Brain Targeted Nasal Microspheres of Gabapentin

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ABSTRACT

Intranasal administration is an attractive option for local and systemic delivery of many therapeutic agents. The nasal mucosa is – compared to other mucous membranes – easily accessible and provides a practical entrance portal for small and large molecules. Intranasal administration offers a rapid onset of therapeutic effects, no first-pass effect, no gastrointestinal degradation or lung toxicity, non-invasive, essentially painless application for brain targeted nasal drug delivery. And to improve its bioavailability, Intranasal administration offers a variety of attractive options for local and systemic delivery of diverse therapeutic agents.[1] The nature of the nasal mucosa provides a series of unique attributes, all of which may help to maximize the patient’s safety, convenience and compliance. Over the recent decades the interest in intranasal delivery as a non-invasive route for drugs is increased. Since the nasal mucosa offers numerous beneficial as a target tissue for drug delivery, a wide variety of therapeutic compounds may be administered intranasally for topic, systemic and central nervous system action. The unique relationship between nasal cavity and cranial cavity tissues makes intranasal delivery to the brain feasible. An intranasal delivery provides some drugs with short channels to bypass the blood-brain barrier (BBB), especially for those with fairly low brain concentrations after a routine delivery, thus greatly enhancing the therapeutic effect on brain diseases. The nasal mucosa is nearby the brain, cerebrospinal fluid (CSF) and the drug concentrations can exceed plasma concentrations. Intranasal delivery provides a non-invasive method of bypassing the BBB to rapidly deliver therapeutic agents to the brain, spinal cord, lymphatic’s and to the vessel walls of the cerebrovasculature for treating CNS disorders. Intranasal delivery also offers the advantage of simple administration, cost effectiveness and convenient.[2] This novel delivery method allows drugs, therapeutic proteins, polynucleotides and viral vectors that do not normally cross the BBB to be delivered to the CNS. Additionally, intranasal targeting of drugs to the CNS avoids first pass elimination by the liver allowing a lower therapeutic drug dose and fewer systemic side effects. Delivery from the nose to the CNS occurs within minutes along both the olfactory and trigeminal nerves. Delivery occurs by an extracellular route and does not require that the drugs bind to any receptor or undergo axonal transport.[3].

Criteria of selecting drug for nasal delivery

It must pass through mucus layer and epithelial membrane before reaching CNS, Molecular size, complexity and lipophilicity of drug, pH of the solution and Pka of the drug.[4], Properties of formulation vehicles used

The drug must pass

Blood flow, Enzymatic degradation, Should be Stable, Should have sufficient Viscosity, Should be of required pH

All types of microspheres that have been used as nasal drug delivery systems are water-insoluble but absorb water into the sphere’s matrix, resulting in swelling of the spheres and the formation of a gel. The building materials in the microspheres have been starch, dextran, albumin and hyaluronic acid, and the bioavailability of several peptides and proteins has been improved in different animal models. Also, some low-molecular weight drugs have been successfully delivered in microsphere preparations.[5] The residence time in the cavity is considerably increased for microspheres compared to solutions. However, this is not the only factor to increase the absorption of large hydrophilic drugs. Microspheres also exert a direct effect on the mucosa, resulting in the opening of tight junctions between the epithelial cell.

Key words: Nasal microspheres, CNS acting, BBB, CNS disorders

INTRODUCTION

The diseases of central nervous system (CNS) requires delivery of drug in to brain for treatment; however such transport remains problematic. Especially for hydrophilic drug and Drugs with high molecular weight. Due to the impervious nature of the endothelial membrane separating the systemic circulation and central interstitial fluid, the Blood–Brain Barrier (BBB) It has been shown in the literature from animal and human investigations, that transport of exogenous materials directly from nose-to-brain is a potential route for by-passing the BBB. This route, involves the olfactory or trigeminal nerve systems which initiate in the brain and terminate in the nasal cavity at the olfactory neuroepithelium or respiratory epithelium, respectively.[6] They are the only externally exposed portions of the CNS and therefore represent the most direct method of non-invasive entry into the brain. However, the quantities of drug administered nasally that have been shown to be transported directly from nose-to-brain are very low, normally less than 0.1%, and hence the system is not currently used therapeutically and no product is licensed specifically via this route. Microspheres are solid spherical particles ranging in size from 1-1000µm. They are spherical free flowing particles consisting of proteins or synthetic polymers. The microspheres are free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. There are two types of microspheres; microcapsules and micrometrics, which are described as: Microcapsules are those in which entrapped substance is dispersing throughout the microspheres matrix.[7] Solid biode...
gradable microspheres incorporating a drug dispersed or dissolved through particle matrix have the potential for the controlled release of drug. They are made up of polymeric, waxy, or other protective materials, that is, biodegradable synthetic polymers and modified natural products.

