

Mechanisms and solutions for nasal drug delivery – a narrative review

S. ULUSOY^{1,2}, N. BAYAR MULUK³, S. KARPISCHENKO⁴, G.C. PASSALI⁵,
H. NEGM⁶, D. PASSALI⁷, M. MILKOV⁸, G. KOPACHEVA-BARSOVA⁹,
I. KONSTANTINIDIS¹⁰, M. DILBER¹¹, C. CINGI¹²

¹Department of Otorhinolaryngology, Medical Faculty, Halic University, Istanbul, Turkey

²Istanbulthe Private Clinic, Istanbul, Turkey

³Department of Otorhinolaryngology, Faculty of Medicine, Kirikkale University, Kirikkale, Turkey

⁴Department of Otorhinolaryngology, The First Pavlov State Medical University of Saint Petersburg, Saint Petersburg, Russia

⁵Head and Neck Department, Università Cattolica del Sacro Cuore, Otorhinolaryngology and Head and Neck Surgery Unit, Fondazione Policlinico Universitario "A. Gemelli"- IRCCS, Rome, Italy

⁶Department of Otorhinolaryngology, Faculty of Medicine, Cairo University, Cairo, Egypt

⁷Department of Medical, Surgical and Neuroscience Sciences, Department of Otorhinolaryngology, University of Siena, Siena, Italy

⁸Department of Otorhinolaryngology, Faculty of Medicine, Varna University, Varna, Bulgaria

⁹Department of Otorhinolaryngology, Faculty of Medicine, Cyril and Methodius University of Skopje, Skopje, Republic of North Macedonia

¹⁰Second Academic Department of Otorhinolaryngology, Academic Faculty of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

¹¹Otorhinolaryngology Section, Dilber Private Clinic, Istanbul, Turkey

¹²Department of Otorhinolaryngology, Medical Faculty, Eskisehir Osmangazi University, Eskisehir, Turkey

Abstract. – The aim of this paper is to review mechanisms and solutions for nasal drug delivery.

Literature survey was performed via PubMed, Google Scholar, Google, and ProQuest Central database of Kirikkale University.

The nasal lining presents a large area of endothelium of variable permeability and with a rich vascular supply. Advantages of this route include eliminating first-pass metabolism and being easily accessible. The nasal route enables some agents which are otherwise difficult to administer to enter the systemic circulation, for example, low molecular mass compounds with high polarity, peptides, or proteins. There are three principal factors that influence the extent to which drugs can be absorbed through the nasal lining, namely the physico-chemical characteristics of the drug molecule itself, the action of the mucociliary system within the nose, and the presence of any factors increasing nasal absorption. A key factor limiting the use of the intranasal route of administration is insufficient absorption through the nasal mucosa.

A number of drugs in development cannot be administered intranasally because their bioavailability following nasal administration is too low. There has been considerable research focus on methods to enhance absorption via the

nasal mucosa. In this chapter, we review the literature related to this problem and discuss potential solutions.

Key Words:

Nasal drugs, Delivery, Mechanism, Mucociliary system, Bioavailability, Absorption.

Introduction

The delivery of drugs *via* the nose is sometimes used for agents that can otherwise only be delivered intravenously. The nasal lining presents a large area of endothelium of variable permeability and with a rich vascular supply. Advantages of this route include eliminating first-pass metabolism and being easily accessible. There is rapid absorption of medications administered intranasally which allows for rapid systemic bioavailability to occur. This chapter addresses several different methods for improving the duration over which medications remain in contact with the nasal mucosa, thereby increasing the bioavailability of these agents¹.

The nasal route enables some agents which are otherwise difficult to administer to enter the systemic circulation, for example, low molecular mass compounds with high polarity, peptides, or proteins. This route is even suitable for the high molecular weight proteins or polysaccharides which are components of vaccinations, including the DNA plasmids utilised in vaccines based on DNA².

Use of the nose for delivery of medications goes back several hundred years. The respiratory tract is a key interface between the body and the surrounding environment. As such, it represents a potential portal of entry for pathogens, either bacterial or viral, but also an alternative route of administration for pharmacotherapeutic agents. Within the 20th century, intranasal medications were essentially confined to topical agents used in the treatment of seasonal allergic rhinitis or upper respiratory tract infections. However, within the last 20 years, intranasal delivery has achieved more prominence as a way of administering systemically agents to treat a wider variety of conditions, for example circulatory disorders. It was not until 1991 that the first agent used in treatment of a neurological disorder was administered *via* the nasal route. At that time, a patent was applied for by William Frey II for a method to transport medications to the central nervous system *via* the nasal route³. This development sparked increasing enthusiasm for intranasal administration of drugs generally, but especially in the rapidly developing area of nose-to-brain delivery (NTB). The greatest advantage of NTB agents is that they more readily enter the central nervous system than when the intravenous route is used, since they effectively bypass the blood-brain barrier. Conventional methods of delivering agents to the central nervous system are invasive, but NTB delivery is a non-invasive method for drugs to enter the CNS. This is achieved through their penetrating the olfactory or fifth cranial nerve. Different pharmaceutical formulations involve different ways for the agent to be absorbed, both into cells and *via* the extracellular matrix. The agent passes from the nasal interior into the more central portions of the central nervous system. Design of an appropriate pharmaceutical formulation needs to take into account the degree to which the agent is absorbed into the systemic vasculature, lymphatics and/or the cerebrospinal fluid. Biological treatments have already been developed for a number of specific neurological conditions, whilst some disorders still lack an effective therapeutic biolog-

ical agent. A common feature of these biologics is the promise of superior clinical efficacy and diminished adverse effects in comparison with agents in current licensed usage for systemic delivery. Furthermore, a more efficient route of administration should allow lower doses than those currently employed to be effective. Although several pharmaceutical formulations delivered by the nose do currently exist, using this route for the treatment of neurological disorders is an area which continues to present many difficulties⁴.

