Maciej Koźmiński, Maciej Kupczyk

Department of Internal Diseases, Asthma and Allergy, Medical University of Lodz, Poland

Thixotropy of nasal medications — its role in clinical practice

Tiksotropia leków donosowych — znaczenie w praktyce klinicznej

The authors declare no financial disclosure

Abstract

Optimal medication should be characterized by good bioavailability, rapid onset of action, a long period of therapeutic activity, with preserved high safety profile and the lowest possible risk of side effects. Therefore, in addition to traditional drug administration routes, such as oral or injection, novel methods for drug applications, for example in the form of a nasal application have been developed. Because of the anatomy of the nose, drugs administered intranasally can be rapidly absorbed and, depending on the nature of the active substance, may act locally on the mucosa or can have a significant systemic effect. Most nasal drugs are developed in the form of solution administered as aerosol. In some cases, these solutions are thixotropic. They are able to change their physical properties under agitation to facilitate supply of the drug and its adhesion to the mucosa. Intranasal corticosteroids represent the mainstay of treatment for any form of chronic allergic rhinitis (AR) and moderate to severe periodic AR, especially with impaired nasal obstruction and frequent occurrence of symptoms. The article discusses the rheological properties of intranasal corticosteroids, their role in therapy and efficacy in the everyday clinical practice.

Key words: nasal spray, thixotropy, adhesion, nasal glucocorticosteroids

Pneumonol Alergol Pol 2015; 83: 157–163

Streszczenie

Optymalny lek powinien charakteryzować się bardzo dobrą przyswajalnością, szybkim początkiem działania, długim okresem aktywności terapeutycznej, przy zachowanym wysokim profilu bezpieczeństwa i najniższym możliwym ryzyku działań niepożądanych. Dlatego oprócz tradycyjnych dróg podawania leków, jak doustna czy iniekcyjna, wprowadza się nowe metody ich podaży, na przykład w postaci aplikacji donosowej. Ze względu na warunki anatomiczne nosa leki podawane donosowo mogą być szybko wchłaniane i w zależności od charakteru substancji czynnej działać miejscowo na błonę śluzową lub mieć wpływ ogólnoustrojowy. Preparaty donosowe najczęściej mają postać roztworu aplikowanego w postaci aerozolu. W niektórych przypadkach roztwory te mają charakter tiksotropowy, czyli zmieniają swe własności fizyczne pod wpływem wstrząsania, co ułatwia podaż leku i jego przyleganie do śluzówki. Glikokortykosteroidy donosowe są podstawą leczenia każdej postaci przewlekłego alergicznego nieżytu nosa (ANN) oraz umiarkowanej i ciężkiej postaci okresowego ANN, zwłaszcza przy upośledzeniu drożności nosa i częstym występowaniu objawów. W artykule omówiono właściwości reologiczne glikokortykosteroidów donosowych oraz ich miejsce w terapii i skutecznośc w codziennej praktyce klinicznej.

Słowa kluczowe: aerozol donosowy, tiksotropia, adhezja, glikokortykosteroidy donosowe

Pneumonol Alergol Pol 2015; 83: 157–163

Address for correspondence: dr hab. n. med. Maciej Kupczyk, Klinika Chorób Wewnętrznych, Astmy i Alergii UM, ul. Kopcińskiego 22, 90–153 Łódź, Polska, tel/fax: +48 42 677 69 51, e-mail: maciej.kupczyk@umed.lodz.pl

DOI: 10.5603/PiAP.2015.0025
Received: 13.01.2015

ISSN 0867–7077

Introduction

Intranasal administration of the drugs could be used either as an application route of topic drugs used in patients with upper airways diseases or as an alternative route of absorption of systemic drugs with low bioavailability or high molecular weight, such as proteins, peptides or steroids. To date many drugs have been successfully used intranasally, including drugs constricting the vessels of nasal mucosa (α-mimetics — e.g. adrenaline, xylomethazoline, cholinolytics — ipratropium bromide), mucolytics (mesna), antihistaminic drugs (azelastine), glucocorticosteroids (e.g. budesonide, beclomethasone, fluticasone, mometasone), chromones (e.g. sodium cromoglicate, nedocromil), antibiotics (mupirocin, neomycin). The systemic drugs which could be administered intranasally include hormones (e.g. calcitonin, insulin, and vasopressin) and antihypertensive agents (e.g. hydralazine, propranolol, nifedipine). Another group constitute immunomodulatory drugs e.g. vaccines (e.g. anti-influenza) and allergens-containing extracts used in specific immunotherapy. To note, some of intranasally administered drugs could penetrate into central nervous system (CNS) passing the blood-brain barrier (e.g. apomorphine, buprenorphine, cocaine).

