

NOVEL NASAL DRUG DELIVERY SYSTEMS – CURRENT STATUS ON GLOBAL AND BULGARIAN PHARMACEUTICAL MARKET

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ABSTRACT

Recently, with elucidation of drug transport mechanisms through the tissues, current pharmaceutical technologies have been focused on alternative drug delivery pathways and incorporation of drug molecules into novel drug delivery systems.

Nasal route, which has been an object of increased interest since antiquity, is nowadays widely used for the delivery of vaccines, hormones, peptides and other systemically acting drugs. By intranasal administration medicinal substances fall directly into the systemic circulation in an easy, affordable and painless way. On the other hand nasal administration avoids hepatic "first pass" effect associated with oral delivery and eliminates the problem of decreased absorption due to instability in the gastrointestinal system or rapid biotransformation.

Advances in biotechnology, genomics and combinatorial chemistry in recent years gave rise to new therapeutic agents with potent therapeutic effect, often accompanied by reduced stability and poor water solubility. On the other hand, studies on various innovative drug-delivery systems confirmed their potential in extending the life cycle of well-known molecules for both conventional and alternative routes of administration.

In this paper we will discuss the current status of nasal drug delivery systems on global and Bulgarian pharmaceutical market focusing on innovative therapeutic systems.

Keywords: *Novel drug delivery systems, nasal drug delivery.*

INTRODUCTION

Novel drug delivery systems (NDDSs) have proven to be one of the most fast-growing sectors in pharmaceutical industry. Global sales uplift is around 5% per year. By 2010 the market for NDDSs is estimated at more than 130 billion dollars and is expected to reach 175.6 billions by 2016 (1). NDDSs have undeniable clinical advantages. These systems have been developed for assuring of better control of the pharmacokinetic and pharmacodynamic behavior after administration of the dosage form and to achieve higher efficiency and greater safety as compared to conventional formulations. NDDSs make feasible opportunities for optimizing therapeutic efficacy, extending drug molecules lifecycle, improvement of patient's compliance, reduction of health care costs.

In pharmaceutical technology, there are several areas that use innovative approaches in solving problem cases. These areas include: (i) research on alternative routes of administration such as pulmonary, nasal, transdermal, (ii) novel techniques for improving low aqueous solubility of drugs, and drug candidates, (iii) nanotechnology and particulate design, (iv) delivery of biotech drugs, peptides and proteins, (v) testing the toxicity and efficacy of new excipients and (vi) development of *in vitro* screening test systems.

ALTERNATIVE ROUTES OF ADMINISTRATION

Delivery of drugs into the human body is generally achieved by several anatomical paths. For obtaining the desired therapeutic goal it is of great importance to choose the most appropriate route of administration. Therefore, factors such as drug properties, disease features or duration of the desired therapeutic effect should be taken into account in drug administration. Medicines can be applied directly on target tissues and organs, or to be delivered systemically. The various routes for systemic administration of drugs are summarized in Figure 1.

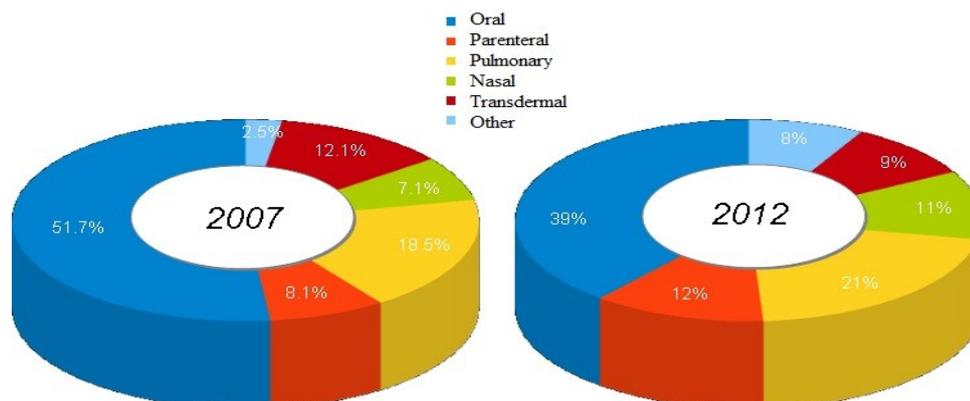


Figure 1. Routes of administration - market share by 2007 and 2012 (Source: Frost & Sullivan)