NASAL CAVITY ANATOMY, PHYSIOLOGY AND HISTOLOGY

In humans and other animal species the major functions of the nasal cavity are breathing and olfaction. However, it also affords an important protective activity once it filters, heat and humidify the inhaled air before reaching the lowest airways. Nasal cavity is lined with mucus layer and hairs which are involved in those functions, trapping inhaled particles and pathogens. Moreover, resonance of produced sounds, mucociliary clearance MMC, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures.[8]Anatomic and histological characteristics of the different areas of nasal cavity are such that allow these functions to be performed optimally. Thus, anatomically, human nasal cavity fills the space between the base of the skull and the roof of the mouth; above, it is supported by the ethmoid bones and, laterally, by the ethmoid, maxillary and inferior conchae bones. The human nasal cavity has a total volume of 15-20mL and a total surface area of approximately 150 cm². It is divided by middle (or nasal) septum into two symmetrical halves, each one opening at the face through nostrils and extending posterior to the nasopharynx.[9][10][11] Both symmetrical halves consist of four areas (nasal vestibule, atrium, respiratory region and olfactory region) that are distinguished according to their characteristics. Like their characteristics related to their anatomy and histology.

NASAL VESTIBULE

Nasal vestibule is the most anterior part of the nasal cavity, just inside the nostrils, and presents an area about 0.6 cm². Here, there are nasal hairs, also called vibrissae, which filter the inhaled particles. Histologically, this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands, these nasal vestibular characteristics are desirable to afford high resistance against toxic environmental substances but, at the same time, the absorption of substances including drugs becomes very difficult in this region.

ATRIUM

Atrium is the intermediate area between nasal vestibule and respiratory region. It’s anterior section is constituted by a stratified squamous epithelium and the posterior area by the pseudo stratified columnar cells presenting microvilli.

RESPIRATORY REGION

The nasal respiratory region, also called conchae, is the largest part of the nasal cavity and it is divided in superior, middle and inferior turbinates which are projected from the lateral wall. These specialized structures are responsible for humidification and temperature regulation of inhaled air. Between them there are spaces, called meatus, which are passageways where airflow is created to assure a close contact of the inhaled air with the respiratory mucosal surface.[12] The inferior and middle meatus receive nasocochlear ducts and paranasal sinuses which are air-filled pockets located inside the bones of the face and around the nasal cavity. The nasal respiratory mucosa, considered the most important section for delivering drugs systemically, is constituted by the epithelium, basement membrane and lamina propria. The nasal respiratory epithelium consists of pseudo stratified columnar epithelial cells, goblet cells, nasal cells and mucous and serous glands. Many of the epithelial cells are covered on their apical surface with microvilli and the major part of them also have fine projections, called cilia. Actually, microvilli are important to enhance the respiratory surface area, while cilia are essential to transport the mucus toward the nasopharynx.

Under physiological conditions, nasal epithelium is covered with a thin mucus layer produced by secretary glands and goblet cells.[13][14] These ones secrete granules filled with mucin, a glycoprotein that determines the viscosity of the mucus. The nasal mucus layer is only 5 µm thick and it is organized in two distinct. Layers: an external, viscous and dense, and an internal, fluid and serous. Overall, nasal mucus layer consists of 95% of water, 2.5-3% of mucin, and 2% of electrolytes, proteins, lipids, enzymes, antibodies, sloughed epithelial cells and bacterial products. Nasal mucus is indispensable for several physiological functions, such as humidification and warming of the inhaled air, and also offers physical and enzymatic protection.

OLFACTORY REGION

The olfactory region is located in the roof of the nasal cavity and extends a short way down the septum and lateral wall. Its neuroepithelium is the only part of the CNS that is directly exposed to the external environment .Similarly to the respiratory epithelium, the olfactory one is also pseudo stratified but it contains specialized olfactory receptor cells important for smell perception.[15] In this area there are also small serous glands (glands of Bowman) producers of secretions acting as a solvent for odorous substances .

ADVANTAGES OF NASAL MICROSPHERES:

- Drug degradation does not occur
- Hepatic first – pass metabolism is absent
- The drug absorption is rapid.
- The onset of action is quick.
- The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
- Better nasal bioavailability for smaller drug molecules.
- Drugs which cannot be absorbed orally may be delivered to the systemic circulation through nasal drug delivery system.
- Convenient route when compared with parenteral route.

