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A Review on In Vitro Methods and Factors Affecting Nasal Drug Absorption

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ABSTRACT

Nasal drug delivery is an excellent approach for avoiding first pass effect of oral dosage form. It offers a direct systemic delivery of drugs. Nasal administration can therefore be used as an alternative to oral administration for example tablets and capsules if a fast effect is desired or if the drug is extensively degraded in the gut or liver. The primary goal of this article is to study factors affecting nasal drug absorption and the in-vitro methods available for nasal absorption of drugs. There are many in-vitro models for testing absorption studies and it has many advantages over in-vivo methods such as a controlled environmental study of epithelial cell growth and differentiation, drug transport pathways and mechanisms are elucidated easily, it has very fast means of evaluating drug permeability and to minimize expensive use of animals. Cell culture and cell line models were found to be best for nasal in-vitro absorption studies. Similar results are obtained from in-vitro studies. So by using in-vitro methods one can mimic the in-vivo conditions. It avoids disadvantages of in-vivo study. It was concluded that in-vitro models mimics the results of in-vivo study. But up till now no any system is superior to one another.

Keywords- In-vitro methods, nasal drug absorption, PDMS and Culture models.

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INTRODUCTION

Nasal drug delivery is gaining importance as alternative over parenteral route. It has been proved that the problem of first pass metabolism of amlodipine besylate was solved by preparation of mucoadhesive microsphere's of amlodipine besylate for nasal delivery resulting increase in bioavailability. Nasal drug delivery is also alternative for delivery of vaccines and proteins such as drugs which are susceptible for enzymatic or acidic degradation. Now for variety of indications nasal route is preferred therapeutically. A research work is going on diabetes, endometriosis, hypoglycemia, vomiting and prostate cancer to deliver nasally[1].

Nasal administration provides no. of advantages for systemic delivery of drug such as nasal mucosa provides a large surface area, relatively high apparent permeability for both in hydrophilic and lipophilic molecules and thin epithelium. Nasal delivery has few limiting factors such as rapid mucocilliary clearance resulting low retention time of drug (15 – 30 min), enzymatic degradation (carboxyl esterase, aldehydes dehydrogenase, epoxide hydrolases glutathione S-transferases and cytochrome P-450 isoenzyme), mucus layer, epithelium as physical barrier, small dose volume, (25 - 200µl).

The approach of this article is to study factors affecting nasal drug absorption and the in-vitro methods available for nasal absorption of drugs. The in-vitro models has many advantages over in-vivo such as a controlled environmental study of epithelial cell growth and differentiation, drug transport pathways and mechanisms are elucidated easily, it has very fast means of evaluating drug permeability and to minimize expensive use of animals. Although utilization of human nasal primary cell culture method technique leads to show very promising results, but some problems needs to be resolved, such as, problem of epithelial cell differentiation, amount of obtainable cells are very small. By using tissue culture plate's primary culture of human nasal epithelial cells gives natural cell differentiation. For the development of primary culture method of human nasal epithelium the reliable sources of human nasal tissue is a major limiting factor. So the passage culture method of nasal epithelial cells could be the bypass for human nasal tissues [2,3]

Factors Affecting Nasal Drug Absorption [1,2]

Physiological factors-

Mucocilliary Clearance- The function of mucocilliary clearance is very much important in preventing and removing foreign substances and particle's from reaching to lowest airways. This system is also named as a "conveyer belt" in which ciliated cells (See fig. no. 1) are responsible

for providing driving force. For this reason the productivity of the mucocilliary clearance system is relay on the rheological properties of the mucus layer and on the physiological control of the ciliated cells. It has been reported that the normal mucocilliary transit time in humans is 12 – 15 min. More than 30 min. is considered to be abnormal and that is signal of mucocilliary clearance dysfunction. 8 mm/min. is average rate of nasal clearance ranging from less than 1 min. to more than 20 mm/min.