Pharmacological aspects of intranasal therapy

Relatively large nasal mucosal surface area and its extensive vascularization enable effective absorption, which in practice leads to fast therapeutical effect. Due to bypassing of portal circulation the absorbed substances avoid the first-pass effect and metabolism in liver. Additionally, the enzymatic activity of nasal mucosa is lower as of gastrointestinal tract mucosa and this enhances the bioavailability of proteins and peptide. The lower risk of overdose in comparison to other routes of administration is also of importance, and in case of need to remove the excess of a drug the nasal cavities could be irrigated. Moreover, easy and non-invasive way of administration of the drugs improves the compliance and patient's adherence.

It should be underlined, that, as all the other administration routes, nasal application of the drugs have some limitations. Speed of absorption in different parts of nasal cavity varies. Natural sneeze reflex could eliminate some portion of the drug and estimation of the amount of removed drug is usually impossible. Intranasally administered agents should not irritate the mucosa. Another natural mechanism of eliminating of the drugs is mucociliary clearance. The single dose of applied drug should not be too large to not disturb the physiological functions of nose cavity, and thus the volume of single application should not exceed 25–200 μl. Different abnormalities of nasal mucosa could impair the absorption, as well as the administration of the substances of molecular weight of more than 1kDa [1].

Anatomy and physiology of the nose

Nose is the first section of the upper respiratory tract. It contributes to gas exchange though air transportation, which is warmed, moisturized and cleared during inspiration. According to excessive vascularization and innervation the nose also plays a role in reflexive immune reactions, intending to eliminate external harmful factors [2]. Nose is the organ of smell. Intrinsic surface of the nose cavities is covered by mucosa, stretching away on nose-lacrimal ducts, maxillary, ethmoidal, sphenoidal and frontal paranasal sinuses as well as nasal part of pharynx. The mucosa of nose consists of multilayered ciliated epithelium with cilia, which are moving with frequency of up to 1000 movements per minute [3]. The mucociliary clearance speed is estimated of about 5 mm/min. It means that half-time of the clearance of mucosa takes app. 15 minutes [4]. The mucosal surface is in folds and additionally enlarged owing to presence of microvilli, which number is estimated of app. 400 on each cell. The total mucosal surface area is estimated of app. 150−160 cm^2. As compared to the mucosa in other organs and tracts, the nasal mucosa in relatively thin and basal layer is more porous. In physiological situation the nasal mucosa produces app. 160 mL mucus discharge daily. It is estimated that number of mucus glands in nose cavities amount app. 10^5. The mucus layer of the thickness of about 5 μm is two-layered with external gel layer as well as internal layer of sol. The mucus consists of water in 95%, 2% of mucine, 1% — proteins such as immunoglobulins, albumins, lysozyme and lactoferrin 1% — the salts and lipids below of 1%. Stability and permeability of mucus layer is based on surface tension, connected to the presence of phospholipids. These heterogeneous microparticles are built of peptic core and incorporated oligosaccharide chains. Verdugo et al. [5] proposed the model in which randomly tangled macromolecules are connected forming the loose net. The inflammatory cells, e.g. neutrophils and eosinophils could alter the physicochemical properties of mucus. Disintegration of cells of contained DNA cause

the binding of glycoproteins of mucus discharge. Mentioned changes in the mucus structure could lead to changes of its physicochemical properties, which subsequently could negatively impact on absorption of drugs built of proteins and peptide.

