REVIEW ARTICLE

Accepted 5 February 2005
Revised 11 October 2004
Received 6 February 2004
Indian J. Pharm. Sci., 2005, 67(1): 19-25

Nasal Drug Delivery: An Overview

SARASIJA SURESH* AND SHYAMALA BHASKARAN
Department of Pharmaceutics, Al-Ameen College of Pharmacy, Bangalore-560 027

Recently, it has been shown that many drugs have better bioavailability by nasal route than by oral route. This has been attributed to rich vasculature and a highly permeable structure of the nasal mucosa coupled with avoidance of hepatic first-pass elimination, gut wall metabolism and/or destruction in the gastrointestinal tract. The nasal route could be particularly important for drugs used in crisis management such as for pain and for centrally acting drugs where the pathway from the nose to brain might provide a faster and more therapeutic effect. This article focuses on newer developments and strategies for nasal delivery along with nasal absorption mechanism

Nasal administration offers an interesting alternative for achieving systemic drug effects of the parenteral route, which can be inconvenient or the oral route, which can result in unacceptably low bioavailability, in particular of proteins and peptides. The nasal epithelium is a highly permeable monolayer; the submucosa is highly vascular with relatively high blood flow, which promotes rapid absorption and also by passes hepatic first-pass metabolism. Other attractive features include the rather large surface area of the nasal cavity and importantly ease and convenience of administration[1-4]. The nasal route can be important for drugs that are used for crisis management such as for pain and for centrally acting drugs where the direct pathway from the nose to the brain might provide a faster and more specific therapeutic effect[5]. Another important application of nasal delivery would for vaccines in terms of efficacy and patience acceptance[6].

The world market has seen an increasing number of systemically acting drugs being marketed as nasal formulations. For example, Imitrex® nasal spray containing sumatriptan (GlaxoSmithKline, http://www.gsk.com), Zomig® containing zolmitriptan (AstraZeneca, http://www.astrazeneca.com), ergotamine nasal spray containing ergotamine (Novartis, http://www.novartis.com), Stadol® NS containing butorphanol (Bristol-Myers Squibb, http://www.bms.com) are nasal formulations for treatment of migraine, which have the advantage of faster onset of action. Aerodiol nasal spray containing estradiol (Servier, http://www.servier.com) has the advantage of improved bioavailability as compared to oral delivery. Peptides are normally being administered as an injection because of their low permeability and susceptibility to degradation by enzymes in the gastrointestinal tract. Suprecur nasal spray containing buserelin (Aventis, http://www.aventis.com), desmopressin acetate, Rhinal Tube containing desmopressin (Ferring, http://www.ferring.se) and Miacalcin® nasal spray containing calcitonin (Novartis) are peptides formulated for nasal delivery which have better systemic bioavailability by self-medication through the nasal mucosa than by oral administration. Recently a number of companies are specializing in the development of innovative nasal delivery systems and formulations. Examples include Nastech (http://www.intranasal.com), Britannia Pharmaceuticals (http://www.britannia-pharm.co.uk), Intranasal Technologies (http://www.intranasal.com), Bentley Pharmaceuticals (http://bentleypharm.com) and West Pharmaceutical Services (www.westpharma.com). These companies are actively developing nasal formulations for conventional generic drugs such as apomorphine, triptans, morphine, midazolam, fentanyl, non-steriod antiinflammatory drugs as

*For correspondence
E-Mail: sarasija_s@hotmail.com

well for peptides and proteins such as leuprolide, parathyroid hormone, insulin and interferon. This review attempts to discuss the newer developments and strategies for nasal delivery including nasal absorption mechanism, physicochemical and formulation factors to be considered in the development of nasal drug delivery systems. The advantages of nasal delivery of vaccines and nose to brain drug delivery also will be discussed.

NASAL ANATOMY AND PHYSIOLOGY

The nasal septum divides the nasal cavity into a right and left side. The lateral nasal wall consists of inferior and middle turbinate and occasionally a superior or supreme turbinate bone. The opening of the sinuses is also found under the middle turbinate on the lateral nasal wall. The lachrymal system drains into the nasal cavity below the anterior inferior aspects of the inferior turbinate. The general architecture and morphology of the human nasal cavity is shown in fig. 1.

The respiratory region consists of the inferior, middle and superior turbinates attached to the lateral wall. It occupies most of the nasal cavity. The nasal absorption of drugs is considered mainly to take place in this region. As in the case of all biological membranes, drugs can cross the nasal mucosal membrane using two different pathways, transcellularly- across the cell and paracellularly- between the cells. Lipophilic drugs are transported transcellularly