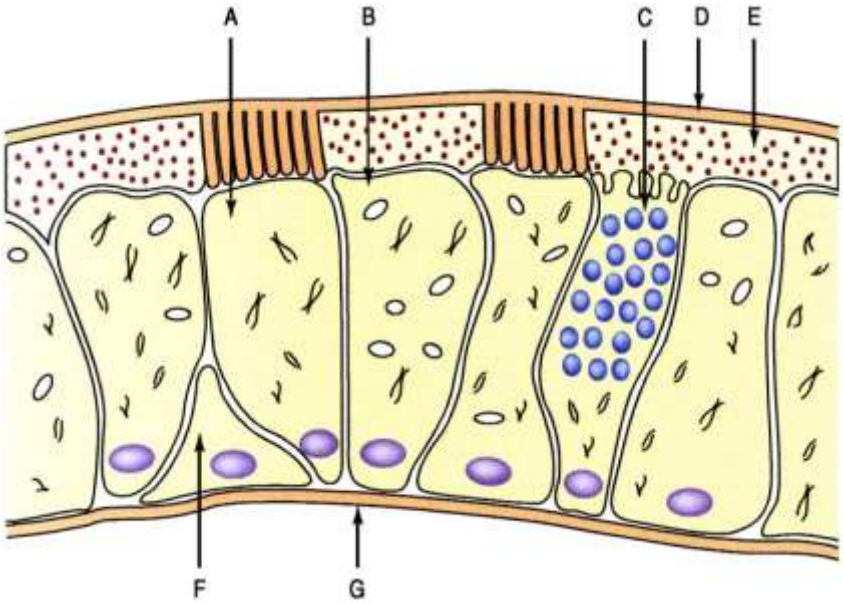

Figure 1- Cell types of the nasal epithelium showing ciliated cell (A), non-ciliated cell (B), goblet cells (C), gel mucus layer (D), sol layer (E), basal cell (F) and basement membrane (G).

Enzymatic Degradation- Enzymatic degradation is possible but at low extent in nasal mucosa. So this limits the bioavailability of some drugs especially drugs which contains peptides and proteins. Broad range of metabolic enzymes present in nasal mucosa. Oxidative phase I enzymes (e.g. cytochrome P-450), non-oxidative enzymes, conjugative phaseII enzymes and proteolytic enzymes such as endo peptidases e.g. serine, cysteine, attacks on internal peptide bonds and exopeptidases e.g. mono and diamino peptidases cleaves the N and C terminals of peptide.

Nasal Pathophysiology

The absorption of drugs from nasal cavity in many pathophysiological conditions in many different ways such as seasonal rhinitis, common cold, cancer and nasal polyps. In-vitro rhinovirus infection causes sloughing of epithelial cells and destruction of the epithelial layer. See table 1

Table 1- Structural features of different sections of nasal cavity and their relative impact on permeability [3]

Region	Structural features	Permeability
Nasal vestibule	Nasal hairs(vibrissae) Epithelial cells are stratified, squamous and keratinized Sebaceous glands present	Least permeable because of the presence of keratinized cells
Atrium	Trans epithelial region Stratified squamous cells present anteriorly and pseudo stratified cells with micro villi present posteriorly Narrowest region of nasal cavity	Less permeable as it has small surface area and stratified cells are present anteriorly
Respiratory region(inferior turbinate middle turbinate superior turbinate)	Pseudo stratified ciliated columnar cells with microvilli (300percell),large surface area Receives maximum nasal secretions because of the presence of seromucusglands, nasolacrimal duct and goblet cells Richly supplied with blood for heating and humidify-cation of inspired air, presence of paranasal sinuses	Most permeable region because of large surface area and rich vasculature
Olfactory region	Specialized ciliatedol factory nerve cells for smel lperception Receives ophthalmic and maxillary divisions of trigeminal nerve.	Direct access to cerebro spinal fluid
Nasopharynx	Upper part contains ciliated cells and lower parts contains squamous epithelium.	Receives nasal cavity drainage

Low Bioavailability

Bioavailability of polar drugs is reduced in nasal epithelium up to 10 % for low molecular weight drugs and for calcitonin and insulin above 1 %. Low membrane permeability is the important factor which limits the absorption of large mol. Wt. polar drugs such as proteins and peptides. Drugs can cross epithelial cell membrane by transcellular route or by vesicular transport mechanism or by paracellular route through the tight junctions between the cells. Polar drugs (below 1000 Da) will generally pass the epithelial membrane by paracellular route. Using an endocytic transport process larger proteins and peptides are able to pass the nasal membrane but in reduced amount. This can be improved by administration of trans-nasal absorption enhancers such as sodium lauryl sulfate (laurenth-9), bile salts and its derivatives (sodium glycocholate, sodium deoxycholate, and sodium taurodidrofusidate), fatty acids and its derivatives (linoleic acid), cyclodextrins, cationic compounds such as chitosan and its derivatives, phospholipids (lysophosphatidylcholine). These trans-nasal absorption enhancers works by variety of ways but generally act by modifying the phospholipid bilayers, leaching of proteins by the membranes or even stripping off the mucosa, these all alters permeability of epithelial cell layer.