DISADVANTAGES OF NASAL MICROSPHERES

- Dose is limited because of relatively small area available for absorption
- Time available for absorption of drug is limited
- Diseased condition of nose may result in impaired absorption of drug
- Little is known of the effect of common cold on transnasal drug delivery
- And it is likely that instilling a drug in to a blocked nose or a nose with the
- Surplus of watery rhinorrhea may expel the medication from the nose
- The nasal route of drug delivery is not applicable for all the drugs, polar
- Drugs and some macromolecules are not absorbed in sufficient concentration Because of poor membrane permeability, rapid clearance and enzymatic degradation In to the nasal cavity

LIMITATION

The absorption enhancers used to improve nasal drug delivery system may have histological toxicity which is not yet clearly established.

1. Absorption surface area is less when compared to GIT.
2. Once the drug administered cannot be removed.

USE OF ABSORPTION ENHANCERS

By using absorption enhancers we can increase the absorption Of drug in the nasal cavity, thus increasing the bioavailability of drug. We can use surfactants (laureth-9), bile salts, fatty acids .poly l-arginine. [16][17][18]

MATERIALS USED IN NASAL MICROSPHERES

Polymers-mucoadhesive polymers are water soluble polymers which are swellable Networks jointed with cross linking agents. We can use both natural and synthetic polymers in natural polymers we can use chitosan,guar gum and sodium alginate,and in synthetic polymers we can use ethylcellulose,hpme and polyvinyl alcohol.cross linking agents that can be used are citric acid,glutaraldehyde and triopolyphosphate.[19]

METHODS OF PREPERATION

PREPERATION OF MICROSPHERES BY THERMAL CROSS LINKING

Citic acid as cross linking agent was added to 30ml of an aqueous acetic acid
PREPARATION OF MICROSPHERES BY GLUTARALDEHYDE CROSSLINKING
A 2.5% (wt/vol) chitosan solution in aqueous acetic acid was prepared. This dispersed phase was added to continuous phase (125 mL) consisting of light liquid paraffin and heavy liquid paraffin in the ratio of 1:1 containing 0.5% (wt/vol) Span 85 to form a w/o emulsion. Stirring was continued at 2000rpm using a 3-blade propeller stirrer (Remi Equipments, Mumbai, India). A drop-by-drop solution of a measured quantity (2.5 mL each) of aqueous glutaraldehyde (25% vol/vol) was added at 15, 30, 45, and 60 minutes. Stirring was continued for 2.5 hours and separated by filtration under vacuum and washed, first with petroleum ether (60°C-80°C) and then with distilled water to remove the adhered liquid paraffin and glutaraldehyde, respectively. The microspheres were then finally dried in a vacuum desiccators.[20][21]

PREPARATION OF MICROSPHERES BY TRIPOLYPHOSPHATE
Chitosan solution of 2.5% wt/vol concentration was prepared. Microspheres were formed by dropping the bubble-free dispersion of chitosan through a disposable syringe (10 mL) onto a gently agitated (magnetic stirrer) 5% or 10% wt/vol TPP solution. Chitosan microspheres were separated after 2 hours by filtration and rinsed with distilled water, then they were air dried.

PREPARATION OF MICROSPHERES BY EMULSIFICATION AND IONOTROPIC GELATION BY NAOH
Dispersed phase consisting of 40 mL of 2% vol/vol aqueous acetic acid containing 2.5% wt/vol chitosan was added to the continuous phase consisting of hexane (250 mL) and Span 85 (0.5% wt/vol) to form a w/o emulsion. After 20 minutes of mechanical stirring, 15 mL of 1N sodium hydroxide solution was added at the rate of 5 mL per min at 15-minute intervals. Stirring speed of 2200 rpm was continued for 2.5 hours. The microspheres were separated by filtration and subsequently washed with petroleum ether, followed by distilled water and then air dried.

PREPARATION OF ETHYLCELLULOSE MICROSPHERES
A solution of Ethyelcellulose in acetone was added to liquid paraffin containing emulgent (Span 85) while stirring at a speed of 1500 rpm. The emulsion was stirred for 5 to 6 hours at 25°C to 30°C. Subsequently suit able amount of petroleum ether was added to the dispersion, filtered, and dried at ambient temperature. The resultant microspheres were washed with water followed by petroleum ether to remove traces of liquid paraffin. The microspheres were desiccated under vacuum.