Factors Affecting the Absorption of Medications through the Nasal Lining

There are three principal factors that influence the extent to which drugs can be absorbed through the nasal lining, namely the physico-chemical characteristics of the drug molecule itself, the action of the mucociliary system within the nose, and the presence of any factors increasing nasal absorption. A key factor limiting the use of the intranasal route of administration is insufficient absorption through the nasal mucosa. A number of drugs in development cannot be administered intranasally because their bioavailability following nasal administration is too low. There has been considerable research focus on methods to enhance absorption *via* the nasal mucosa. In this research, we review the literature related to this problem and discuss potential solutions.

Literature survey was performed *via* PubMed, Google Scholar, Google, and ProQuest Central database of Kırıkkale University.

Physicochemical Characteristics of Medications

A number of different physicochemical parameters influence the speed and degree to which drugs may be absorbed. These parameters include the partition coefficient of the medication between the aqueous and lipid compartments of the body, pKa, the molecular mass of the agent, the rate of perfusion, the volume of perfusate, the acidity of the solution and the concentration of the agent⁵. For drug molecules, the mass of which is below 300 Daltons, the physicochemical characteristics of the drug do not meaningfully affect the extent to which it can be absorbed⁶. However, the molecular mass, expressed logarithmically, does usually correlate directly with the degree of nasal absorption, also expressed logarithmically⁷.

Clearance by the Mucociliary System

Mucus acts as a trap for small particles within the nose and, as the mucus is cleared by the mucociliary mechanism, these particles are also removed from the interior of the nose. The cilia and mucus act together to provide this protective mechanism. In this way, potentially harmful inhaled particles can be removed without the need for specific recognition⁸. The time between a particle being captured by the mucus layer and removed from the nose is reported in the literature as between 12 and 15 minutes⁹. There are a number of different factors which can influence the extent and rate of mucociliary clearance. These factors include age, gender, the sleeping condition whether asleep or awake¹⁰ and at rest or exercising¹¹. Furthermore, atmospheric pollution, such as sulphur dioxide, sulfuric acid, nitrogen, hairspray or cigarette smoke, affects mucociliary clearance, as does the presence of specific disorders, notably those affecting the motility of the cilia, such as primary ciliary dyskinesia (e.g., Kartagener Syndrome), asthma, bronchiectasis, chronic bronchitis, cystic fibrosis or acute infections of the respiratory system¹². Medications¹³ and some food additives^{2,14} also affect mucociliary function.

Barriers Preventing the Absorption of Medications

In order for a medication to be absorbed, the first stage is for the active component within the formulation, i.e. the drug itself, to be transported to the initial barrier. Respiratory drugs need to reach the lining epithelium of the airway before they can be absorbed. Following absorption, drugs undergo metabolism before they are finally cleared from the body. For absorption of an active drug to occur in a satisfactory manner, it may need to be formulated in such a way that it is released variably as it passes across several different barriers in the body. Some of the barriers which respiratory drugs must overcome are the mucus layer, the epithelium, the basement membrane and connective tissues and the endothelial lining of the capillaries¹⁵.

The initial obstacle is the mucus layer. A drug that reaches the mucus layer must either dissolve in it or cross the mucus before it can be broken down by proteolytic enzymes in the mucus or physically removed by the mucociliary system. Since mucociliary clearance occurs within a few minutes, any addition to the formulation which aims

to increase barrier permeability and thereby the bioavailability of the drug, must act quickly. Techniques developed to assist with drug transit across the mucus layer need to take into account how thick this layer is and how rapidly clearance occurs. Within the pulmonary tissues, the mucus lining the lumina is between 5 and 10 microns in depth¹⁶. There is also, deep to the mucus, another layer with lower viscoelasticity, termed the periciliary liquid. This liquid coats the cilia and adds a further 5 to 10 microns of depth to the initial barrier¹⁶. Research^{17,18} using confocal fluorescence microscopic techniques has ascertained that the mucous depth may vary from 5 to 55 microns. In comparison with lower portions of the respiratory tract, the nose is lined by a relatively thin layer of mucus and this layer has both greater permeability and is more readily accessed than elsewhere in the tract¹⁹. Within the nose, any particles trapped in mucus flow at a rate of around 5 millimeters each minute. The entire mucus layer is replaced within intervals of around 20 minutes^{20,21}.

After the mucus layer, intranasally administered drugs must transit the outer plasma membrane of the epithelial cells. The epithelium is of pseudostratified type. The cells have a columnar morphology and are tightly bound to each other by intercellular zonulae occludentes. Absorption of the majority of drugs occurs by diffusion across the outer plasma membrane of the mucosal cells. Lipophilic drug molecules of low molecular weight diffuse across the plasma membrane due to the concentration gradient alone, however, non-lipophilic drugs typically can only cross the membrane through specific transport channels. Drugs of high molecular weight which are polarized can undergo absorption by paracellular transfer, in which case they must be able to get past the intercellular junction proteins¹⁵.

Absorption Enhancers

Absorption enhancers are additional ingredients in pharmaceutical formulations, the purpose of which is to facilitate increased passage of the agent past barriers to absorption. Research²² into absorption enhancers dates back a long time and has been applied to agents which are typically blocked by barriers, such as peptides or biologicals. Ideally, an absorption enhancing excipient should prevent the active ingredient being modified enzymatically and facilitate rapid passage across the barrier for the specific agent¹⁵.

