IJPSR (2014), Vol. 5, Issue 5 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 16 December, 2013; received in revised form, 29 January, 2014; accepted, 24 March, 2014; published 01 May, 2014

ANTIEMETIC DRUGS AS A NASAL DRUG DELIVERY – A REVIEW

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Keywords:

Antiemetic, nasal drug delivery, superior bioavailability

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ABSTRACT: Antiemetic drugs are used in the treatment of nausea and emesis. Development of novel delivery systems for antiemetic drugs, as an alternative to conventional preparations, is essential in terms of good patient compliance and improving bioavailability. The nasal route offers exclusive superiorities, such as rapid and high drug absorption, and high patient compliance. Consequently, a considerable amount of research has been carried out on the development of nasal delivery systems for antiemetic drugs. This review deals with the importance of nasal delivery of antiemetic drugs and the studies performed on this subject. The present review illustrates the studies conducted on the development of nasal delivery systems. Due to its better stability and bioavailability, the nasal route could be considered as an attractive alternative to oral and parenteral routes.

INTRODUCTION: Over the recent decades the interest in intranasal delivery as a non-invasive route for drugs is increased. Since the nasal mucosa offers numerous benefits as a target tissue for drug delivery, a wide variety of therapeutic compounds may be administered intranasal for topic, systemic and central nervous system action. Intranasal drug delivery is now recognized to be a useful and reliable alternative to oral and parenteral routes. However, recently, the nasal mucosa has seriously emerged as a therapeutically viable route for the systemic drug delivery [1]. Promising results with enhanced bioavailability have been obtained upon nasal administration and have prompted more extensive investigations in this area.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.5(5).1624-29

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.5(5).1624-29

The nasal route of administration among other promising nonparenteral routes may very well satisfy the prerequisites for nonoral, nonparenteral systemic medication purposes. The systemic bio-availability and thus the efficacy of drugs are quite often influenced by their route of administration [2]. During the past several decades, the feasibility of drug delivery via the nasal route has received increasing attention from pharmaceutical scientists and clinicians. Drug candidates ranging from small ions to large macromolecular proteins have been tested in various animal models [3].

It has been documented that nasal administrations of certain hormones and steroids have resulted in a more complete absorption [4]. In recent years, increasing investigations of the nasal route have focused especially on nasal application for systemic drug delivery[5]. The Therapeutic areas under development or with potential for nasal delivery include cancer therapy, epilepsy, antiemetic, rheumatoid arthritis and insulin-dependent diabetes [6].

Researchers became interested in the nasal route for the systemic delivery of medication due to high degree of vascularization and permeability of the nasal mucosa [7]. Despite the obvious advantages of intranasal drug delivery, the nasal cavity presents a number of limitations for drug absorption, including low intrinsic permeability for some drugs, such as hydrophilic molecules, peptides, proteins and nucleotides, rapid mucociliary clearance, and enzymatic degradation [8, 9].

Antiemetic agents are the most common intervention in the management of treatment-related nausea and vomiting (emesis) (N&V). The basis for antiemetic therapy is the neurochemical control of vomiting. Although the exact mechanism is not well understood, peripheral neuroreceptors and the chemoreceptor trigger zone (CTZ) are known to contain receptors for serotonin, histamine (H1 and H2), dopamine, acetylcholine, opioids, and numerous other endogenous neurotransmitters [10, 11].

Drugs available as Nasal Drug Delivery: Currently, nasal administration is used therapeutically for the systemic absorption of drugs in a variety of indications, including sumatriptan for migraine[12], the antidiuretic desmopressin for the treatment of diabetes insipidus[13] and oxytocin for stimulation of breast milk ejection. Other drugs still in the research and development pipeline, which have potential for administration nasally, include vitamin B12 or hydroxocobalamin [14], various benzodiazepines [15, 16, 17, 18] and the dopamine agonist apomorphine for patients with parkinsonism [19].

