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An overview of Intranasal Thermoreversible In-situ Gel for brain-targeted drug delivery

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ABSTRACT

Intranasal delivery of drugs is a promising alternative for bypassing the blood-brain barrier, avoiding systemic side effects of pharmaceuticals, and reducing doses to be provided. The drug reaches the central nervous system through olfactory and trigeminal nerve pathways. Recent developments have been made in designing intranasal drug delivery systems for central nervous system therapies to the brain, with a particular focus on thermoreversible hydrogels. These hydrogels possess sol-to-gel transition in response to temperature changes. Various natural, synthetic and semi-synthetic polymers can use for the formulation of thermoversible hydrogels. The mucoadhesive polymers can be incorporated into the gel to improve the retention time of gel at the nasal mucosa. Different kinds of nasal drug delivery models, including *in vivo*, *in vitro* and *ex vivo* models can be employed to evaluate drug transporter interactions, drug absorption, permeability, toxicity, and electrophysiology in nasal mucosa.

INTRODUCTION

Intranasal administration is a simple and non-invasive way to enter the blood-brain barrier (BBB) and deliver therapeutic drugs to the brain and spinal cord. Oral drug delivery is a most simple and convenient method. But many pharmaceutically active materials have low oral bioavailability due to first-pass hepatic metabolism, low permeability across gastrointestinal tract and chemical/ proteolytic degradation [1]. The intranasal route is currently being explored as a possible administration site for central nervous system therapeutics in attempts to get over these limitations [2]. From the perspective of the pharmaceutical industry (no need to sterilize nasal preparations) and the patient (rapid onset of action, non-invasiveness, essentially painless, ease of delivery, favorable tolerability profile, improved patient compliance, ease of convenience, self-medication), intranasal administration offers several practical advantages. However; the primary rate-limiting constraints for nasal medication absorption are the nasal cavity's restricted capacity, hydrophilic molecules' low membrane permeability, and the mucociliary clearance effect's quickness. Because of this, research has primarily focused on using bioadhesive agents and/or permeation enhancers to develop delivery systems that can prolong the residence of formulations in the nasal cavity, thereby enhancing drug absorption and polar compound bioavailability. More recently, attention has been drawn to clever stimulus-responsive systems [3].

Anatomy of the human nasal cavity

The nose is responsible for multiple physiological functions such as olfaction and respiration. The nose can be divided into external nose and internal nose (nose cavity). The external nose is shaped like a triangular pyramid and is composed of bones and cartilage. It is located in the middle of the face. The external nose is attached to small muscle groups that are controlled by the facial nerve and contribute to facial expression. The nasal cavity (internal nose) extends around 12 cm in length from the external nose to the nasopharynx, and it is separated in two sections (left and right) by the nasal septum.

Structurally and functionally the nasal cavity can be divided into three regions: vestibular, olfactory, and respiratory [4].

The vestibular region, which is the smallest and outermost portion of the nasal cavity, its surface area is around 0.6 cm^2 and contains nasal hairs which serve to filter inhaled particles [5]. This

region composed of squamous epithelial cells. The drug absorption from this region is limited due to the smaller surface area. The respiratory region is the largest region which covers the lateral walls of the nasal cavities. There are four main categories of cells: goblet, ciliated, non-ciliated columnar and basal cells. Associated with some nasal glands, goblet cells release mucin to form the mucus layer. The key cells in the nasal cavity are called basal cells, which can differentiate into all other types as necessary [5]. The surface area of the ciliated and columnar cells is further increased by their abundance of microvilli and cilia. Due to its high degree of vascularity and huge surface area, the respiratory region is an excellent location for drug absorption into the systemic circulation as opposed to the central nervous system (CNS) [6]. The trigeminal nerve (V1, V2), which begins in the brainstem and innervates this respiratory region, presents an additional target nerve for drug delivery to the central nervous system (CNS) in addition to the olfactory pathway [7].