The key absorption enhancers under current development include four different types: (a) surface active agents (surfactants), (b) cyclodextrins, (c) protease inhibitors, (d) cationic polymers, and (e) tight junction modulators¹⁵.

Surface Active Agents

Surface active agents contain both a hydrophilic and hydrophobic portion, i.e., they are amphiphilic. Surface active agents are employed in the lungs for a range of pharmacotherapeutic objectives, not merely to increase absorption²³. These excipients may improve absorption through various mechanisms, such as causing membrane proteins to be lost from the cell outer membrane, loosening of intercellular adhesion complexes, or preventing the action of degradative enzymes that would otherwise inactivate the drug²⁴. Surface active agents have been most extensively investigated for agents given by mouth. Nonetheless, a small literature exists for surfactants employed in increasing absorption across nasal or pulmonary membranes. There are five classes of surface-active agents with the ability to increase absorption, namely phospholipids²⁵, bile acids (including sodium taurocholate)²⁶, non-ionic compounds²⁴, the salts of aliphatic acids²⁷ and alkyl glycosides, such as tetradecylmaltoside or *N*-lauryl- β -D-maltopyranoside^{15,28}.

Enzyme Inhibitors

The liquid and mucus that coats the lumen of the air passages is rich in various enzymes, in particular proteases and nucleases. These enzymes can inactivate drugs, preventing absorption²⁹. Most of the enzymes present are either serine proteases or aminopeptidases. Their ubiquity in pulmonary tissues presents a major obstacle to active agents entering the lining cells of the airways. In particular, these enzymes are highly efficient at degradation of peptides, proteins or nucleic acids, all of which may be used as therapeutic agents. This situation may call for an excipient with the ability to inhibit enzymatic attack to be included in formulations to aid absorption. There have been several excipients studied within the last ten years that can prevent proteolysis by proteases and have been added to formulations of nasal or pulmonary medications. These include nafamostat mesilate³⁰, aprotinin³¹, bacitracin³², soybean trypsin inhibitor³², phosphoramidon³³, leupeptin³⁴, and bestatin³⁵. One study^{31,32} used a rat model for pulmonary drug delivery to evaluate absorption enhancers added to formulations of insulin and eel calcitonin.

This study looked at compounds capable of inhibiting proteases (aprotinin, bacitracin, and soybean trypsin) acting together with other types of absorption enhancer, namely sodium glycocholate, linoleic acid-surfactant mixed micelles, and *N*-lauryl- β -D-maltopyranoside.

Cationic Polymers Acting as Absorption Enhancers

Cationic polymeric molecules contain positively charged moieties, either as part of the main chain or on side chains³⁶. This type of molecule can increase the degree to which macromolecular drugs are absorbed³⁷. Examples of cationic polymers used in this way are positively charged gelatines, pullulans, poly-L-arginine, poly(iminoethylene) and chitosan. These absorption enhancers act on the mucosal surface, causing alterations in the intercellular adhesion molecules and allowing high molecular weight, hydrophilic molecules to cross the barrier. Insulin, for example, is negatively charged in a neutral environment, where it interacts with the positively charged absorption enhancers and thereby is more readily absorbed. When insulin interacts to a moderate extent with the cationic polymer, this allows the hormone to approach the plasma membrane. If there is too much interaction, however, insulin is actually less likely to be absorbed. Poly(iminoethylene) is a positively charged, highly hydrophilic molecule which appears promising as an absorption enhancer for intranasally administered drugs. In a rat model, the absorption of extraneous insulin by the lung was enhanced by poly(iminoethylene). Since there was a linear correlation between the charge on the molecule and the degree of absorption, it appears that electrostatic interactions play a key role in how it exerts this useful effect^{15,38}.

Tight Junction Modulators

The intercellular spaces in epithelia are closed off by tight junctions (zonulae occludentes). Paracellular absorption of drugs can be enhanced by modifying the zonula occludens. This route, however, can only be effectively utilised where a molecule is of moderate molecular weight and does not exceed 11Å in radius. A low bioavailability is a feature common to many water-soluble medications of low molecular mass, or those consisting of peptides or proteins. The paracellular route of absorption has been demonstrated to occur in certain peptide medications, in particular octreotide, desmopressin and thyrotropin-releasing hormone,

with zonulae occludentes controlling how this may occur³⁹. Tight junction modulators possess high potency for loosening zonulae occludentes, including the claudins and occludin. They are, in fact, 400 times more potent than other agents capable of achieving this effect⁴⁰. Most research currently focuses on their role in administering drugs via the gut or skin⁴¹⁻⁴³ or overcoming the blood-brain barrier⁴⁴. However, there have been two studies focusing on the respiratory system, namely the lung, as a route of administration¹⁵.

Further Potential Methods for Increasing Drug Absorption

Liposomes

Liposomal delivery has been investigated for several different routes. One study, undertaken by Alpar et al⁴⁵, examined how liposomes may increase the efficacy of tetanus toxoid immunization. They looked at using liposomes to aid delivery *via* the mucosae of the nose or mouth and intramuscularly. These were then compared with delivery in a simple solution. The aim was to offer an alternative to the current parenteral route of vaccine administration, and one which provokes vigorous systemic immunity. Tetanus toxoid delivered in 1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC) liposomes remained unaltered and was absorbed through the intestinal lining⁴⁵. Another study⁴⁶ compared liposomal-wrapped insulin with a simple solution of insulin. The liposomal preparation was either pretreated with sodium glycocholate or left untreated. These three alternative formulations were applied to rabbit nasal mucosa. The highest level of absorption occurred with the liposomal preparation pretreated by sodium glycocholate^{1,46}.