Analysis of the global market of drug-delivery systems for 2007 shows that oral formulations occupy about 50 % market share, followed by transmucosal at about 26% (including pulmonary (18.5 %), buccal (0.6%) and nasal systems (7.1%)) and transdermal - 2.3 %. A significant growth over the past five years has been marked by drug-delivery system for transmucosal administration. According to a GIA report (Global Industry Analysts, Inc.) the estimated market for nasal drug-delivery systems is expected to reach 5.2 billion dollars by 2017 (2). This market growth can be attributed to the increasing needs for product differentiation and expansion of therapeutic applications.

Key factors for market growth are: more rapid onset of therapeutic effect, reduced dosing frequency compared to oral formulations, better patient's compliance, and economic efficiency and increased safety as well.

At present, a large number of drug-delivery systems for intranasal administration are under research and development or in various stages of clinical trials, which proves recognition of the undoubted benefits of the nasal route of administration.

NASAL DRUG DELIVERY

The nasal route of administration has been an object of interest since ancient times. In the Ayurvedic system of Indian medicine nasal therapy as a form of treatment is known as "Nasaya Karma". A number of drugs have long been administered nasally to achieve a local effect on the mucosa (including antihistamines, decongestants, vasoconstrictors, and antibiotics). Recently there have been numerous studies on the systemic bioavailability of substances after nasal administration with plasma profiles identical to those after intravenous administration. There is a growing interest in nasal administration of vaccines, hormones, peptides and other medicinal substances with systemic effect that are usually delivered mainly via parenteral route. When applied into the nasal cavity medicinal substances enter directly into the systemic circulation in a simple and painless way. What is more, with intranasal delivery hepatic "first pass" metabolism associated with oral administration is avoided and the problem with decreased absorption due to the instability or rapid biotransformation is eliminated. Targeted drug delivery to the CNS via absorption in the olfactory region of the nasal cavity is another proof of nasal route significance (3).

NOVEL DRUG-DELIVERY SYSTEMS

Recently, with elucidation of drug transport mechanisms through the tissues, current pharmaceutical technologies have been focused on alternative drug delivery pathways and incorporation of drug molecules into novel drug delivery systems. The NDDSs are classified according to the drug therapeutic class, its physical form, route of administration, mechanism of action, etc. Some of the most popular and promising NDDSs are presented in Figure 2.

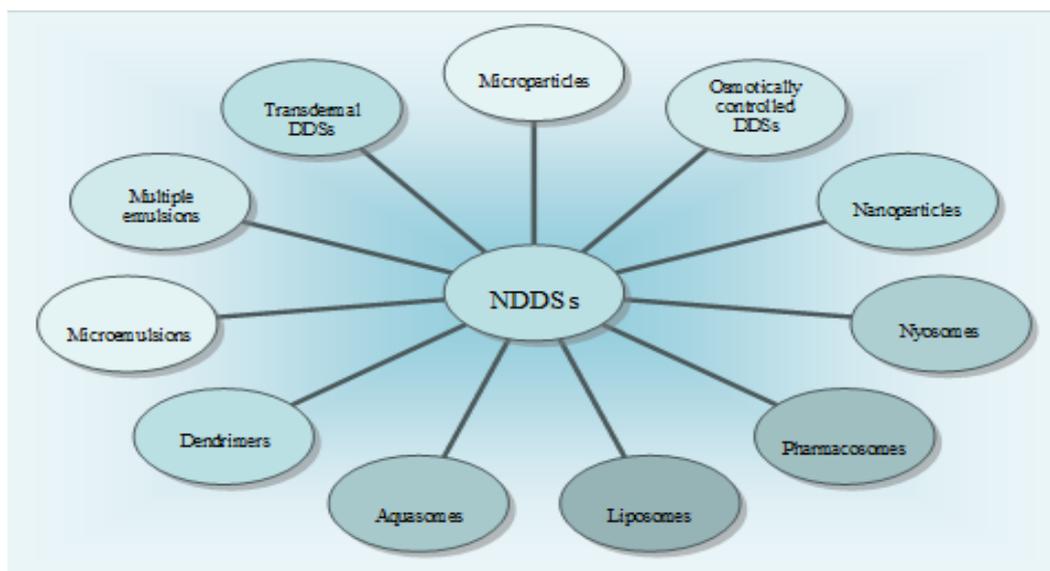


Figure 2. Different types of novel drug delivery systems

For optimization of the nasal route and as a result of prominent physiological limitations, various technological approaches have been developed, based mainly on the particulate design.