The transportation of molecules from the nasal cavity to the parenchyma of the brain occurs along both the olfactory or trigeminal nerves. Once the molecules are delivered to the origins of the nerves in the cerebrum and pons, respectively, they are able to distribute throughout the brain following certain pathways such as intracellular and extracellular pathways [5]. The intracellular mechanism starts with internalization of the molecule by an olfactory neuron, transporting of the endocytic vesicle within the cell to the neuron's projection site, and finally release via exocytosis. The drugs first enter the extracellular pathway by passing through the nasal epithelium and into the lamina propria, which is where the neurons are located. This is especially true in the olfactory region of the nasal cavity. From there, bulk flow processes carry the drug externally along the length of the neural axon. The axon leads into the CNS, where the drug is distributed further via fluid movement. The ability of molecules to cross the blood-CSF barrier and the blood-brain barrier is predicated by the penetration of drugs across endothelial cells in the lamina propria or from the subarachnoid CSF into the brain parenchyma [7].

Olfactory pathway

The olfactory pathway has been long considered to be the main pathway for the nose-to-brain delivery of drugs. Olfactory neuronal cells in the olfactory area terminate as olfactory receptors into the mucus layer and project into the olfactory bulb, creating a direct link between the nose and the central nervous system.

The drug cross olfactory epithelium by both paracellular and transcellular mechanisms. Lipophilic medications are transported across the olfactory epithelium by the transcellular pathway, which mostly involves sustentacular cells and passive diffusion or endocytosis (a fluid phase or receptor-mediated process), depending on the lipophilicity of the drug. In contrast, hydrophilic medications mostly penetrate the olfactory epithelium by means of paracellular diffusion, which occurs via tight junctions and/or clefts surrounding the olfactory neuron and sustentacular cells. This process is influenced by the molecular weight of the drug. Drugs are transported extracellularly to the central nervous system through the perineural space, within olfactory ensheathing cells and olfactory nerve fibroblasts, by bulk flow; once they have crossed the olfactory epithelium and reached the lamina propria [8]. Olfactory neural cells have ability to absorb some pathogens, large molecules such as enzymes and proteins, gold nanoparticles and aluminium salt etc [9].

Trigeminal pathway

The branches of the trigeminal nerve that connect to the respiratory and olfactory regions are part of the trigeminal pathway. The trigeminal nerve is divided into the ophthalmic, maxillary, and mandibular branches. These branches provide sensory information to the central nervous system from the nasal canal, ocular mucosa, and oral cavity. The ophthalmic and maxillary divisions innervate the nasal mucosa, making them the primary participants in the nose-to-brain pathway. The pons and the olfactory bulb, respectively, are the two distinct entry points into the central nervous system provided by the trigeminal branches [10].

The intra-axonal transport, via the trigeminal route, has been observed for several intranasally administrated agents such as lidocaine, insulin-like growth factor-I, interferon β, vascular endothelial grow factor, nanoparticles, etc [11].

Mucoadhesive Thermoreversible in-situ gel

By generating a temporary adhesion between the delivery system and the mucous membrane or epithelial cell surface, mucoadhesive or bioadhesive polymers increase the residence period of the delivery system. Since these polymers are not absorbed, systemic toxicity is unlikely to occur in them

The advantages of using mucoadhesive polymers as carries have some advantages like

a) An increased residence time within the nasal cavity.

b) Increased drug concentration at the site of deposition.

c) Facilitated drug permeation through the mucosa by opening the tight junction between the epithelial cells [12].

Mucoadhesive nasal delivery systems can be prepared as gel, spray, dry power solution, or microspheres. Nowadays, a variety of polymers are accessible that function as a mucoadhesive substances such polyacrylic acid, hydroxypropylcellulose, chitosan, carbopol, carboxymethylcellulose, and hyaluronic acid [13].

Thermo-responsive systems

The concept is to develop mucoadhesive formulations using polymers that show temperature-triggered sol-to-gel transitions between 25 and 37ºC. Various natural, synthetic thermosensitive polymers are used in various studies.