Physico-chemical characteristics of the substance-

Physic-chemical factors such as dissolution rate, particle size, solubility, molecular weight, partition coefficient, polymorphism, charge affects the nasal absorption of drugs. Lipophilicity is

an important factor. In contrast with quaternary ammonium compounds where a decrease in absorption is results with increase in lipophilicity and molecular weight.

Donovan studied on rat for an inverse relationship between molecular weight and percent absorption based on polyethylene glycol of different molecular weight and reported that good bioavailability for compounds with molecular weight up to 1000 kDa in formulations except adjuvants. He also demonstrated on contrary of findings, absorption characteristics varies between nasal and gastrointestinal mucosa in rats.

Formulation factors [2-7]

Formulation parameters such as osmolarity, pH, pKa, viscosity, and dose, volume of distribution, drug concentration, absorption enhancers, different excipient and even dosage form affects the nasal absorption of drug. Administration way and devices used to administer the drug also affects the nasal bioavailability.

pH of the formulation

pH of the formulation and pKa both affects the nasal bioavailability. For avoiding nasal irritation the pH range must be 4.5 to 6.5. The enzyme lysosome is present in secretions of nose and it is responsible for destroying bacteria's in acidic pH. For good nasal absorption of drug, it should be in un-ionized form.

Osmolarity

It is advisable to adjust tonicity of formulation. Hypertonic solutions are responsible for shrinkage of nasal epithelial mucosa and it also ceases or inhibits nasal ciliary activity. Animal model study shows that increased bioavailability for salmon calcitonin from nasal spray formulations. Other studies shown that improved drug permeability resulted from hypotonic nasal sprays. Existing marketed products e.g. Zomig (zomitriptan nasal spray) has osmolarity of 420 - 470 mOsmol/L and pH 5.

Viscosity- Eccleston et.al study suggest that high viscosity was the controlling factor for prolonged residence time of the spray in nasal cavity. The product investigated by him has a shear thin and thixotropic characteristics.

Non-aqueous nasal sprays

In the market, prescription nasal spray product are of mostly aqueous formulations. Many patents are covered by non-aq. Nasal spray formulations which contains poorly water soluble products. Use of propylene glycol and PEG 400 in nasal formulations are shown to cause local irritation and hyper osmolarity and also use of isopropyl alcohol reported to cause acute damage to nasal mucosa in animal models and similar effects are suspected in humans. So chronic use of non-

aqueous formulations reported to cause increases level of safety risk to human health. The FDA has recently accepted an new drug application for a non-aqueous (dry)beclomethasone dipropionate nasal spray for treatment of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR) and hydro fluroalkane propellant is used in formulation.

Dose and dosage volume

The drug deposition is highly dependent on dosage form of drug, volume and delivery device. For dosage administration limited volume is available in nasal cavity. The reports of nasal bioavailability of desmopressin study suggest that by delivering drug twice in each nostril optimal dose may be obtained. It was reported that from that observation 100 µL rather than from 200 µL dose is optimal for administration. The clearance time reported are 240 min. and 120 min. for 100 µL and 200 µL respectively. According to another study 100 µL single spray occupied a greater area than 2 sprays of 50 µL. Spray formulations containing different level insulin's were evaluated (1.25, 2.5, 5 and 10 U/Kg) in 1% w/v sodium taurocholate in normal rabbits. Increased hypoglycemic effects was observed for 10 U/Kg spray while the minimum effect was suspected with 1.25 U/Kg spray. But there is no proportional increase in glucose reduction when compared to increasing dose indicating that the amount of insulin that can absorbed is limited. According to these reports it suggest that only drug mass (applied amount) and available absorption surface area determines the nasal absorption of drug.