SPRAY DRYING
In Spray Drying the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane. Acetone, etc. The drug in the solid form is then dispersed in the polymeric solution under high-speed homogenization.[22] This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100µm. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions.see fig-2

CHARACTERIZATION OF MICROSPHERES
PARTICLE SIZE, SHAPE AND MORPHOLOGY
All the microspheres were evaluated with respect to their size and shape using optical microscope fitted with an ocular micrometer and a stage micrometer. The particle diameters of more than 100 microspheres were measured randomly by optical microscope. Scanning Electron photomicrographs of drug-loaded microspheres were taken. A small amount of microspheres was spread on gold stub. Afterwards, the stub containing the sample was placed in the Scanning electron microscopy (SEM). A Scanning electron photomicrograph was taken at an acceleration voltage of 20KV.[23][24].
through a cuffed endotracheal tube gives the ventilation. The body temperature is maintained at 37-38°C by a heating pad. The blood sampling is carried out from the jugular vein.

IN-VITRO STUDIES

IN-VITRO WASH OFF TESTS
A 1 cm x 1 cm piece of rat stomach mucosa was tied onto a glass slide (3 inch x 1 inch) using a thread. Microsphere was spread onto the wet, rinsed, tissue specimen and the prepared slide was hung onto one of the groves of the USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen regular up and down movements in a beaker containing the simulated gastric fluid. At the end of every time interval, the number of microsphere still adhering on to the tissue was counted and there adhesive strength was determined using the formula.[27]-[31]

IN-VITRO DRUG RELEASE
To carry out invitro drug release accurately weighed 50 mg of loaded tissue was counted and there adhesive strength was determined using the formula.

IN-VITRO DIFFUSION STUDIES
In Vitro diffusion studies were performed using in vitro nasal diffusion cell. The receptor chamber was filled with buffer maintained at 37±2°C. Accurately weighed microspheres equivalent to 10 mg were spread on sheep nasal mucosa. At selected time intervals 0.5 ml of diffusion samples were withdrawn through a hypodermic syringe and replaced with the same volume of pre-warmed fresh buffer solution to maintain a constant volume of the receptor compartment. The samples were analyzed spectrophotometrically. The released drug content was determined from the standard calibration curve of given drug.

TRANSPORT PATHWAYS FROM NOSE TO BRAIN
The different route via which drug delivered nasally can reach to CSF and brain are shown. Where the thickness of arrows indicates the likelihood of drugs exploiting the route in question. When drugs are administered Nasally the drug will normally be rapidly cleared by the mucociliary clearance system. Some of the drugs will be absorbed in the blood stream, from where it reaches the systemic Circulation directly and subsequently is eliminated from the body by the body’s clearance Mechanism. The drug can reach the brain from blood by crossing blood brain barrier (BBB) But can not be eliminated from csf in the blood.in order for a drug to travel from olfactory region in the nasal cavity to the cef of the brain parenchyma it has to transverse the nasal Olfactory epithelium an depending on the pathway followed, also the arachnoid system Surrounding the subarachnoid space.[32][33]

MECHANISM OF NASAL DRUG ABSORPTION
The first step in the absorption of drug from the nasal cavity is passage through the mucus . Small, unchanged particles easily pass through this layer. However, large or charged particles may find it more difficult to cross. Mucin, the principle protein in the mucus, has the potential to bind to solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature, etc.) two mechanisms have been considered predominantly. 1) The first mechanism involves an aqueous route of transport, which is also known as the paracellular route. This route is slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons. 2) The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions.[34][35]

FUTURTE OPPORTUNITIES
NOSE TO BRAIN
When the target organ is the central nervous system (CNS) and especially the brain, some researcher claim a new route of drug delivery: direct transport of drugs from the nose to the brain/CNS. Clearly deposition in the olfactory region and a good absorption are essential. [36]-[40]

NASAL VACCINATION
To create mass and rapid immunization, a nasally applied aerosol vaccine has a great potential. Development of nasal immunity and generalized immunization in a whole population has been proven successfully in several pilot studies in Russia and South America

CONCLUSION
Considering the widespread interest in nasal drug delivery and the potential benefits of intranasal administration, it is expected that novel nasal products will continue to reach the market.[47] They will include not only drugs for acute and long term diseases, but also novel nasal vaccines with better local or systemic protection against infections. The development of drugs for directly target the brain in order to attain a good therapeutic effect in CNS with reduced systemic side effects is feasible. [48] However, it was also stated that intranasal routes presents several limitations which must be overcome to develop a successful nasal medicine. Physiological conditions, physicochemical properties of drugs and formulations are the most important factors determining nasal drug absorption.[49] The use of prodrugs, enzymatic Inhibitors, absorption enhancers, mucoadhesive drug delivery systems and new pharmaceutical formulations are, nowadays, among the mostly applied strategies. Each drug is one particular case and, thus, the relationship between the drug characteristics, the strategies considered and the permeation rate is essential.[50]

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