Dextran Microspheres

Bioadhesive microspheres of known composition were evaluated by Illum et al⁴⁷ in terms of their remaining *in situ* following application to the nasal mucosa. The most persistent type were the DE-AE-dextran microspheres, with 60% still resident in the nasal interior 3 hours after administration⁴⁷. When the same type of microsphere was applied to the problem of insulin delivery, using a rat model, the results were concerning⁴⁸. The bonds between insulin and DEAE resisted dissolution at physiological solute concentrations. It was further noted that the freeze-drying process had affected the structure of the insulin-containing microspheres, and these

structural alterations potentially also inhibited release of insulin from the delivery vehicle^{1,49}.

Gels

There has also been research addressing the use of chitin or chitosan in modified release formulations. Gel formulations were prepared using indomethacin and papaverine as examples of typical medications. Chitin included within gel preparations acted to ensure sustained release, unlike when present as a powder⁵⁰. Chitosan in negatively charged, polymeric form possessed greater ability to adhere to mucosal surfaces than polycarbophil, in a study undertaken by Lehr et al⁵¹. These authors propose distinguishing between the ability of a dry polymer to adhere to mucosal surfaces exposed to air and the situation where adhesion occurs between the mucosa and a saturated hydrogel, i.e., liquid-to-liquid⁵¹. Studies^{1,52} have examined the absorption of nifedipine by the nasal mucosa in a rat model where the delivery vehicle was in gel form, i.e., PEG 400, aqueous carbopol or carbopol-PEG. The PEG formulation permitted nifedipine to be swiftly absorbed and a high C_{max} to be obtained, although plasma clearance was undesirably high. The carbopol preparation resulted in minimal plasma nifedipine levels. However, although gels containing PEG400 do permit good bioavailability, this solution suffers from the disadvantage that PEG400 irritates the nasal lining when present at a concentration above 10%.

Bile Acid Salts and Surface-Active Agents

The bile salts most frequently added as excipients are the sodium salts of cholic, deoxycholic, glycocholic, taurocholic, taurodeoxycholic and glycodeoxycholic acid⁵³. There are numerous studies which have concluded that these molecules offer benefit as pharmaceutical excipients in medications for intranasal application, but caution is required as irritation to the lining of the nose has been noted when bile salts are present at concentrations exceeding 0.3%^{1,54}.

Intranasal Administration for Topical Effects

Medications designed to act topically are frequently delivered to the nasal lining by nasal sprays or as aerosolised liquids⁵⁵. This type of delivery has the advantage of moistening the nasal cavity alongside spreading the agent across a large surface area of nasal mucosa, which is the goal of topical application⁵⁶. The principal constraints in developing

and using such aqueous liquid formulations is ensuring they remain sterile during manufacture and use and the need to add preservatives. The preservatives may, unfortunately, trigger hypersensitivity or irritate the mucosa^{55,57}. Development of better spray formulations is an area of constant activity, leading to progressively longer times for the active agent to remain before being cleared and ensuring more uniform deposition of the agent, eliminating variation due to, e.g., the position of the head when the spray is used. One example of highly optimised metered-dose inhalers are those for budesonide^{4,57}, inhaled particles were reported as adhere nasal mucosa; and ciliary activity carries mucus^{58,59}, therefore distribution of the particles occur.

Antihistamines and corticosteroids are commonly employed as treatments of choice for rhinitis, whether allergic, seasonal allergic or infectious. They reduce nasal blockage. The method of delivery is usually intranasal application⁶⁰. Topical preparations are beneficial in terms of rapid action. In addition, the low systemic bioavailability associated with intranasal application is an advantage for these agents, since it lowers the potential for side effects, including neurological effects. Furthermore, intranasal doses of corticosteroid or antihistamine are less than those required when these agents are given by mouth^{60,61}. Antihistamines have been in clinical use for symptomatic relief of allergic rhinitis for around one hundred years. Antihistamines of the second generation do not cause excess sedation and produce fewer side effects when used intranasally than when given by mouth. They are selective for the H1 receptor^{62,63}. An example of a second-generation antihistamine is levocabastine. Nasal corticosteroids are also frequently administered to patients with seasonal allergic rhinitis. These agents are anti-inflammatory and attach themselves to the cytoplasmic glucocorticoid receptor. Their mode of action is transactivation or transrepression, resulting in inhibition of inflammatory responses. Corticosteroids modulate cytokine and other immunomodulatory signal release, in addition to lessening the recruitment of cells involved in inflammation to the nasal lining⁶⁴. There are several licensed corticosteroid preparations available, including budesonide, flunisolide, fluticasone, mometasone and triamcinolone^{4,61}.

In acute rhinosinusitis (ARS patients), sodium hyaluronate and saline solution were given to the patients in a nebulizer ampoule; and it was reported to improve the symptoms⁶⁵.

Combination therapies of intranasal corticosteroid (INCS) and intranasal antihistamine

(INAH) was recommended in allergic rhinitis^{66,67}. INCS/INAH combination therapy reduced total nasal symptom scores more than INCS monotherapy; and also increased the total mean Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) score^{66,67}.

Nasal Lysine Aspirin Desensitization in Aspirin Exacerbated Respiratory Disease (AERD)

In AERD patients, nasal challenge can be performed by using lysine aspirin(L-ASA) which is the soluble form of aspirin^{68,69}. In this method, highly aspirin-sensitive patients react at low doses. Nasal symptoms mainly develop, and asthma exacerbation were detected in a little group of patients. It is reported as safe method for aspirin desensitization^{68,69}.