TABLE 1: VARIOUS INTRANASAL DRUG DELIVERY SYSTEMS AND THEIR PURPOSE [20]

Drug	Delivery system	Purpose
Pentazocine	Microspheres	Avoiding first pass effect
Ketorolac Trimethamine	Microspheres	Avoid gastric complications
Sildenafil Citrate	Microspheres	Avoid first pass metabolism
Metoclopramide HCl	Microspheres	Permeation enhancement
Propranolol HCl	Microspheres	Open tight junction without cell damage
Cyclopentyladenosine	Microspheres	Selective brain targeting
Propranolol HCl	Microspheres	Avoiding first pass effect
Ondansetron	Microspheres	Avoiding first pass effect and improve therapeutic efficacy
Domperidone	Microspheres	Selective brain targeting
Sumatriptan Succinate	Microspheres	Avoid hepatic first pass metabolism and brain targeting
Clonazepam	Microspheres	Brain targeting
Clonazepam	Microemulsion	Brain targeting
Valproic Acid	Microemulsion	Enhanced bioavailability with brain targeting
Clobazam	Microemulsion	Brain targeting
Lomotrigone	Microemulsion	Brain targeting
Lorazepam	Microemulsion	Brain targeting
Sumatriptan	Microemulsion	Enhanced the bioavailability
Zolmitriptan	Microemulsion	Enhanced bioavailability
Zolmitriptan	Microemulsion	Enhanced bioavailability & rapid onset of action
Eucalyptus oil	Microemulsion	Enhanced bioavailability with brain targeting
Nimodipine	Microemulsion	Enhanced solubility and brain targeting
Nobiletin	Microemulsion	Improve bioavailability in the brain
Tacrine	Microemulsion	Targeting to brain
Zolmitriptan	Microemulsion	Targeting to brain
Diazepam	Microemulsion	Rapid absorption
Raltitrexe	Microemulsion	Targeting to brain tissue
Sildenafil Citrate	Microemulsion	Improve bioavailability with shorter Tmax
Insulin	Microemulsion	Enhanced the Bioavailability
Midazolam	Microemulsion	To investigate the pharmacokinetic & pharmacodynamic profile
Tetanus toxoid	Liposome	Improved immun responce
Insulin	Liposome	Increased insulin permeability
Desmopressin	Liposome	Enhancement of antidiuresis
Diphenhydramine	Liposome	Increased drug retention in the nasal cavity
Insulin, calcitonin	Polyacrylic acid gel	Enhanced absorption
Insulin	Powder	Improve bioavailability

Novel nasal formulations: These are the novel formulations which is available at present in the nasal delivery system.

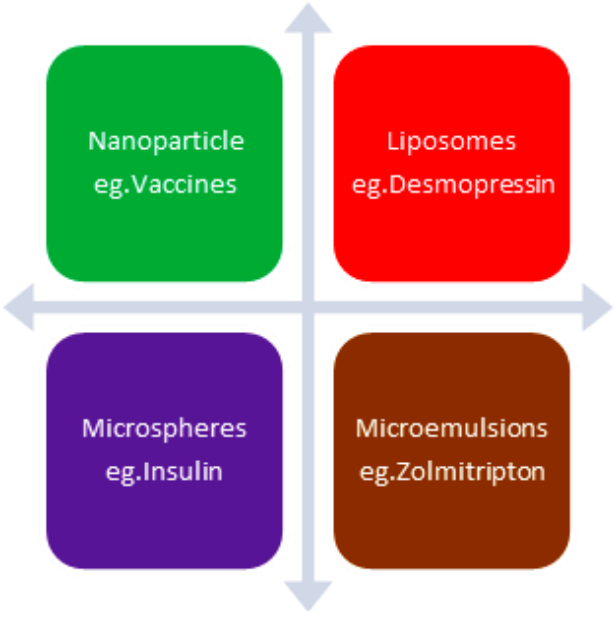

FIGURE 1: NOVEL NASAL FORMULATION

Antiemetic drug as Nasal Drug Delivery: Metoclopramide hydrochloride is reported as micro particulate nasal delivery [21]. Ondansetron loaded with chitosan microsphere for nasal route and insitu gel are available in literature [22, 23]. Freeze dried microparticles of granisetron-cyclodextrin complex and carboxymethylcellulose for intranasal delivery was prepared by Cho *et al* 24, M. Menaka *et al* formulated nasal spray of Ondansetron hydrochloride [25]. Freeze-dried xanthan / Guar Gum nasal inserts, ion dependent and mucoadhesive insitu nasal gel of metoclopromide hydrochloride was formulated and reported [26, 27, 28]. The phase II clinical studies has completed and in preparation for pivotal studies in US for Granisetron as intranasal powder dosage form [29]. Emphasis and importance for nasal drug delivery may be visualized easily by knowing that there are minimum 17 leading international pharmaceutical companies engaged in manufacture, research, development innovation and patenting of products in nasal delivery [30] .