In allergic rhinitis, after allergen exposure, specific IgE antibodies bound to the high affinity IgE receptor (FcξRI) on mast cells are cross linked by allergen which leads to degranulation of mast cells and release of preformed mediators (including histamine) and synthesis of several pro-inflammatory cytokines and chemokines. Symptoms of acute allergic reaction including itching and sneezing are followed by nasal obstruction which is associated with edema of nasal mucosa, influx of proinflammatory cells, mucus production due to stimulation of glandular cells and extravasation from capillaries. Influx of immunocompetent cells (eosinophils, basophils, lymphocytes T) is led by chemokines (RANTES, eotaxin, Il-8). Other proinflammatory cytokines: Il-1 and TNF-α induce expression of selectins and VCAM-1 which improve the migration of cells. Several cytotoxic proteins released from eosinophils and basophils lead to tissue damage, decrease in mucociliary clearance, and desquamation of the epithelium. In conclusion patomechanisms involved in chronic inflammation in allergic rhinitis are complex and include activation and migration of inflammatory cells, vascular dilatation, increase and changes of glandular activity, activation of nerve endings, onset of a neurogenic inflammation and morphologically demonstrable alterations in the nasal mucosa.

Intranasal drugs application

The particles of a drug, administered by pressure application are deposited in target location, which is nasal mucosa surface covered by mucus. They are further spontaneously spread on mucosa surface according to the concentration gradient, e.g. diffusion. The migration of the particles through the mucosa depends on its properties of mucus layer, such as size of mucus bowls, as well as the properties of applied substance which are as follow:

— the size of particle (smaller particles move faster as compare to larger ones),
— dissociation rate — nondissociated substances diffuse faster than substances with negative charge,
— solubility in lipids — with more solubility the diffusion of particles is easier.

Of note is that quite fast diffusion of relatively large particles, enclosed by liposomes, niosomes or microspheres has been observed. Some of the drugs are transported actively, due to mechanism of transcytosis, with the use of transport proteins and intracellular channels [6, 7].

The separate aspect is delivering the intranasally administered drugs to CNS. Olfactory area located in the upper part of nasal cavity is the only part of CNS directly contacting with external environment. The particles of the drug deposited on this area migrate through the mucosa according to the mechanism already mentioned or could be transferred using axonal transport by projections of the olfactory neurons to the olfactory bulb placed in the basal part of the telencephalon. This is the way the active substance could reach CNS bypassing the blood-brain barrier [4].

Intranasal drug as a fluid under mechanics rules

The **suspension** is the physical system of at least two substances, in which the solid bodies particles (e.g. drug) are dispersed in the external phase, usually liquid (diluter). The homogeneity of the suspension depends on the size of dispersed particles and viscosity of diluter. In case that density of dispersed phase is higher than diluter the dispersed particles could go down which is called **sedimentation**. In this phenomenon the particles of the fluid are able to freely move relative to each other. Forces of friction between moving particles or layers created by themare called **viscosity**. The viscosity depends on small distances between liquid particles as well as connecting cohesive forces. The viscosity is greater with greater cohesive forces and greater friction resistance within the liquid. The **coagulation** of the liquid means the flow of liquid layers moving relative to each, and decreasing of the flow speed is called the **speed of coagulation**.

According to the viscosity the fluids could be divided to so-called newtonian liquids (with stable viscosity) and so-called non newtonian liquids (with changeable viscosity). The latter among others encompass the suspensions. The viscosity of non newtonian liquids, called structural viscosity, depends not only on the size and shape of dispersed particles but also on their volume and electric charge. In some non newtonian liquids the changers of internal structure could be observed, caused by energy delivered by coagulation forces. **Thixotropy** or "liquid memory" describes the relation between viscosity of such liquid end duration of acting of coagulation forces, for example the decreasing of the viscosity of thixotropic liquid under intensive blending and shaking. This pro-

cess is reversible and after some time the previous viscosity of the fluid is restored [8].

