra nasal route of drug delivery, curr. Ther. (1978) Res.23:596.
4. Harris A: Review: Clinical opportunities provided by the nasal administration of peptides. Journal of Drug targeting.1(2):101-16 (1993)
5. Liang T, Davies M, Toth I. Encapsulation of Lipopeptides within Liposomes: Effect of number of Lipid Chains, Chain Length and Method of Liposome Preparation. International Journal of Pharmaceutics (2005); 301: 247
6. Liang T, Davies M, Toth I. Encapsulation of Lipopeptides within Liposomes: Effect of number of Lipid Chains, Chain Length and Method of Liposome Preparation. International Journal of Pharmaceutics (2005); 301: 247
7. Kamble M, Bhalerao K, Bhosale A, Chaudhari P. A Review on Nose to Brain Drug Delivery. International Journal of Pharmaceutical and Chemical Sciences (2013); 2(1):516
8. Kublik H, Vidgren MT. Nasal delivery systems and their effect on deposition and absorption. Adv Drug Deliv Rev., 29: 157-177,1998
9. Inagaki M, Sakakura Y, Itoh H, et al. Macromolecular permeability of the tight junction of human nasal mucosa. Rhinology. 23: 213-221,1985
10. Nilsson IM, Wagner ZG, et al. Intranasal administration of peptides: nasal deposition, biological response, and absorption of desmopressin. J Pharm Sci., 75:1085-1088,1986.
11. Pisal SS, Paradkar AR et al. Int. J Pharm.: 270: 374

12. Michael H, Lisbeth I. Intra Nasal Insulin Delivery and Therapy. Adv Drug Del Rev (1999); 35:199-234.
13. Osth K, Bjork G, Edsman K. Evaluation of Drug Release from Gel on Pig Nasal Mucosa in a Horizontal using Chamber. J. Control. Rel (2002); 83: 377-378.
14. Prashant K, Prashant W, Narkhede Y, Nehete J. Formulation & in vitro Evaluation of Thermoreversible Rizatriptan Benzoate Nasal Gel. International Journal of pharmacy & Pharmaceutical Science (2011); 3:250-256.
15. Balsubramanyam J, Kant S, Pandit K. In vitro and In vivo Evaluation of Gelrite Gellan Gum based Ocular Delivery System of Indomethacine. Acta pharma (2003); 53: 251-261
16. Cho E, Gwak H et al. Int J Pharm .: 349: 101-107,2008
17. Dondeti P, Zia H. Int. J. Pharm.: 127: 115-133,1996
18. Mehta MR, Surve SA et al. Ind J Pharm Sci.: 59: 153- 180, 2010
19. Talasahaz AHH, Ali A. J ApplPolym Sci.: 109: 23692374,2008
20. Costantino R, Sileno P, JohnsonH. Pharmacokinetic Attributes of Intranasal Delivery: Case Studies and New Opportunities. On Drug Delivery (2005); 3: 811.
21. Martin M, Hutchinson E, Hyde R, Peters E. Analysis of Structural Requirements for the Absorption of Drugs and Macromolecules from Nasal Cavity. J Pharm Sci (1987); 76: 535-543.
22. Mao K, Chen J, Wie Z, Lie H, Bi D. Intranasal Administration of Melatonin Starch Microspheres Int. J. Pharm(2004); 272: 37-43.
23. Masteikova R, Chalupova Z. Stimuli-Sensitive Hydrogels in Controlled and Sustained Drug Delivery. Biomaterials (2003); 28: 134–146.
24. Miyazaki S, Takeuch, S, Yokouchi C, Takada, M, Pluronic F-127 gels as vehicles for Topical administration of Anticancer Agents, Chem. Pharm. Bull, 32(10), , 42054208,1984.
25. Singh, K, Arora, N, Garg, T. RFID: a trustable security tool in pharmaceutical industry. Am J Pharm Tech Res. 2012
26. Singh, O, Garg, T, Rath, G, Goyal, AK. Microbicides for the treatment of sexually transmitted HIV infections. J Pharm.2014. 1–18