In-Vitro Screening Methods [8-11]

For both topical and systemic action the nasal route is widely preferred for administration of drug. It is essential to gain a thorough insight of the nasal absorption potential, metabolism and toxicity of the active compound and the components of the drug formulation at an early stage in drug discovery and during the development process. Human nasal epithelial cell cultures may provide a very reliable and important screening tool for pharmaco-toxicological assessment of potential nasal drug formulations. The approach of this article is to study the factors affecting nasal drug absorption and the in-vitro methods available for nasal absorption of drugs.

A primary goal in the development of in vitro cell culture systems is to maintain differentiated morphology and biochemical features, resembling the original tissue as closely as possible. The potential and limitations of the existing in vitro human nasal models are summarized. Several considerations with respect to the use of in vitro systems for pharmaceutical applications (transport, metabolism, assessment of ciliary toxicity) are also discussed.

Cell Culture Methodology[12,13]

Due to species differences, the use of human nasal epithelial cells in culture (primary and cell

lines) is a promising system enabling the prediction of nasal drug transport, metabolism and toxicity in humans. The human origin of the cells gives more direct clinical relevance of the studies performed on these cells. The use of in vitro cultures of nasal epithelial cells in pharmacological and toxicological studies has several advantages such as more standardized systems due to control of the experimental conditions and elimination of pre- and post-mucosalfactors; rapid evaluation of the potential permeability, metabolism and toxicity; in vitro exposure of human cells to compounds that could not be investigated in humans in vivo, allowing an understanding of the mechanisms of drug transport, metabolism, and toxicity as well as the evaluation of the strategies for their modulation; limited number of experimental animals and amount of research compound required in the screening phase.

Due to the difference in the nasal epithelium, for initiation of primary cell culture intended to be used in permeation, metabolism and toxicity studies the sampling sites should be restricted to regions where drugs are deposited for systemic delivery. The most relevant region is the respiratory epithelium lining the middle and inferior turbinate. The nasal respiratory area is covered by a pseudo stratified columnar epithelium and it is composed of basal cells, goblet cells, and nonciliated and ciliated columnar cells. The basal cells are believed to be progenitors of the other cell types; they dwell on the basement membrane and do not reach the airway lumen. Desmosomes mediate their adhesion to adjacent cells, and hemi desmosomes to the basement membrane. The columnar (ciliated and non-ciliated) and goblet cells rest on the basement membrane and reach the airway lumen.

A primary approach in the development of in vitro cell culture systems is to maintain differentiated morphology and biochemical features, resembling the original tissue as closely as possible. From several studies, carried out on human and rodent airway epithelial cells, it is clear that various factors may affect cell proliferation and differentiation in vitro: isolation procedure, medium composition (growth factors, hormones), cell-support substrate, seeding density, and the presence of an air–liquid interface.

Primary culture Methodology[12,13]

Human nasal epithelial tissue is easy to obtain, which enables the use of fresh and relatively normal tissue for cell isolation. Specimens of human nasal epithelium, obtained from patients treated by endonasal surgery because of nasal polyps, septum deviation, hyperplastic conchae, or nasal reconstruction have been normally used as a source of nasal epithelial cells. A number of traumatic techniques (nasal brushing, lavage, scraping, nasal smears, blown secretion) to sample human nasal tissue; these are nonsurgical procedures, which are well tolerated, no anesthesia