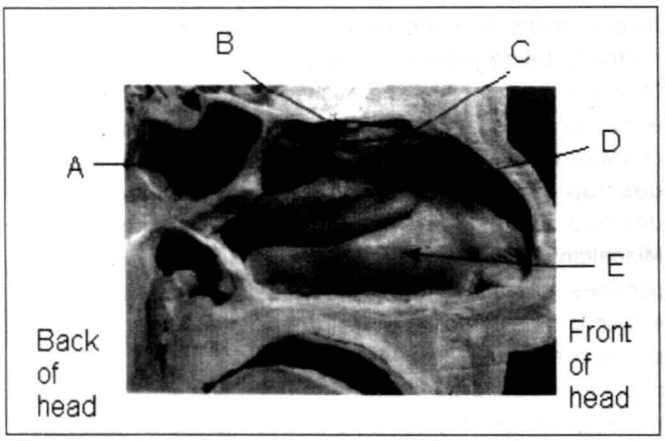

Fig.1: Nasal architecture and morphology of human nasal cavity

Human nasal cavity shown as vertical slice through the head from tip of the nose to the back of the nose: Sphenoid sinus (A), Olfactory region (B), Superior turbinate (C), Middle turbinate (D), Inferior turbinate (E). Slide has been obtained from Ref. 12 with modification.

by an efficient concentration dependent passive diffusion process, by receptor or carrier mediation and by vesicular transport mechanisms. Polar drugs are believed to pass through the epithelium via the gaps or pores between the cells (the tight junctions). Although, the tight junctions are dynamic structures that can open and close to certain extent, the size of these channels is less than 10 Å[7,8]. Hence, the paracellular route will be less efficient for large molecules and is dependent upon the molecular weight of the drug with a general molecular size cut-off of 1000 Da[7].

Lipophilic drugs, such as propranolol, progesterone, pentozocine and fentanyl, generally demonstrate rapid and efficient absorption when given nasally. For such drugs, it is possible to obtain pharmacokinetic profiles similar to those obtained after an intravenous injection with bioavailabilites for some drugs approaching 100%[5]. The nasal absorption of more polar compounds is however poor with bioavailabilities not exceeding 10 % of small molecular drugs such as alnidatan, morphine, sumatriptan and less than 1% for peptides such as insulin, calcitonin and leuprolide. For higher molecular weight proteins, the nasal absorption has been shown to be even lower although there is some evidence that even large proteins such as horseradish peroxidase can pass through the membrane, though to a small extent and is believed to be transported by the transcellular vesicular mechanism[9].

The mucociliary clearance system provides is an efficient defense system, protecting the respiratory system against inhaled bacteria, irritants and particles. It transports such agents backwards in the nose and downwards into the throat. This action is correlated with the beat of the cilia present in the respiratory epithelial cells. With a beat of around 1000 strokes per minute, the cilia transports the mucus with a speed of 5 mm/min. Formulation administered to the human respiratory epithelium has been found to be cleared from the nasal cavity with half-life of clearance of about 15 min[10]. There are several enzymes present in the nasal mucous including proteases and amino-peptidases at the mucosal membrane. However, the level of amino-peptidases is much lower than in the gastrointestinal tract. Peptides may form complexes with immunoglobulins in the nasal cavity leading to an increase in the molecular weight and reduction in permeability.

The poor transport of polar drugs across the nasal mucosa can be associated with three major factors, low membrane permeability, especially for large molecular drugs, a rapid clearance of drug formulation from the nasal

cavity as a result of mucociliary clearance mechanism and a possible enzymatic degradation of drug in the nasal cavity. Low membrane permeability of proteins and peptides is associated with their large molecular weight. The mucociliary action can in turn move the drug away from absorption site in the nasal cavity into the oesophagus whereby the drug is swallowed and absorption minimized[11]. A good example of this phenomenon is the marketed nasal spray of sumatriptan (Imigram, GSK) which has the bioavailability of 15.8%[12]. The sumatriptan spray is formulated as a simple aqueous solution and hence should be cleared rapidly from the nasal cavity. However, even the small quality absorbed nasally is able to bring rapid relief of migraine as compared to the oral tablet formulation[12].

ENHANCEMENT OF NASAL ABSORPTION

It is possible to greatly improve the nasal absorption of polar drugs by administrating them in combination with an absorption enhancer that promotes the transport of the drug across the nasal membrane. Also, a nasal drug-delivery system that combines an absorption enhancing activity with a bioadhesive effect, which increases the residence time of the formulation in the nasal cavity, has been shown to be even more effective for improving the nasal absorption of polar drugs[9]. Generally, the absorption enhancer act by one the following mechanisms; inhibition of enzyme activity, reduction of mucus viscosity or elasticity, decrease in mucociliary clearance, open tight junctions and solubilization or stabilization of drug substance.

Enhancers such as surfactants, bile salts, fatty acids and most phospholipids and lysophopholipids are chemical enhancers which work by modifying the phospholipid bilayer structure of cells, leaching out proteins or even stripping off the outer layers of the mucosa, thereby promoting the observed improved transcellular transport of drugs. For these systems, there is a direct correlation between the bioavailability and damage caused to the membrane[11]. For other chemical enhancers, those that work by transiently opening the tight junctions between cells such as chitosan[13,14], selected cyclodextrins and phospholipids, the absorption enhancing effect can greatly outweigh any modification caused to the mucosa[9]. For example, nasal oestradiol marketed recently by Servier in Europe has used cyclodextrin to solubilise the drug and thus enhance permeation[9]. Work on nasal insulin using phospholipids has been attempted in the 1990s by Nordisk and recently by Bentley Pharmaceuticals but not with encouraging results so far[15].