FACTORS AFFECTING NASAL PERMEABILITY OF DRUGS [31]

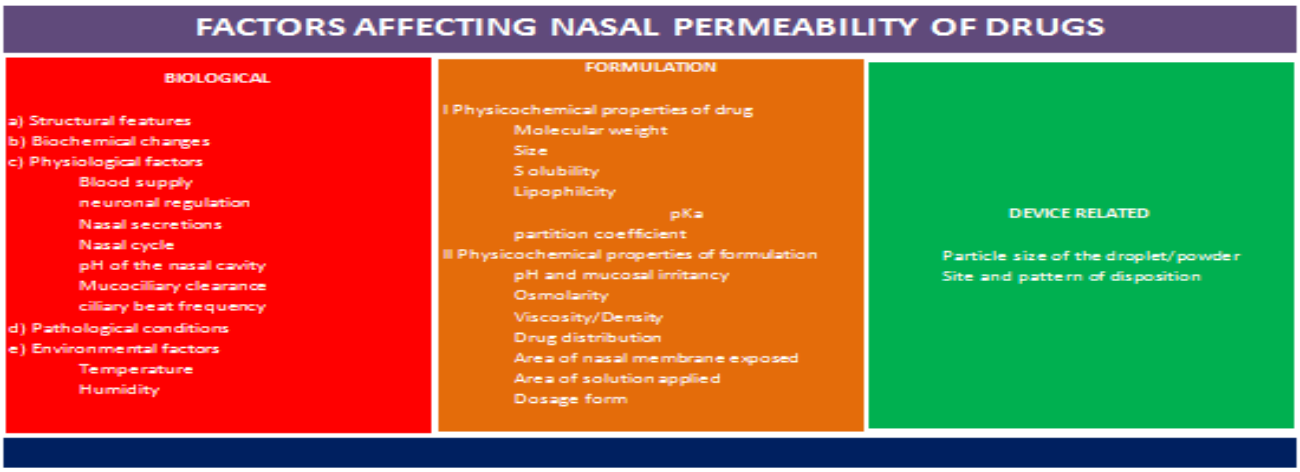

FIGURE 2: FACTORS AFFECTING NASAL PERMEABILITY OF GRUGS

Nasal drug delivery system dosage forms: The selection of dosage form depends upon the drug being used, proposed indication, patient population and marketing preferences. The basic formulations considered are solution, suspension, emulsion and dry powder system.

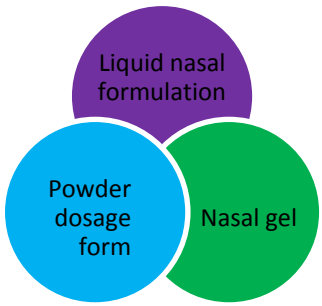

FIGURE 3: NASAL DOSAGE FORMS

Liquid Nasal Formulations: Liquid preparations are the most widely used dosage forms and are mainly based on aqueous state formulations. Microbiological stability, irritation and allergic rhinitis are the major drawbacks. The preservatives impair mucociliary function and the reduced chemical stability of the dissolved drug substance and the short residence time of the formulation in the nasal cavity are major disadvantages of liquid formulations [32]. The several types are described below;