Use of the Nasal Route to Administer Systemic Drugs

Besides the use of intranasal application for topical nasal treatment, the use of this route for systemic drug delivery may also be undertaken. This then allows for pharmacotherapeutic treatment of a wide range of disorders. Currently, there is considerable research focusing on this latter possibility. Studies^{70,71} have been undertaken for treatments used in migraine, headache, microbial prophylaxis, analgesia, hormone replacement therapy and to aid in quitting smoking. It is also a potential route for emergency treatment, e.g. in epilepsy. This research is motivated by the perceived advantages of the intranasal route for systemic pharmacotherapy. The nasal lining provides a considerable surface area from which absorption can occur, although the precise extent of absorption and subsequent bioavailability varies according to the active agent, pharmaceutical formulation and delivery vehicle. Different animal models produce different results. According to Costantino et al⁷², there is a consistently high level of bioavailability for drugs of low molecular mass, whereas the bioavailability of high molecular mass drugs by this route is low and inconsistent, compared with parenteral administration^{72,73}. The abundant vascular supply to the nasal interior is an especially key factor in choosing this route. Moreover, the time to the onset of effect is low, drugs do not undergo first pass metabolism and administration is not invasive, therefore patients find this type of administration less painful and more acceptable than injection^{74,75}.

Conclusions

A number of drugs in development cannot be administered intranasally because their bio-availability following nasal administration is too low. There has been considerable research focus on methods to enhance absorption *via* the nasal mucosa. In this chapter, we review the literature related to this problem and discuss potential solutions.

Conflict of Interest

The authors declare that there is no conflict of interest.

Funding

There are no funds for this article.

Authors' Contributions

Seçkin Ulusoy: Planning, designing, literature survey, active intellectual support.

Nuray Bayar Muluk: Planning, designing, literature survey, active intellectual support, writing, submission.

Sergei Karpischenko: Planning, designing, literature survey, active intellectual support.

Giulio Cesare Passali: Planning, designing, literature survey, active intellectual support.

Hesham Negm: Planning, designing, literature survey, active intellectual support.

Desiderio Passali: Planning, designing, literature survey, active intellectual support.

Mario Milkov: Planning, designing, literature survey, active intellectual support.

Gabriela Kopacheva-Barsova: Planning, designing, literature survey, active intellectual support.

Iordanis Konstantinidis: Planning, designing, literature survey, active intellectual support.

Muhammet Dilber: Planning, designing, literature survey, active intellectual support.

Cemal Cingi: Planning, designing, literature survey, active intellectual support. No funding was obtained from any companies or organisations for this study.

ORCID ID

Seçkin Ulusoy: 0000-0003-1689-1103

Nuray Bayar Muluk: 0000-0003-3602-9289

Sergei Karpischenko: 0000-0002-2159-6793

Giulio Cesare Passali: 0000-0002-8176-0962

Hesham Negm: 0000-0002-7516-9930

Desiderio Passali: 0000-0002-4791-012X

Mario Milkov: 0000-0003-0794-7355

Gabriela Kopacheva-Barsova: 0000-0002-2917-7921

Iordanis Konstantinidis: 0000-0002-9244-464X

Muhammet Dilber: 0000-0001-5835-3181

Cemal Cingi: 0000-0003-3934-5092

References

- 1) Türker S, Onur E, Ozer Y. Nasal route and drug delivery systems. *Pharm World Sci* 2004; 26: 137-142.
- 2) Illum L. Nasal drug delivery--possibilities, problems and solutions. *J Control Release* 2003; 87: 187-198.
- 3) Keller LA, Merkel O, Popp A. Intranasal drug delivery: opportunities and toxicologic challenges during drug development. *Drug Deliv and Transl Res* 2022; 12: 735-757.
- 4) Frey WH III. Neurologic agents for nasal administration to the brain. Available at: <https://pubchem.ncbi.nlm.nih.gov/patent/WO-9107947-A1> (Accessed: October 11, 2022).
- 5) Chien YW. Nasal drug delivery systems. In: Swarbrick J, editor. *Novel drug delivery systems*. New York: Marcel Dekker 1992; 139-196.
- 6) Hussain AA. Intranasal drug delivery. *Adv Drug Del Rev* 1998; 29: 39-49.
- 7) Fisher AN, Brown K, Davis SS, Parr GD, Smith DA. The effect of molecular size on the nasal absorption of water-soluble compounds in the albino rat. *J Pharm Pharmacol* 1987; 39: 357-362.
- 8) Schipper NGM, Verhoef JC, Merkus HM. The nasal mucociliary clearance: relevance to nasal drug delivery. *Pharm Res* 1991; 8: 807-814.
- 9) Merkus FW, Verhoef JC, Schipper NG, Marttin E. Nasal mucociliary clearance as a factor in nasal drug delivery. *Adv Drug Deliv Rev* 1998; 29: 13-38.
- 10) Hasani A, Agnew JE, Pavia D, Vora H, Clarke SW. Effect of oral bronchodilators on lung mucociliary clearance during sleep in patients with asthma. *Thorax* 1993; 48: 287-289.
- 11) Wolff RK, Dolovich MB, Obminski G, Newhouse MT. Effects of exercise and eucapnic hyperventilation on bronchial clearance in man. *J Appl Physiol* 1977; 43: 46-50.
- 12) Verra F, Escudier E, Lebargy F, Bernaudin JF, Crémoux HD, Bignon J. Ciliary abnormalities in bronchial epithelium of smokers, ex-smokers, and non-smokers. *Am J Respir Crit Care Med* 1995; 151: 630-634.
- 13) Haxel BR, Schäfer D, Klimek L. Prostaglandin E2 activates the ciliary beat frequency of cultured human nasal mucosa via the second messenger cyclic adenosine monophosphate. *Eur Arch Otorhinolaryngol* 2001; 258: 230-235.
- 14) Cho JH, Kwun YS, Jang HS, Kang JM, Won YS, Yoon HR. Long-term use of preservatives on rat nasal respiratory mucosa: effects of benzalkonium chloride and potassium sorbate. *Laryngoscope* 2000; 110: 312-7.
- 15) Ghadiri M, Young PM, Traini D. Strategies to Enhance Drug Absorption via Nasal and Pulmonary Routes. *Pharmaceutics* 2019; 11: 113.