Liposomes have proven to increase nasal absorption of peptides such as insulin (4) due to better retention in the nose. There is evidence for the successful use of liposomes for the delivery of influenza vaccine (5) and non-peptides such as nifedipine (6). Ding et al. achieved rapid onset and sustained release of levonorgestrel after intranasal administration of liposome suspension (7). Good results were obtained after intranasal administration of acyclovir, incorporated into a liposome gel (8).

Microspheres, which are typically based on mucoadhesive polymers, are widely applied in nasal formulations. Wang et al. evaluated gelatin microspheres for the nasal delivery of insulin and reported a significant hypoglycemic effect in rats (9). Similar studies have been carried out and promising results have been obtained for the nasal delivery of carbamazepine using chitosan microspheres (10), carvedilol - by alginate microspheres (11) and many others which confirm the huge potential of these systems in nasal route of administration.

Controversial results have been obtained from studies on **nanoparticles** intended for nasal administration. In fact, there are very few publications on nanoparticulate formulations and results did not show any significant improvement in drug transport across the nasal membrane. Low bioavailability is probably due to nanoparticles uptake by M-cells in the nasal-associated lymphoid tissue, where they are transported from to the lymphatic or blood system (12). Other studies, however, show that nanoparticles can be successfully used for nasal delivery of vaccines (13).

CURRENT STATUS OF NDDSs ON THE PHARMACEUTICAL MARKET

Considering the arising complications associated with the discovery of new therapeutically active molecules, many opportunities are available. They are mainly directed towards innovative pharmaceutical products intended for intranasal administration of well-known substances or those with a status of the gold standard in therapy. These products feature good receptivity by patients and ease of use, and offer real benefits. A key advantage of this approach is the data available that is supporting the efficacy and safety of such drugs. Furthermore, for these substances clearly defined regulatory procedures are available and a lower risk of new product development is taken. Procedures for authorization may be further facilitated by the availability of good regulatory status of the nasal drug delivery platform itself, particularly in terms of quality and safety of the excipients through the available history of their clinical application.

Opioid analgesic fentanyl is probably the best example of a drug fully exploited in innovative drug - delivery technologies. In the late 1980s, a transdermal patch has been launched for the treatment of chronic pain; recently a number of fentanyl formulations have been reported, which use other routes of administration especially for specific indications such as cancer pain. Several transmucosal fentanyl products for oral administration are already on the market (Table 1), others are in research and development process. An example of such a formulation using patented technology of in situ gelling system is PecSys (14); data obtained from clinical trials show onset of action within 5 min and clinically significant pain relief after 10 min and is characterized by excellent safety, tolerability and receptivity. Subsequently, this product has been licensed for use in Europe under the trade name PecFent.