Synthetic thermo-responsive polymers

Poloxamer 407 is a frequently used mucoadhesive polymer with a track record for having thermosensitive qualities. Poloxamer 407 exhibits micellization that is dependent on temperature and concentration before transitioning to micellar packing and gel formation. The underlying mechanism of gel formation depending on temperature, suggests polymer desolvation accompanied with side chain conformational changes, resulting in displacement of the water molecules and modifications of micelles orientation. Poloxamer 407's thermoresponsive qualities have been heavily utilized in the development of In-situ nasal gels in conjunction with mucoadhesives, which are necessary to extend the formulation's residence time in the nasal cavity.

Influenced by the limited oral bioavailability of sumatriptan (15%), which is used to treat migraines, Majithiya et al [19]. used

Carbopol 934P and Poloxamer 407 to create an in situ gel. With decreasing Carbopol content, the gel's Tsol-gel temperature ranged from 23.9 8°C to 29 8°C. The decrease of the gelation temperature as a function of polymer concentration was partially attributed to the subsequent increase in viscosity following polymer dissolution. In comparison to the solution form, the gel formulation containing 0.3% carbopol demonstrated good mucoadhesive qualities and markedly increased the in vitro drug permeability without causing any structural flaws to the nasal membrane [14].

Due to the brain's limited capacity to absorb hydrophilic compounds, Gabal et al. had to choose to develop the anti-parkinsonian ropinirole hydrochloride using cationic and anionic nanostructured lipid carriers, which they then included into Poloxamer 188 in situ gels.

Natural thermo-responsive polymers

Xyloglucans are a class of naturally occurring, thermosensitive compounds found in plants that can change from sol to gel forms when the temperature rises. Based on this, xyloglucan In-situ gels with ondansetron hydrochloride as a model medication were created by Mahajan et al. Following a 4-hour ex vivo research on sheep nasal mucosa, gel formulations containing 2.5% (w/w) xyloglucan showed good gel strength values and almost complete drug penetration. When the in situ gel was supplied intranasally to rabbits, the bioavailability values were much higher than when the drug solution was administered orally, indicating the promise of this formulation.

Natural polysaccharide chitosan is produced by N-deacetylating chitin and is regarded as a biocompatible and biodegradable polymer with mucoadhesive qualities.

In an attempt to create a system for the delivery of the antidepressant doxepin, Naik and Nair created thermosensitive gels with glycerophosphate and chitosan (2%, w/v) in both the presence and absence of polyethylene glycol. PEG addition greatly increased drug retardation but had no effect on gelation temperature. Both formulations demonstrated appropriate compatibility with the nasal epithelium while also demonstrating efficacious antidepressant action. Given that doxepin has a weak and inconsistent absorption when taken orally (1345%), nasal delivery of the medication is highlighted as a potentially effective substitute [15].

Synthetic thermo-responsive derivatives from natural polymers

When co-formulated with polyethylene glycol and glycerophosphate, chitosan derivatives (TMC) exhibited thermosensitive behavior with varying average molecular weights and degrees of quaternization. With a Tsol-gel at 32.5 8°C, the gels containing TMC with a medium average molecular weight and low degree of quaternization had remarkable mucoadhesive activity and rheological characteristics, suggesting that they might be used for nasal distribution .

Models for testing direct nose-to-brain delivery

Nasal drug delivery models can be used to analyze drug absorption, permeability, PK/PD, toxicology, and electrophysiology, and also to assess drug transporter interactions and the nasal barrier. Nasal delivery of drugs studies often involve *in vitro*, *in vivo*, and *ex vivo* models. *In vitro* methods are able to investigate permeability and diffusion, whereas in vivo models may describe nasal absorption and determine drug pharmacokinetic profiles. *Ex vivo* techniques are able to study nasal perfusion.

***In vivo* models**

For carrying out *in-vivo* nasal absorption tests, it's essential to first understand the structure of the animal's nasal cavity. Rat was the first animal model used, but absorption studies on rabbit, sheep, dog, and monkey were used as well. Mouse and rat models are suitable for studying drug absorption from nose to brain. Rabbit, dog, and sheep models are more commonly used to conduct pharmacokinetic investigations. However; results of studies obtained from animal models do not always correlate well with those of humans, because of the anatomical and physiological differences of their nasal cavities.