- 16) Sleight MA, Blake JR, Liron N. The propulsion of mucus by cilia. *Am Rev Respir Dis* 1988; 137: 726-741.
- 17) Clunes MT, Boucher RC. Cystic fibrosis: The mechanisms of pathogenesis of an inherited lung disorder. *Drug Discov Today Dis Mech* 2007; 4: 63-72.
- 18) Verkman AS, Song Y, Thiagarajah JR. Role of airway surface liquid and submucosal glands in cystic fibrosis lung disease. *Am J Physiol Cell Physiol* 2003; 284: C2-C15.
- 19) Rosen H, Aribat T. The rise and rise of drug delivery. *Nat Rev Drug Discov.* 2005; 4: 381-385.
- 20) Ali MS, Pearson JP. Upper airway mucin gene expression: A review. *Laryngoscope* 2007; 117: 932-938.
- 21) Mainardes RM, Urban MC, Cinto PO, Chaud MV, Evangelista RC, Gremiao MP. Liposomes and micro/nanoparticles as colloidal carriers for nasal drug delivery. *Curr Drug Deliv* 2006; 3: 275-285.
- 22) Helmstadter A. Endermatic, epidermatic, enepidermatic-the early history of penetration enhancers. *Int J Pharm* 2011; 416: 12-15.
- 23) Shubber S, Villasaliu D, Rauch C, Jordan F, Illum L, Stolnik S. Mechanism of mucosal permeability enhancement of CriticalSorb® (Solutol® HS15) investigated in vitro in cell cultures. *Pharm Res* 2015; 32: 516-527.
- 24) Li Y, Li J, Zhang X, Ding J, Mao S. Non-ionic surfactants as novel intranasal absorption enhancers: In vitro and in vivo characterization. *Drug Deliv* 2016; 23: 2272-2279.
- 25) Brockman JM, Wang ZD, Notter RH, Dluhy RA. Effect of hydrophobic surfactant proteins sp-b and sp-c on binary phospholipid monolayers ii. Infrared external reflectance-absorption spectroscopy. *Biophys J* 2003; 84: 326-340.
- 26) Johansson F, Hjertberg E, Eirefelt S, Tronde A, Bengtsson UH. Mechanisms for absorption enhancement of inhaled insulin by sodium taurocholate. *Eur J Pharm Sci* 2002; 17: 63-71.
- 27) Ghadiri M, Canney F, Pacciana C, Colombo G, Young PM, Traini D. The use of fatty acids as absorption enhancer for pulmonary drug delivery. *Int J Pharm* 2018; 541: 93-100.
- 28) Chen-Quay SC, Eiting KT, Li AWA, Lamharzi N, Quay SC. Identification of tight junction modulating lipids. *J Pharm Sci US* 2009; 98: 606-619.
- 29) Candiano G, Bruschi M, Pedemonte N, Musante L, Ravazzolo R, Liberatori S, Bini L, Galletta LJ, Zegarra-Moran O. Proteomic analysis of the airway surface liquid: Modulation by proinflammatory cytokines. *Am J Physiol Lung Cell Mol Physiol* 2007; 292: L185-L198.
- 30) Morita T, Yamamoto A, Takakura Y, Hashida M, Sezaki H. Improvement of the pulmonary absorption of (Asu1,7)-eel calcitonin by various protease inhibitors in rats. *Pharm Res* 1994; 11: 909-913.
- 31) Yamamoto A, Umemori S, Muranishi S. Absorption enhancement of intrapulmonary administered insulin by various absorption enhancers and protease inhibitors in rats. *J Pharm Pharmacol* 1994; 46: 14-18.
- 32) Yamamoto A., Fujita T., Muranishi S. Pulmonary absorption enhancement of peptides by absorption enhancers and protease inhibitors. *J. Control. Release.* 1996; 41: 57-67.
- 33) Kobayashi S, Kondo S, Juni K. Study on pulmonary delivery of salmon calcitonin in rats: effects of protease inhibitors and absorption enhancers. *Pharm Res* 1994; 11: 1239-1243.
- 34) Yamahara H, Morimoto K, Lee VH, Kim KJ. Effects of protease inhibitors on vasopressin transport across rat alveolar epithelial cell monolayers. *Pharm Res* 1994; 11: 1617-1622.
- 35) Machida M, Hayashi M, Awazu S. The effects of absorption enhancers on the pulmonary absorption of recombinant human granulocyte colony-stimulating factor (rhg-csf) in rats. *Biol Pharm Bull* 2000; 23: 84-86.
- 36) Schulz JD, Gauthier MA, Leroux JC. Improving oral drug bioavailability with polycations? *Eur J Pharm Biopharm* 2015; 97: 427-437.
- 37) Seki T. Enhancement of insulin absorption through mucosal membranes using cationic polymers. *Yakugaku Zasshi* 2010; 130: 1115-1121.
- 38) Zhang H, Huang X, Sun Y, Lu G, Wang K, Wang Z, Xing J, Gao Y. Improvement of pulmonary absorption of poorly absorbable macromolecules by hydroxypropyl- β -cyclodextrin grafted polyethylenimine (hp- β -cd-pei) in rats. *Int J Pharm* 2015; 489: 294-303.
- 39) Pauletti GM, Okumu FW, Borchardt RT. Effect of size and charge on the passive diffusion of peptides across Caco-2 cell monolayers via the paracellular pathway. *Pharm Res* 1997; 14: 164-168.
- 40) Smedley JG, Saputo J, Parker JC, Fernandez-Miyakawa ME, Robertson SL, McClane BA, Uzal FA. Noncytotoxic clostridium perfringens enterotoxin (cpe) variants localize cpe intestinal binding and demonstrate a relationship between cpe-induced cytotoxicity and enterotoxicity. *Infect Immun* 2008; 76: 3793-3800.
- 41) Nakajima M, Nagase S, Iida M, Takeda S, Yamashita M, Watari A, Shirasago Y, Fukasawa M, Takeda H, Sawasaki T, Yagi K, Kondoh M. Claudin-1 Binder Enhances Epidermal Permeability in a Human Keratinocyte Model. *J Pharmacol Exp Ther* 2015; 354: 440-447.
- 42) Saaber D, Wollenhaupt S, Baumann K, Reichl S. Recent progress in tight junction modulation for improving bioavailability. *Expert Opin. Drug Dis* 2014; 9: 367-381.
- 43) Uchida H, Kondoh M, Hanada T, Takahashi A, Hamakubo T, Yagi K. A claudin-4 modulator enhances the mucosal absorption of a biologically active peptide. *Biochem Pharmacol* 2010; 79: 1437-1444.