required, permit repeated isolation from the same source, and avoid the use of proteolytic enzymes. The main disadvantage of these methods is the limited number of cells that can be obtained in a given procedure. It was reported that isolation of 100–500 epithelial cells for each brushing, which is insufficient to establish a high density cell culture. There are two basic approaches for initialization of epithelial cell cultures using human nasal surgical specimens: the explant outgrowth technique and the enzymatically dissociation of isolated tissue. An explant outgrowth culture system maintains human nasal epithelial cells with ciliary activity for long term, this approach is complicated by the presence of nonepithelial cell types that provide ‘‘factors’’ that are difficult to define. Another disadvantage of the outgrowth approach is the longer time needed to establish the cell culture, compared to the direct plating of enzymatically dissociated cells. The relatively high amount of tissue and cells harvested is the main advantage of traumatic methods. Different enzymes have been used forthe isolation of nasal epithelial cells; pronase (0.1–0.5%) is the most commonly used. The advantage of plating dissociated cells is the possibility to reduce fibroblast contamination, which is an important factor in establishing pure long-term nasal epithelial cell culture. Differential attachment on plastic (1–2 h) and discharge of the adherent cells has been used to eliminate most contaminating fibroblasts. Other factors reducing fibroblast contamination are incubation with pronase at low temperature, and serum-free culture media. Different approaches exist to reduce cell cluster formation: use of deoxyribonuclease (DNase, Type I) during protease incubation, and/or filtering the cell suspension through filters (40–100 lm). The usefulness of plating a single cell suspension versus cell clusters is not explained. Individual ciliated cells do not anchor on collagen gel because of the ciliary beating or lose their cilia after attachment. On the other hand, cell aggregates complicate accurate cell enumeration and induce spotty attachment, factors leading to experimental variations. Although the primary cell cultures of human nasal epithelial cells are a distinguished tool for pharmaco-toxicological, biochemical and electrophysiological studies, they have some limitations. The main disadvantages are related to: limited number of cells available from one donor; relatively short-term cultures; heterogeneity within cultures and between cultures (because of changes in the differentiation pattern); contamination with pathogens; significant donor-to-donor variability; and difficulties in culturing. In general, most of these limitations can be overcome by sub culturing the cells while maintaining their ability to differentiate into secretory and ciliated epithelial cells; however the passaging of respiratory epithelial cells is limited to a maximum of two to three subsequent passages have developed a

suspension culture system which consists of epithelial vesicles and aggregates, and promotes ciliogenesis. The in vitro induced ciliogenesis results in normal and intercellularly coordinated ciliary activity for up to 6 months. For studying ciliogenesis, ciliary beat frequency, ciliotoxicity and the mechanism involved in their regulation the suspensionculture approach is a useful tool**.** Another study showed that cultured human nasal epithelium may be used to study strategies to improve nasal absorption of peptides via protease inhibition and absorption enhancement. Additionally, cytotoxicity and membrane perturbation with respect to nasal drug delivery using excipients may also be elucidated using human nasal primary cultures. Based on the results of this study, a combination of protease inhibitors (bestatin, puromycin) with absorption enhancers possessing peptide stabilization characteristics in some cases resulted in a significant increase in nasal Leu-Enk permeation. It is yet to be seen whether the membrane perturbation and cytotoxicity observed with the various combinations of protease inhibitors with absorption enhancers really raise safety concerns when used under in vivo condition. This is because the literature is full or articles using in vitro cell cultures with absorption enhancers for oral delivery in which cytotoxicity was seen even at very low concentrations.

Cell lines[12-16]

To overcome the serious problem of the short supply of human nasal tissue, studies to transform primary cultures of epithelial cells to cell lines with extended or permanent in vitro lifespan were performed. Cell lines are derived from carcinomas of epithelial origin with their extended lifespan, improved proliferation and homogeneity, this may overcome some limitations of primary cell cultures methodology. For studying epithelial-specific diseases such as cystic fibrosis, inflammatory processes, mucin genes expression, and mucin production they provided the model system. The nasal cell lines most often used in these studies are RPMI 2650, BT and NAS 2BL. It has been shown that, the human lung adenocarcinoma cell line Calu-3 model is used as a surrogate for nasal epithelium. Human nasal anaplastic squamous cell carcinoma of the nasal septum is used to derive RPMI 2650 cell lines. In culture, RPMI 2650 cells form clusters made up of round and slightly flattened cells or show a tendency to spread, which depends on the support and extracellular matrix used. It do not form monolayers and do not express goblet and ciliated cells. This carcinoma cell line expresses MUC1 mRNA. RPMI 2650 cell cultures found to be unsuitable for the evaluation of nasal transport and tolerability because of the poor differentiation and lack of polarization, but they can be a useful model for metabolism studies. The amino peptidase activity of RPMI 2650 cells is comparable with that of surgically excised human nasal tissue. They express leucine aminopeptidase, aminopeptidase N, A, B and

lysosomal amino peptidase, enzymes which may influence the nasal delivery of peptides and proteins. Cell lines that do not develop functional tight junctions and transepithelial resistance may be valuable for studies that do not depend on cell polarization. It is postulated by many researchers working with RPMI 2650 cells that this immortalized cell line was found to be not suitable for permeation studies and preferred to work with primary cultures of nasal epithelial cells. Only few authors suggest that this cell line has some potential for permeation studies. According to this assumption, they analyzed different culture conditions, especially coculture of human nasal fibroblasts, and their influence on barrier properties of RPMI 2650 cells and results shoes that it is possible to form a permeation model of the nasal mucosa with RPMI 2650 cells. Of major importance is the cultivation at air–liquid interface, which permits a confluent growth. A lack of organotypic differentiation is certainly a limit of the model, which is morphologically not wholly organotypic. However, the permeation co-efficients of the RPMI epithelial model were in the same range as human nasal mucosa and only about a factor of 1–2 higher than the excised tissue.