Nasal administration of medicine generally involves inserting a pipette or a polyethylene tube attached to a micropipette around 3 mm (in mice) or 5 mm (in rats) into the nostrils. In a study conducted Westin et al., mice received 5 µl and rats received 50 µl of intranasal administration. The medication was administered into the right nostril (right-sided administration), allowing the left olfactory bulb to serve as control [16].

***In vitro* models**

In vivo studies are crucial for nasal drug absorption and permeation tests. However, *in vitro* research can provide an improved knowledge of the mechanisms of nasal absorption and transport. Nasal absorption and permeability are determined employing two cell lines: RPMI 2650 and CaCo-2. The cellular models' receiving lumen fails to accurately represent the necessary transfer from the mucosa to the receiving nerves.

a) RPMI 2650 a cell culture model of the nasal barrier

RPMI 2650 is derived from human nasal epithelial tissue, namely squamous cell carcinoma of the nasal septum, which occurs spontaneously. A cell culture model based on human RPMI 2650. This cell line, which grows into multilayers rather than monolayers, is frequently used in investigations on nasal metabolism and toxicity [17].

b) CaCo-2 cell line

The CaCo-2 cell line, which has been used for three decades, is a reliable model for evaluating nasal absorption of formulations.

***Ex vivo* models**

To test the harmful effects of excipients and transmucosal transport of drugs, nasal mucosa from laboratory or slaughtered animals are typically used *ex vivo*. *Ex vivo* animal tissue models can be obtained from rats, rabbits, dogs, sheep, monkeys, and even humans. *Ex vivo* models are limited by the thickness of animal nasal epithelial tissues and the absence of interstitial flow beneath the mucosa. So extrapolating permeability data to *In vivo* models might be challenging.

Intranasal administration of various medicines for CNS diseases

Intranasal delivery of CNS medicines will help in crossing the BBB, limiting peripheral adverse effects, and rapid elimination via first pass metabolism. Intranasal (IN) administration is an alternative approach to intravenous delivery. Intranasal delivery of insulin-like growth factor 1 (IGF-1) resulted in much higher CNS exposure than intravenous dosage [18]. IN drug administration has been used to treat a range of CNS-related

diseases, which includes obesity, eating disorders, Alzheimer's disease, Parkinson's disease, Huntington disease, depression, anxiety, autism, seizures, addiction, and stroke. New promising drugs are now being researched for IN use.

Marketed products and clinical studies

Research has focused on producing In-situ gelling systems using pectins, a natural polysaccharide. PecFent1, a pectin-based system contains fentanyl, was licensed for marketing in Europe in 2009 and the United States in 2011[19]. The FDA has approved human testing for an inactivated H5N1 influenza vaccine with the GelVac1 nasal powder formulation, having a phase I clinical research currently underway [20].

CONCLUSION

Intranasal drug delivery offers a promising and innovative approach to drug administration; it enhances bioavailability, efficacy, and patient compliance. Direct drug delivery to the brain is possible by olfactory and trigeminal nerve pathways. Mucoadhesive thermoreversible in-situ gel is suitable for intranasal delivery of many drugs. It has been used to treat a range of CNS-related diseases, which include obesity, eating disorders, Alzheimer's disease, Parkinson's disease, Huntington disease, depression, anxiety, autism, seizures, addiction, and stroke. The Nasal drug delivery models such as *in-vitro*, *in-vivo*, and *ex-vivo* models can be used to analyze drug absorption, permeability, PK/PD, toxicology, and electrophysiology in the nasal mucosa.