- 44) Helms HC, Waagepetersen HS, Nielsen CU, Brodin B. Paracellular tightness and claudin-5 expression is increased in the bcec/astrocyte blood-brain barrier model by increasing media buffer capacity during growth. *AAPS J* 2010; 12: 759-770.
- 45) Alpar HO, Bowen JC, Brown MRW. Effectiveness of liposomes as adjuvants of orally and nasally administered tetanus toxoid. *Int J Pharm* 1992; 88: 335-344.
- 46) Maitani Y, Asano S, Takahashi S, Nakagaki M, Nagai T. Permeability of insulin entrapped in liposome through the nasal mucosa of rabbits. *Chem Pharm Bull* 1992; 40: 1569-1572.
- 47) Illum L, Jorgensen H, Bisgaard H, Krogsgaard O, Rossing N. Bio-adhesive microspheres as a potential nasal drug delivery system. *Int J Pharm* 1987; 39: 189-199.
- 48) Rydén L, Erdman P. Effects of polymers and microspheres on the nasal absorption of insulin in rats. *Int J Pharm* 1992; 83: 1-10.
- 49) Morath LP. Microspheres as nasal drug delivery systems. *Adv Drug Deliv Rev* 1998; 29: 185-194.
- 50) Witschi C, Mrsny R. In vitro evaluation of microparticles and polymer gels for use as nasal platforms for protein delivery. *Pharm Res* 1999; 16: 382-390.
- 51) Lehr CM, Bouwstra JA, Schacht EH, Junginger HE. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers. *Int J Pharm* 1992; 78: 43-48.
- 52) Morimoto K, Tabata H, Morisaka K. Nasal absorption of nifedipine from gel preparations in rats. *Chem Pharm Bull* 1987; 35: 3041-3044.
- 53) Romeo VD, deMeireles JC, Gries WJ, Xia WJ, Sileno AP, Pimplaskar HK, Behl CR. Optimization of systemic nasal drug delivery with pharmaceutical excipients. *Adv Drug Deliv Rev* 1998; 29: 117-133.
- 54) Brime B, Ballesteros MP, Frutos P. Preparation and in vitro characterization of gelatin microspheres containing Levodopa for nasal administration. *J Microencap* 2000; 6: 777-784.
- 55) Djupesland PG. Nasal drug delivery devices: characteristics and performance in a clinical perspective—a review. *Drug Deliv Transl Res* 2013; 3: 42-62.
- 56) Kublik H, Vidgren M. Nasal delivery systems and their effect on deposition and absorption. *Adv Drug Deliv Rev* 1998; 29: 157-177.
- 57) Hussein NR, Omer HK, Elhissi AM, Ahmed W. Advances in nasal drug delivery systems. In *Advances in Medical and Surgical Engineering*. Academic Press 2020: 279-311.
- 58) Duran M, Ulkü CH. Effect of radiofrequency thermal ablation treatment on nasal mucociliary clearance in patients with isolated inferior turbinate hypertrophy. *Kulak Burun Bogaz Ihtis Derg (Turkish Journal of Ear, Nose and Throat)* 2014; 24: 185-189.
- 59) Yildiz S, Yankuncu A, Zer Toros S, Tepe Karaca Ç. Nasal Mucociliary Clearance and Sinusoidal Symptoms in Healthcare Professionals Wearing FFP3 Respirators: A Prospective Cross-Sectional Study. *ORL J Otorhinolaryngol Relat Spec* 2022; 84: 406-411.
- 60) Pires A, Fortuna A, Alves G, Falcão A. Intranasal drug delivery: how, why and what for? *J Pharm Pharm Sci* 2009; 12: 288.
- 61) Salib RJ, Howarth PH. Safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis. *Drug Saf* 2003; 26: 863-893.
- 62) Janssens MM, Vanden Bussche G. Levocabastine: an effective topical treatment of allergic rhinoconjunctivitis. *Clin Exp Allergy* 1991; 21 Suppl 2: 29-36.
- 63) Hampel FC, Martin BG, Dolen J, Travers S, Karcher K, Holton D. Efficacy and safety of levocabastine nasal spray for seasonal allergic rhinitis. *Am J Rhinol* 1999; 13: 55-62.
- 64) Barnes PJ. Molecular mechanisms of glucocorticoid action in asthma. *Pulm Pharmacol Ther* 1997; 10: 3-19.
- 65) Ciofalo A, Zambetti G, Altissimi G, Fusconi M, Soldo P, Gelardi M, Iannella G, Pasquariello B, Magliulo G. Pathological and cytological changes of the nasal mucosa in acute rhinosinusitis: the role of hyaluronic acid as supportive therapy. *Eur Rev Med Pharmacol Sci* 2017; 21: 4411-4418.
- 66) Kim M, Ryu G, Kang S-Y, Kim M-A, Yang S-I, Lee IH, Choi G-S, Kim H-J, Lee SM, Kim D-K, Choi JH, Yang H-J, Kim SW, Work Group for Rhinitis, the Korean Academy of Asthma, Allergy and Clinical Immunology. Intranasal antihistamine and corticosteroid to treat allergic rhinitis: A systematic review and meta-analysis. *Allergy* 2022; 77: 3436-3440.
- 67) Bousquet J, Schünemann HJ, Togias A, Bachert C, Erhola M, Hellings PW, Klimek L, Pfaar O, Wallace D, Ansotegui I, Agache I, Bedbrook A, Bergmann KC, Bewick M, Bonniaud P, Bosnic-Anticevich S, Bossé I, Bouchard J, Boulet LP, Brozek J, Brusselle G, Calderon MA, Canonica WG, Caraballo L, Cardona V, Casale T, Cecchi L, Chu DK, Costa EM, Cruz AA, Czarlewski W, D'Amato G, Devillier P, Dykewicz M, Ebisawa M, Fauquet JL, Fokkens WJ, Fonseca JA, Fontaine JF, Gemiciglu B, van Wijk RG, Haahela T, Halken S, Ierodiakonou D, Inuma T, Ivancevich JC, Jutel M, Kaidashvili I, Khaitov M, Kalayci O, Kleine Tebbe J, Kowalski ML, Kuna P, Kvedariene V, La Grutta S, Larenas-Linnemann D, Lau S, Laune D, Le L, Lieberman P, Lodrup Carlsen KC, Lourenço O, Marien G, Carreiro-Martins P, Melén E, Menditto E, Neffen H, Mercier G, Mosques R, Mullol J, Muraro A, Namazova L, Novellino E, O'Hehir R, Okamoto Y, Ohta K, Park HS, Panzner P, Passalacqua G, Pham-Thi N, Price D, Roberts G, Roche N, Rolland C, Rosario N, Ryan D, Samolinski B, Sanchez-Borges M, Scadding GK, Shamji MH, Sheikh A, Bom AT, Toppila-Salmi S, Tsiligianni I, Valentin-Rostan M, Valiulis A, Valovirta E, Ventura MT, Walker S, Wasserman S,