RPMI 2650 epithelial model[14] For the standard RPMI 2650 epithelial model for permeation experiments, RPMI 2650 cells were seeded onto Tran swell filter inserts (3 µm pore size, polycarbonate) at a density of 200,000 cells/1.13 cm^2 . The cultures were maintained in a liquid-covered culture for 8 days, and medium was replaced every 2–3 days. After 8 days, the inserts were either lifted to an air–liquid interface culture, or kept in liquid-covered culture. After two more weeks (days 21–23), the RPMI models could be used for experiments. Permeation experiments were conducted in triplicate.

Excised nasal tissue[8]

Tissue models- Excised nasal mucosae of different species are frequently used tools to study nasal transport and metabolism. Taking the difficulties into account to obtain human tissue from nasal biopsies, it becomes obvious that most studies were performed with epithelia excised from animals. Rabbit tissue has been used for the majority of studies. In addition, mucosae from ovine, canine and human origins were selected. They has been chosen bovine nasal mucosa obtained from the local slaughterhouse as model membrane, mainly because of its ready and economic availability in sufficient quantity and reproducible quality. This model has been shown to be well suited for studies on nasal permeation and nasal metabolism of peptides. When using animal tissue, species differences in the activity of the various nasal enzymes between various species and between test animals and human nasal mucosa become an important issue. Studies on enzyme activities by Zhou in rats, rabbits, guinea-pigs, and dogs using nasal tissue

homogenates showed species differences in the activity of amino peptidases and esterases. So far however, the data base available is insufficient to allow more detailed interspecies or animal versus human differentiation.

Tissue preparation and characterization

The dissection techniques of animal nasal epithelium may widely depend on the species selected. Slaughterhouses is used to provide ready access to bovine nasal tissue in sufficient quantity and reproducible quality. Tissue containing nasal mucosa is dissected immediately after slaughter. Tissue containing the mucosa is obtained by removing the skin around the nose and cutting out the frontal part of the nasal conchabove the os incisivum with a sharp knife starting from the incisura nasoin cisiva. Until further preparation storage on ice is necessary. The mucosa consisting of the epithelium and some of the connective tissue is then carefully separated from the lateral cartilage using a pair of tweezers and directly inserted into preheated diffusion chambers for equilibration and subsequent permeation or metabolism studies.

To obtain rabbit nasal mucosal tissue, animals were sacrificed, and a longitudinal incision through the lateral wall was made and the nasal cavity fully opened. After removing the lateral wall, the entire nasal septum was isolated using operating scissors or a scalpel. The nasal mucosa of dogs is obtained by cutting a bone block, with a cast-cutting saw, from just anterior to the orbits to the junction of the nasal bone with the dorsal parietal cartilage. The ethmo and maxilla turbinates are removed and the nasal mucosa carefully stripped from the nasal septum and lateral wall. For obvious reasons studies using human tissue are particularly rare[6]. For preservation of viable nasal tissue only fresh tissue can be used by freezing is unfeasible. How- ever, for studies with tissue homogenates, e.g. for enzyme activity studies, mucosal tissue may be frozen and stored at 70^0 C until further preparation.

IN VITRO DIFFUSION EXPERIMENTS[17-19]

Using human tissue-

It seems obvious that to mimic the conclusions of in-vivo situations, human tissue would be the best appropriate medium to use in a diffusion cell. Excision of the skin does not alter its permeability properties significantly, provided the stratum corneum remains intact, and several studies have shown that the stratum corneum performs similarly in vitro and in vivo, even several days after harvesting. It should, therefore, be possible to design representative in vitro systems using excised human or animal tissue, since a similarity between laboratory animal and human skin has been observed.