On the molecular level thixotropy is connected with presence of the forces of intermolecular interactions. Relative moving of the atoms and particles closer to each other results in the changes of distribution of the electrons in their structure and in inducing mild electromagnetic field. Within this field van der Waals forces, hydrogen bonds, interactions as well as dipole-dipole interactions could be detected. Spatial structure of the substance is based on the shape of particles and magnitude of intermolecular interactions. In liquids prone to coagulation the acting of the forces leads to breaking the weaker physical bonds and structural disintegration of the medium. This is multistep process, progressing proportionally to the coagulation time and magnitude of coagulative forces. During this process there is possibility to organize the particles system along the vector of coagulative forces (which takes place in solutions of polymers) and transformation from semisolid into semiliquid state of matter in gels (e.g. in sol).

The two terms **chronothixotropy** and **mobilothixotropy** could help to describe this phenomenon more precisely. Chronothixotropy means the speed in which the internal structure of the liquid is disintegrated with stable speed of coagulation. The measure of structural disintegration of liquid under increasing speed of coagulation is mobilothixotropy. The structure of liquid, including thixotropic ones, is characterized by some degree of stiffness. Disintegration of that structure relies on the speed of destruction of the interactions. The rebuilding of those interactions could lead do restoration. The stable state achievement is possible when the disintegration as well as building of new intermolecular interaction speeds are the same. The stiffness of the fluid is described by the force of maximum tension which is needed to total disintegration of internal structure of suspension previously in rest and is called the **floating limit** of thixotropic fluid.

The time needed to disintegration as well as restoration of internal structure of fluid is not stable. The rheological properties of the fluid change with duration of time, leading to „aging" of the solution. These changes are irreversible and connected with increasing of stiffness and viscosity of the liquid. The particles of the liquid start to form smaller conglomerates and some of them undergo sedimentation. The conformations of the chains of particles and force of relative organic joints could also be changed.

Similarly to thixotropy, the energy of electric or magnetic field could alter the viscosity of some substances. [8] Thixotropy is confused with pseudoelasticity, which is also based on decreasing of viscosity under acting of coagulative forces, but after yielding the substance is restored only partially and its structure remains changed irreversibly. The attention should be drawn to the liquids, which viscosity is increasing under the coagulation, and that phenomenon is called **anti-thixotropy** [9]. **Rheology** (Gr. *rhéō* — flow, *logos* — science) is the field of knowledge exploring the relationships between deformation of continuous medium and triggering forces.

Rheological properties of intranasal drugs

The topical intranasal aerosols are in the formulation of suspension with thixotropic properties. They are characterized by high basal viscosity, which considerably diminishes sedimentation speed of the drug's particles. After acting of coagulative forces (blending of the contents of the container by shaking) the viscosity of the liquid decreases enabling spraying the dose on the nasal mucosa where the solution restores to the previous consistency with time. It is believed, that increasing viscosity of the substance deposited on mucosal surface could help to increase the adherence of the drug's particles. Subsequently, prolonged duration of adherence increases the absorption of the active substance [1, 10].

In their study Eccleston et al. [2] evaluated the rheological properties of four intranasal glucocorticosteroids available in the United States: triamcinolone acetonide, fluticasone propionate, mometasone furoate and beclometasone dipropionate. Thixotropy phenomenon was observed in all analyzed substances, although its magnitude varied across the drugs. The decreasing of viscosity of the solution under coagulative forces was the highest in mometasone furoate (58,6 Pa ·s), and the lowest in beclometasone dipropionate (3,5 Pa ·s). The time of restoration to the basal viscosity also differed between drugs, ranging from 40 second for beclometasone dipropionate and triamcinolone acetonide, through 120 second fluticasone propionate till up to over 240 second for mometasone furoate. After another test in the same conditions the authors concluded, that the observed changes have been entirely reversible (what was in line with the assumptions making thixotropy different from other, irreversible phenomenon).

Shah et al. indicated the high level of mometasone furoate deposition, especially in posterior part on nasal cavity, which is a typical location of many

abnormalities, including rhinosinusitis and polyps. After administration of the aqueous solution of **mometasone furoate**, radiolabelled with technetium-99 (Tc99) 60% of the drug on average was deposited in the posterior part of the nasal cavity, 26% in the anterior part, app. 10% was swallowed, and below 2% was inhaled into nasopharynx and lungs. During 15 minutes the radioactivity of deposited drug diminished by 60%. This additionally confirmed the location of the drug in posterior part of nasal cavity, which is predominantly covered by multilayered ciliated epithelium with active mucociliary clearance. The results showed the differences in deposition of mometasone furoate compared to remaining intranasal glucocorticosteroids, for which the majority of the drug has been deposited on nasal conchae or in the middle part of the nasal cavity [11].