- Yorgancioglu A, Zuberbier T; Allergic Rhinitis and Its Impact on Asthma Working Group. Next-generation Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines for allergic rhinitis based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and real-world evidence. *J Allergy Clin Immunol* 2020; 145: 70-80.e3.
- 68) Miller B, Mirakian R, Gane S, Larco J, Sannah AA, Darby Y, Scadding G. Nasal lysine aspirin challenge in the diagnosis of aspirin - exacerbated respiratory disease: asthma and rhinitis. *Clin Exp Allergy* 2013; 43: 874-880.
- 69) Milewski M, Mastalerz L, Nizankowska E, Szczeklik A. Nasal provocation test with lysine-aspirin for diagnosis of aspirin-sensitive asthma. *J Allergy Clin Immunol* 1998; 101: 581-586.
- 70) Stamegna JC, Girard SD, Veron A, Sicard G, Khrestchatisky M, Feron F, Roman FS. A unique method for the isolation of nasal olfactory stem cells in living rats. *Stem Cell Res* 2014; 12: 673-679.
- 71) Ghadiri M, Young P, Traini D. Strategies to enhance drug absorption via nasal and pulmonary routes. *Pharmaceutics* 2019; 11: 113.
- 72) Costantino HR, Illum L, Brandt G, Johnson PH, Quay SC. Intranasal delivery: physicochemical and therapeutic aspects. *Int J Pharm* 2007; 337: 1-24.
- 73) Behl C, Pimplaskar H, Sileno A, deMeireles J, Romeo V. Effects of physicochemical properties and other factors on systemic nasal drug delivery. *Adv Drug Deliv Rev* 1998; 29: 89-116.
- 74) Ghadiri M, Young P, Traini D. Strategies to enhance drug absorption via nasal and pulmonary routes. *Pharmaceutics* 2019; 11: 113.
- 75) Battaglia L, Panciani PP, Muntoni E, Capucchio MT, Biasibetti E, De Bonis P, Mioletti S, Fontanella M, Swaminathan S. Lipid nanoparticles for intranasal administration: application to nose-to-brain delivery. *Expert Opin Drug Deliv* 2018; 15: 369-378.