Using sheep nasal mucosae

Franz diffusion cell is used most of the times to mimic the in-vitro study to in-vivo. From the slaughter house collect freshly prepared sheep nasal mucosa in phosphate buffer saline pH 6.4. Identify the superior nasal conche and separate it from nasal membrane. Mount the excised nasal membrane on Franz diffusion cell. Stabilize the tissue by phosphate buffer pH 5.0 in both compartments and allow to stir on magnetic stirrer for 15 min. After 15 min. remove the phosphate buffer solutions from both compartments and fill fresh phosphate buffer pH 5.0 to receptor compartments. Mount the nasal membrane with glue to inhibit leakage of test sample and support with thread.

Using porcine nasal mucosae[17]

A suitable and well controlled in vitro model using porcine nasal mucosa has been established and evaluated using two transport markers. The results from the different methods used were in accordance with each other, showing that the viability and integrity of the epithelium were maintained during several hours of diffusion chamber studies.

Synthetic membranes for diffusion study

It may, theoretically, be possible to adequately simulate the in vivo permeation of a drug using a specific diffusion system and synthetic membrane. The commercial availability, stability, inter batch uniformity and ease of usage make the use of synthetic media highly desirable. The barrier potential of porous membranes is dictated by the probability of a diffusant molecule entering and diffusing through the pores, and the factors governing selectivity to diffusion would be the relative molecular size, molecular shape and its electrostatic interactions with the membrane. Conversely, a porous media appear to offer some rate-limiting factor to permeation and may, therefore, more closely simulate diffusion through biological tissue. The barrier properties here generally relate to the solubility of the diffusant in the polymer matrix (partition coefficient between donor vehicle and membrane) and the ease of diffusant passage through the polymer.

Cellulose media

Cellulose is a relatively rigid structure consisting of glucopyranose rings joined by B-1,4-linkages. This conformation allows only two types of movement in the chains: inversion of the pyranose ring (chair to boat forms) or rotation around the glycosidic linkage. Inaddition, the cellulose chains exist in a partially crystallized form due to interchain hydrogen bonding. Commercial cellulose membranes have a cut off of 8000-15000 Daltons for molecular dialysis. Cellulose acetate (dialysis) media have been extensively used in diffusion cell systems, while cellulose nitrate has been used as a model for the gastric barrier. Corrigan used cellulose dialysis

tubing as a diffusion medium for hydrocortisone and its polyvinyl pyrrolidone co- precipitates.

Filter membranes

Porous filter membranes have seen relatively little usage in diffusion systems in comparison to the synthetic polymers. Some researchers used a polycarbonate filter membrane to separate topical delivery formulations from receptor media in a simple drug release apparatus. Interestingly, they state that this membrane was chosen for investigation in preference to cellulose or silicone media because hydrocortisone acetate was not found to diffuse through the latter two membranes into propylene glycol receptor phase using their particular diffusion cell. Generally, porous filter media appear to be most useful as a support medium where the release rate of drug from the delivery system is under investigation, and not the actual transdermal kinetics of the permeant. In these cases the filter medium does not simulate the skin and provides no significant barrier to diffusant passage.

Synthetic polymers

Silicone polymers such as polydimethylsiloxane (PDMS)have received recent attention because they are lipophilic in nature and highly permeable to many non- ionic drugs which dissolve in the barrier matrix and diffuse across it. They synthesized a number of polydimethyl siloxane membranes in which each alternate bonding oxygen atom between polymeric units was replaced with an organic constituent. Generally, the permeability coefficients of the diffusants varied inversely with the rigidity of the synthesized polymers. Study shows that diffusion coefficients of the same order of magnitude for a number of different progesterone-like steroids through silicone membrane.

CONCLUSION

The primary goal of this article is to study factors affecting nasal drug absorption and the in-vitro methods available for nasal absorption of drugs. Nasal drug delivery is a promising area for delivery of drugs. Because of systemic delivery of drug it gives many advantages over oral dosage form. In-vivo absorption methods are used to study nasal absorption. It is very time consuming and it has many disadvantages. So many researchers developed an in-vitro absorption methods to study nasal absorption. It was concluded that in-vitro models mimics the results of in-vivo study. But up till now not any system is superior to one another. In-vitro methods has many advantages over in-vivo methods. For nasal delivery of drug the factors which affects the nasal drug absorption should be considered during formulation. It has become clear that various factors need to be well defined and standardized to obtain reproducible results.

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