Other factors influencing the efficacy of intranasal drugs

Regardless of producing of the solutions with thixotropic properties, the prolongation of time of adherence to the nasal mucosa is possible due to addition to the intranasal drugs of mucoadhesive substances. They could improve the viscosity of the solution. On the the other hand these substances, usually polymers, are added to slow down the mucociliary clearance, leading to the drug elimination. In this regard, one of the most investigated substance is chitosan. This polysaccharide is the product of deacetylation of chitin from crustaceans' carapace. Chitosan improves the adhesion of different substances to the mucus and facilitates opening of membrane channels, which enables the migration of polarized particles of the drug. Furthermore, it is non-toxic and do not irritate the mucosa [4]. Hyaluronic acid and hudroxyethylcellulose have similar properties. Thioglycolate chitosan, chitosan-4-thio-butyl-amidine (chitosan-TBA) and carboxymethylcellulose-polycarbophil cysteamine conjugates constitute the newest generation of mucoadhesive polymers.

The increasing of mucoadhesion and subsequent prolongation of duration of contact of the drug with nasal mucosa seems to be of particular importance for drug used in the disorders of nasal mucosa itself (e.g. glucocorticoids or adrenomimetics). Of note, the particles of different drugs could require varied modifications. For example the improvement of budesonide adhesion is possible due to formation of new fatty acid esters, while for fluticasone propionate this improvement is reached by increasing of molecular lipophilicity. Nakamura et al. revealed, that conjunction of budesonide with methacrylic acid and polyethylene glycol (MAA-g-EG) in one co-polymer resulted in relatively fast absorption of the drug (T_{max} 45 min.) and stable state lasting more than 8 hours according to the continuous releasing of the drug. It was possible due to the fact, that polymer with carboxyl groups strongly adhered to the mucosal epithelium as a results of forming of hydrogen bonds in the environment of pH <5, in which carboxylic acid does not dissociate. Resembling conjunction with xylomethazoline produced very similar effects.

Cytoadhesion, e.g. direct adhesion to the cells of mucosal epithelium is another factor prolonging the active drugs time of action in the nasal cavity. Lectins and natural glycoproteins show these properties, and this phenomenon was described by Naisbett and Woodley and Lehr. Unfortunately, the possible ability of lectins to trigger toxic reactions (e.g. lectins which is derived from castor oil plant *Ricinus communis*) entail the need of searching for other substances of similar mode of action but more favorable safety profile [1].

Table 1. Indications for intranasal administration of glucocorticosteroids [12, 13]

Indications for intranasal administration of glucocorticosteroids
— moderate-severe acute sinusitis
— seasonal and perennial allergic rhinitis
— chronic nonallergic rhinitis
— polyps of the nose
— prevention of recurrence of polyps of nose after polypectomy
Off-label indications
— medicamental rhinitis (*rhinitis medicamentosa*) induced by overuse of topical drugs constricting nasal mucosa vessels
— rhinitis induced by nonsteroidal anti-inflammatory drugs (NSAIDs) intolerance
— chronic sinusitis without polyps
— upper airways cough syndrome (UACS); cough induced by post-nasal drip syndrome
— nonallergic rhinitis with eosinophilia (NARES)

Table 2. Comparison of action of intranasal glicocorticosteroids with other drugs used in the treatment of allergic rhinitis [13]

	Runny nose	Blocked nose	Sneezing	Itching	Ocular symptoms
Intranasal glucocorticosteroids	+++	+++	+++	+++	++
Oral antihistamine drugs	++	+	++	++	++
Intranasal antihistamine drugs	++	+	++	++	0
A-mimetics	0	++++	0	0	0
Cholinolytics	++	0	0	0	0
Chromones	+	+	+	+	0