1. **Instillation and rhinyle catheter:** Catheters are used to deliver the drops to a specified region of nasal cavity easily. The formulation is placed in the tube. One end is positioned in the nose, and the solution is delivered into the nasal cavity by blowing through the other end by mouth.
2. **Compressed air nebulizers:** Nebulizer is a device used to administer medication in the form of a mist, inhaled into the lungs. The compressed air fills into the device, so it is called compressed air nebulizers. The common technical principle for all nebulizers is to use oxygen, compressed air or ultrasonic power, as means to break up medical solutions/ suspensions into small aerosol droplets, for direct inhalation from the mouthpiece of the device. It is in order to target their effect to the respiratory tract, which speeds onset of action of the medicine and reduces side effects, compared to other alternative intake routes. This device is not suitable for the systemic delivery of drug by patient himself.
3. **Squeezed bottle:** Squeezed nasal bottles are mainly used to deliver decongestants. They include a smooth plastic bottle with a simple jet outlet. While pressing the plastic bottle the air inside the container is pressed out of the small nozzle, thereby atomizing a certain volume. By releasing the pressure again air is drawn inside the bottle. This procedure often results in contamination of the liquid by microorganisms and nasal secretion sucked inside. Dose accuracy and deposition of liquids delivered via squeezed nasal bottles are strongly dependent on the mode of administration.
4. **Metered-dose pump sprays:** Most of the pharmaceutical nasal preparations in the market containing solutions, emulsions or suspensions are delivered by metered-dose pump sprays. Nasal sprays or nasal mists are used for the nasal delivery of a drugs, either locally to generally alleviate cold or allergy symptoms such as nasal congestion or systemically. Although delivery methods vary, most nasal sprays function by instilling a fine mist into the nostril by the action of a hand-operated pump mechanism. Metered-dose pump sprays include the container, the pump with the valve and the actuator. The dose accuracy of metered-dose pump sprays is dependent on the surface tension and viscosity of the formulation. For solutions with higher viscosity, special pump and valve combinations are available in the market.

Powder Dosage Forms: Dry powders are less frequently used in nasal drug delivery. Major advantages are the lack of preservatives, improved stability and Compared to solutions, prolonged contact with the nasal mucosa. The types of powder dosage forms are described below:

Insufflators: Insufflators are the devices to deliver the drug substance for inhalation. It can be constructed by using a straw or tube which contains the drug substance and sometimes it contains syringe also.

Dry powder inhaler: Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales.

Pressurized MDI's: A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is the most commonly used delivery system for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory

diseases. The medication in a metered dose inhaler is most commonly a bronchodilator, corticosteroid or a combination of both for the treatment of asthma and COPD.

The advantages of MDIs are their portability and small size, availability over a wide dosage range per actuation, dose consistency, dose accuracy, protection of the contents and that they are quickly ready for use. To use the inhaler, the patient presses down on the top of the canister, with their thumb supporting the lower portion of the actuator. The propellant provides the force to generate the aerosol cloud and is also the medium in which the active component must be suspended or dissolved.

Propellants in MDIs typically make up more than 99 % of the delivered dose. Actuation of the device releases a single metered dose of the formulation which contains the medication either dissolved or suspended in the propellant. Breakup of the volatile propellant into droplets, followed by rapid evaporation of these droplets, results in the generation of an aerosol consisting of micrometer-sized medication particles that are then inhaled.

Nasal Gels: Nasal gels are high-viscosity thickened solutions or suspensions. The advantages of a nasal gel include reduction of postnasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing/emollient excipients and target delivery to mucosa for better absorption. The deposition of the gel in the nasal cavity depends on the mode of administration. Due to its viscosity, the formulation has poor spreading abilities [32].

CONCLUSION: Nasal drug delivery system is a promising and challenging alternative route of administration for the several systemically acting drugs with poor bioavailability and it has advantages of quick onset of action, reduces systemic exposure and reduces the side effects, bypass the BBB and delivers the drug directly into the CNS, superior patient acceptability and compliance compared to parenteral administration of drugs. The successful application of these attributes requires careful design of characteristics of both the drug formulation and delivery device and a clear understanding of the ways in which they impact on each other. Nasal drug delivery as an antiemetic will help patient better than the use of their routes. If emesis stops, oral route becomes useful for other drugs and help of healthcare personal for administration of drugs not required.

The era of nasal drug delivery is growing and new efforts are required to make this route of delivery more efficient and popular. This provides easy application of drugs, with the possibility of self administration by removing the chance of unwanted painful condition associated with injection form of drug delivery.

ACKNOWLEDGEMENT: The authors thank UGC (Major research project) for sponsoring this study.

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How to cite this article:
Ruby J. J. and Pandey V. P.: Antiemetic drugs as a nasal drug delivery –A review. *Int J Pharm Sci Res* 2014; 5(5): 1624-29.doi: 10.13040/IJPSR.0975-8232.5 (5).1624-29

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