REFERENCES

1. Varma, M.V. et al. (2010) Physicochemical space for optimum oral bioavailability: contribution of human intestinal absorption and first-pass elimination. J. Med. Chem. 53, 10981108
2. Wang, Z.; Xiong, G.; Tsang, W.C.; Schätzlein, A.G.; Uchegbu, I.F. Nose-to-Brain Delivery. J. Pharm. Exp. 2019, 370, 593601.
3. Illum, L. et al. (2003) Nasal drug delivery-possibilities, problems and solutions. J. Control. Release 87, 187198
4. Gänger, S.; Schindowski, K. Tailoring Formulations for Intranasal Nose-to-Brain Delivery: A Review on Architecture, PhysicoChemical Characteristics and Mucociliary Clearance of the Nasal Olfactory Mucosa. Pharmaceutics 2018, 10, 116.
5. Erdő F, Bors LA, Farkas D, Bajza Á, Gizurarson S. Evaluation of intranasal delivery route of drug administration for brain targeting. Brain research bulletin. 2018 Oct 1;143:155-70.
6. Arora, P., Sharma, S., Garg, S., 2002. Permeability issues in nasal drug delivery. Drug Discov. Today 7, 967975.
7. Crowe, T.P., Greenlee, M.H.W., Kanthasamy, A.G., Hsu, W.H., 2018. Mechanism of intranasal drug delivery directly to the brain. Life Sci. 195, 4452.
8. Thorne, R.G.; Pronk, G.J.; Padmanabhan, V.; Frey Ii, W.H. Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administra-tion. Neuroscience 2004, 127, 481496.
9. Van Riel, D.; Leijten, L.M.; Verdijk, R.M.; Kessel, G.C.; van der Vries, E.; van Rossum, A.M.; Kuiken, T. Evidence for influenza virus CNS invasion along the olfactory route in an immunocom-promised infant. J. Infect. Dis. 2014, 210, 419423.
10. Clerico, D.; To, W.; Lanza, D. Anatomy of the Human Nasal Passages. In Handbook of Olfaction and Gustation; Apple Academic Press: Palm Bay, FL, USA, 2003; pp. 116.
11. Thorne, R.G.; Hanson, L.R.; Ross, T.M.; Tung, D.; Frey, W.H., II. Delivery of interferon-beta to the monkey nervous system following intranasal administration. Neuroscience 2008, 152, 785797.
12. Abd El-Hameed M.D, Kellaway I.W. Preparation and in vitro characterization of mucoadhesive polymeric microsphere as intra-nasal delivery system. Eur. J. of Pham. And Biopharm. 1997; 44: 53- 60.
13. Sakagami M, Kinoshita W, Sakon K, Sato JI, Makino Y. Mucoadhesive beclomethasone microspheres for powder inhalation: Their pharmacokinetics and phamacodynamics evaluation. J. Control. Release. 2002; 80: 207-218.
14. Majithiya, R.J. et al. (2006) Thermoreversible-mucoadhesive gel for nasal delivery of sumatriptan. AAPS Pharm. Sci. Tech. 7, 67.
15. Naik, A. and Nair, H. (2014) Formulation and evaluation of thermosensitive biogels for nose to brain delivery of doxepin. Biomed. Res. Int. Article ID 847547.
16. Westin, U., Piras, E., Jansson, B., Bergström, U., Dahlin, M., Brittebo, E., Björk, E., 2005. Transfer of morphine along the olfactory pathway to the central nervous system after nasal administration to rodents. Eur. J. Pharm. Sci. 24, 565573.
17. Kürti, L., Gáspár, R., Márki, Á., Kápolna, E., Bocsik, A., Veszelka, S., Bartos, C., Ambrus, R., Vastag, M., Deli, M.A., Szabó-Révész, P., 2013. In vitro and in vivo characterization of meloxicam nanoparticles designed for nasal administration. Eur. J. Pharm. Sci. 50, 8692.
18. Schiöth, H.B., Craft, S., Brooks, S.J., Frey, W.H., Benedict, C., 2012. Brain insulin signaling and Alzheimer's disease: current evidence and future directions. Mol. Neurobiol. 46, 410.
19. Lyseng-Williamson, K.A. (2011) Fentanyl pectin nasal spray: in breakthrough pain in opioid-tolerant adults with cancer. CNS Drugs 25, 511522.
20. Velasquez, L.S. et al. (2011) Intranasal delivery of norwalk virus-like particles formulated in an in situ gelling, dry powder vaccine. Vaccine 29, 52215231

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