Intranasal administration of glucocorticosteroids

Topical glucocorticosteroids have an anti-swelling, anti-inflammatory and anti-allergic activity and applied intranasally (Table 1) reassure adequately high concentration of the drug at the site of inflammation as well as fast onset of action [11]. On the molecular level the drug binds to the glucocorticoid receptor (GR) in cell cytoplasm and then is transferred to the nucleus, where inhibits the expression of many genes involved in the production of proinflammatory cytokines. Additionally, intranasal glucocorticosteroids decrease the expression of adhesive molecules, enhance apoptosis in eosinophils, decrease mucus production, plug formation, constrict the blood vessels, reduce exudate, and mucosal edema (Table 2).

According to the Polish Standards of Treatment of Rhinitis (Polskie Standardy Leczenia Nieżytów Nosa, PoSLeNN) [13] intranasal glucocorticosteroids are the backbone therapy for all forms of chronic allergic rhinitis as well as moderate-to-severe seasonal allergic rhinitis, especially with nasal airway obstruction and common clinical symptoms. ARIA 2010 (*Allergic Rhinitis and its Impact on Asthma*) consensus [14] suggests the usage of intranasal glucocorticosteroids instead of antihistaminic drugs in the treatment of seasonal and perennial allergic rhinitis in adults and in children. In some patients with allergic rhinitis and concomitant pollen sensitivity and asthma the intranasal glucocorticosteroids reduce the symptoms of asthma and non-specific overactivity of bronchial tree during pollen period. Some of the intranasal glucocorticosteroids (mometasone furoate, fluticasone furoate) significantly reduce the ocular symptoms accompanying allergic rhinitis. The intranasal glucocorticosteroids start their activity app. 7–12 hours after administration, but it should be remembered, that full activity is developed just after few days. So it is worth to start the therapy with intranasal glucocorticosteroids at least 10–14 days before pollen season and keep continuously throughout the whole period of allergen exposure.

The glucocorticosteroids used topically on nasal mucosa are characterized by low bioavailability bioavailability, and thus they have not been demonstrated to suppress the hypothalamic–pituitary–adrenal axis, especially growth and bone mass. This is of special importance in the youngest children. The most common side-effects of intranasal glucocorticosteroids include epistaxis and dryness of nasal mucosa, although the frequency of these symptoms is lower in patients correctly taking the medication. The patient should be informed that the end of applicator should be directed on the lateral wall of nasal cavity instead of the septum. The frequency of other side-effects (sneezing, stinging in nose, scratching in throat etc.) is comparable with placebo. Neither injury of epithelium nor atrophy of nasal mucosa was observed in patients systematically taking intranasal glucocorticosteroids, even for many years. Similarly, no systemic side-effects have been reported, which are typical for systemic steroids.

Pregnant women and children are among special group of patients. It should be underlined, that budesonide and beclomethasone are the safest drugs among intranasal glucocorticosteroids for pregnant women (category B by *Food and Drug Administration*). In children mometasone could be administered the earliest e.g. after 3 years of age. Fluticasone propionate is registered in children after 4 years of age, and fluticasone furoate and budesonide after 6 years of age [13].

Penagos et al. in the metaanalysis of 16 randomized, double-blinded clinical trials investigated the effectiveness of intranasal glucocorticosteroids in the treatment of allergic rhinitis with regard to mometasone furoate. All included trials indicated statistically significant effectiveness

(level Ia by *Evidence Based Medicine*) of mometasone taken in the nose of 100, 200, 400 and 800 μg once a day in reducing symptoms of seasonal and chronic allergic rhinitis. As compared with oral and intranasal antihistaminic drugs intranasal glucocorticosteroids showed significant advantage in reducing the symptoms including nose obstruction and sneezing. Interestingly, there were no differences in alleviating of ocular symptoms of allergy and cough accompanying rhinitis. By contrast, the intranasal glucocorticosteroid administered as add-on therapy to antihistaminic drug helped to additionally reduce the symptoms of allergic rhinitis. The number of side-effects associated with usage of intranasal glucocorticosteroids was comparable to placebo [15]. In a multicenter, randomized, double-blinded clinical trial Kuna et al. indicated the equivalence of two mometasone preparations (original and generic) in effective reducing of nasal and ocular symptoms of allergic rhinitis, with good tolerance and without any serious side-effects [16].