| Product name | INN/ Indication | Formulation | Status on pharmaceutical market | Manufacturer |
|----------------------------|---|------------------|---------------------------------|-----------------------------|
| VACCINES | | | | |
| Nasalflu | Influenza vaccine | Virosomes- spray | Withdrawn | Berna Biotech |
| FluMist | Influenza vaccine | Suspension-spray | Available | MedImmune Inc. |
| StrepAvax | Streptococcus vaccine type A | Proteosomes | Phase II Clinical trial | ID Biomedical |
| FluINSuru | Influenza vaccine | Proteosomes | Phase II Clinical trial | ID Biomedical |
| MACROMOLECULES | | | | |
| Karil 200 IE | Salmon calcitonin/ Osteoporosis | Solution - spray | Available | Novartis Pharma |
| Minirin | Desmopressin/ Diabetes, enuresis | Solution - spray | Available | Ferring Pharmaceutical Ltd. |
| Profact | Buserelin/ Prostate carcinoma | Solution - spray | Available | Sanofi-Aventis |
| Synarela | Nafarelin/ Endometriosis | Solution - spray | Available | Pharmacia |
| Syntocinon | Oxytocin/ Labour induction | Solution - spray | Available | Novartis Pharma |
| Relefact TRH | Protirelin/ Pituitary gland diagnostics | Solution - spray | Available | Sanofi-Aventis |
| Kryptocour | Gonadorelin/ Cryptorchism | Solution - spray | Available | Sanofi-Aventis |
| LOW MOLECULAR DRUGS | | | | |
| Zomig | Zolmitriptan/ Migraine | Solution - spray | Available | Astra Zeneca |
| Imigran | Sumatriptan/ Migraine | Solution - spray | Available | Glaxo SmithKline |
| Migranal | Dihydroergotamine/ Migraine | Solution - spray | Available | Valeant Pharmaceuticals Int |
| Aerodiol | Estradiol/Hormone replacement therapy | Solution - spray | Withdrawn 2006 | Servier |
| Nascobal | Cyancobalamin (Vit. B12) | Solution - spray | Available | Strativa Pharmaceuticals |
| Stadol | Butorphanol/ Analgesia | Solution - spray | Available | Geneva Pharmaceuticals |
| Lazanda,PecFent | Fentanyl/ Analgesia, anesthesia | Solution - spray | Available | Archimedes Pharma US Inc |
| Instanyl | Fentanyl/ Analgesia, anesthesia | Solution - spray | Available | Takeda UK Ltd |
| Pramidin | Metoclopramide/ Nausea and vomiting | Solution - spray | Available | CSC Pharmaceuticals |
| Nicotrol NS | Nicotine/ Smoking cessation | Solution - spray | Available | Pharmacia Upjohn |

Table 1. Systemically acting nasal products available on the global pharmaceutical market

Intranasal influenza vaccine has been launched in the U.S. pharmaceutical market under the name FluMist; a nasal H1N1 vaccine, NasoVac, was released for sale in India. The use of mucosal adjuvants such as chitosan in the development of vaccines for intranasal administration can provide improved mucosal immune response and thereby reduction of dose of the incorporated antigen. This is essential for the expansion of nasal vaccines market.

Several anti-migraine drugs are also subjected to intranasal administration, since rapid effect is necessary and migraine is often accompanied by symptoms such as nausea, which prevents oral administration (15).

Peptide drugs for hormone replacement therapy are also commercially available as nasal sprays to avoid decomposition of the drug following oral administration. Peptide analogue desmopressin is available in both oral and nasal formulations. Bioavailability of commercially available tablets is only 0.1 %, while the same in nasal formulation is 3-5 % according to the summary of product characteristics (16).

FUTURE ASPECTS

Considering the growing interest in nasal route of administration and recognizing the undeniable advantages of this approach, it is reasonable to expect an even wider uptake of innovative nasal products in the pharmaceutical market. In Bulgaria, however, the market share of

nasal drug delivery systems is still below the global trends. No data for experimental studies are available in this field.

| INN | Trade name | Formulation | Manufacturer |
|-----------------------------|------------|-------------|------------------------------|
| Desmopressin | Minirin | Nasal spray | Ferring GmbH |
| Desmopressin | Adiuretin | Nasal drops | Ferring Leciva A.S. |
| Desmopressin | Presinex | Nasal spray | Mipharm S.p.A. |
| Nafarelin | Synarel | Nasal spray | Pfizer Europe MA EEIG |
| Calcitonin-salmon/acetate | Myacalcic | Nasal spray | Novartis Pharma AG |
| Calcitonin-salmon/acetate | Neocalcin | Nasal spray | Pharmanel pharmaceuticals SA |
| Bacterial lysate suspension | IRS 19 | Nasal spray | Solvay Pharma |
| Metoclopramide | Pramidin | Nasal spray | Crinos S.p.A. |

Table 2. Systemically acting nasal products on Bulgarian pharmaceutical market by 2013.

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