Conclusions

The topical drugs administered on nasal mucosa have already established in therapy. In diseases, such as allergic rhinitis or sinusitis, they are first line drugs of choice due to their topical action in the site of inflammation. They also could be a valuable alternative considering faster action compared to other administration routes, for example apomorphine in the treatment of on-off effect in patients with Parkinson disease. Previous experience enabled the development of the drugs with the high absorption rate and the most optimal physicochemical properties. The deposition of the drug on nasal mucosa was optimized due to thixotropy phenomenon. Decreasing of viscosity after shaking the solution facilitates effective application of aerosol dose. Subsequently, due to "liquid memory" the viscosity of the drug restores, to favor adhesion to nasal mucosa and additional mucoadhesive molecules could be very helpful.

The further investigations are focused on searching for new substances acting not only topically but systemically, which could be administered intranasally after possible modification of the molecule as well as developing of additional substances improving the absorption. They are sometimes pioneering in nature, similarly to development of intranasal insulin, which was finally withdrawn from the market for additional research.

Conflict of interest

The authors declare no conflict of interest.

References

1. Ugwoke MI, Remigius U, Verbeke N. et al. Nasal mucoadhesive drug delivery: Background, applications, trends and future perspectives. Advanced Drug Delivery Reviews 2005; 57: 1640–1665.
2. Rapiejko P, Lipiec A. Podział nieżytów nosa. Alergia 2013; 2: 6–8.
3. Sawicki W. Histologia: podręcznik dla studentów. Wyd. V (dodruk). Warszawa: Wydawnictwo Lekarskie PZWL, Warszawa 2009; 449.
4. Illum L. Nasal drug delivery: new developments and strategies. Drugs Discovery Today 2002; 7: 1184–1189.
5. Verdugo P, Tam PY, Butler J. Conformational structure of respiratory mucus studied by laser correlation spectroscopy. Biorheology 1983; 20: 223–230.
6. Flynn GL, Yalkowsky SH, Roseman TJ. Mass transport phenomena and models: theoretical concepts. J Pharm Sci 1974; 63: 479–510.
7. Arora P, Sharma S, Garg S. Permeability issues in nasal drug delivery. Drugs Discovery Today 2002; 7: 967–975.
8. Januszajtis A, Langer J. Ilustrowana encyklopedia dla wszystkich. Fizyka. Wydawnictwa Naukowo-Techniczne, Warszawa 1991.
9. Sikora M, Adamczyk G, Krystyjan M. Tiksotropia miarą niestabilności ciekłych produktów żywnościowych. Żywność. Nauka. Technologia. Jakość 2011; 1: 5–14.
10. Eccleston GM, Bakhshaee M, Hudson NE. et al. Rheological behavior of nasal sprays in shear and extension. Drug Development and Industrial Pharmacy 2000; 26: 975–983.
11. Shah S, Berger R, McDermott J. et al. Regional deposition of mometasone furoate nasal spray suspension in humans. Allergy Asthma Proc 2015; 36: 48–57.
12. Snidvongs K, Kalish L, Sacks R. et al. Topical steroid for chronic rhinosinusitis without polyps. Cochrane Database Syst Rev 2011 Aug 10; (8):CD009274.
13. Polskie Standardy Leczenia Nieżytów Nosa (PoSLeNN). Stanowisko panelu ekspertów Polskiego Towarzystwa Alergologicznego. Alergologia Polska 2013; S1.
14. Allergic Rhinitis and its Impact on Asthma (ARIA) 2010 Revision. http://whiar.org/docs/ariareport_2010.pdf.
15. Penagos M, Compalati E, Tarantini F. et al. Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis. Meta-analysis of randomized, double-blind, placebo-controlled, clinical trials. Allergy 2008; 63: 1280—1291.
16. Kuna P, Wasiak W, Jones S. et al. Comparative safety and efficacy of two formulations of mometasone nasal spray in adult seasonal allergic rhinitis. Allergy Asthma Proc 2014: 35; 332–337.