Chitosan can alter the paracellular transport of drugs by direct effect on the tight junctions between cells. It has been shown that the presence of chitosan at mucosal surface can lead to a transient opening of the tight junctions and opening occurs for a period of 15 minutes[12,16,17]. This can allow molecules as large as growth hormone (20,000 Da) to pass through the nasal lumen into the circulation. For drugs with molecular weights below approximately 10,000 Da, the use of chitosan can lead to an improvement in bioavailability from 5-10 fold[18]. This effect of chitosan has been observed with desmopressin, insulin, leuprolide, calcitonin as well as alniditan, the polar compound for treatment of migraine as well as analgesic agents such as morphine[18] which is shown in fig. 2. Extensive toxicological and tolerance studies in animals and man have shown chitosan to be non-toxic and have a reversible effect on the nasal mucosa[19].

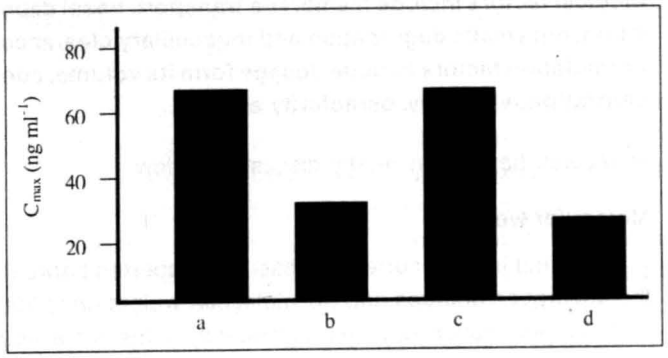

Fig. 2: A comparisons of peak plasma levels obtained after intravenous, intranasal and oral administration of morphine.

Intranasal formulations comprise of morphine solution and morphine-chitosan formulation. Dose of morphine is 15mg for nasal and oral administration and 10mg for intravenous administration. Intravenous morphine (a), Intranasal morphine solution (b), Intranasal morphine chitosan solution (c), Oral morphine (d). Figure obtained from Ref.12

FORMULATION DESIGN

The design of nasal formulations depends on the physicochemical properties of the drug molecule, the diseased condition for which treatment is required, the patient population and the marketing preference (fig. 3). Increase in nasal adhesion maybe required for drugs having poor permeability while drugs for local action may be in the form of a simple solution. The physicochemical properties of the drug

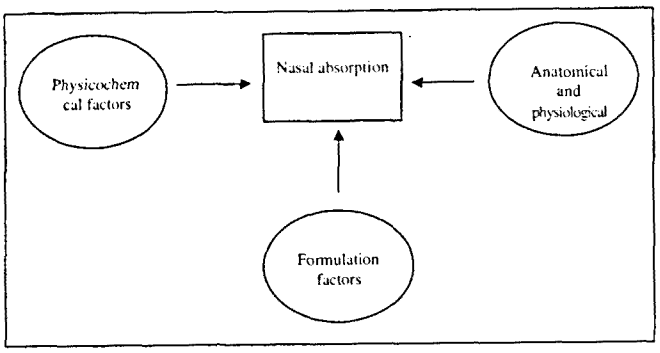

Fig. 3: The physicochemical . anatomical, physiological and formulation factors affecting nasal absorption of drugs

Physicochemical factors include molecular weight, lipophilicity and molecular charge; Anatomical and physiological factors include membrane transport, nasal deposition, enzymatic degradation and mucociliary clearance; Formulation factors include dosage form its volume, concentration, viscosity, osmolarity and pH.

molecules have been briefly discussed below.

Molecular weight:

A linear inverse correlation has been reported between the absorption of drugs and the molecular weight up to 300 Daltons. Absorption reduces significantly if the molecular weight is greater than 1000 Daltons except with the use of penetration enhancers. It has been reported that a good linear correlation exists between the log percentage drug absorbed nasally and the log molecular weight of water soluble compounds suggesting the participation of aqueous channels in the nasal absorption of water soluble of molecules[20].

Chemical form:

The chemical form of a drug is important in determining absorption. For example, conversion of a drug into a salt or ester form can alter its absorption. Huang *et al.*, studied the structural modification of drug on absorption[21]. It was observed that *in situ* nasal absorption of carboxylic acid ester of L-tyrosine was significantly greater than that of L-tyrosine. This phenomenon is associated with the increase in lipophilicity following esterification, which increased the rate and extent of nasal absorption. Similar results were observed using a series of barbiturates at pH 6. It was found that increase in lipophilicity increases the initial concentration, which increased the nasal absorption rate.

Effect of the solution pH:

The extent of absorption is pH-dependent, being higher at a pH lower than the pKa and decreases as the pH increases beyond the pKa[22]. The rate of absorption is thus decreased as pH is increased because of ionization of the penetrant molecule[23]. Similar observations were seen in case of decanoic, octanoic and hexanoic acids where absorption was found to be dependent on pH and maximum absorption was at pH 4.5, beyond which it decreased steadily as the solution becomes more acidic or basic[24]. Similar results were seen in case of peptide-based drugs such as insulin. For e.g., in case of dogs, the pH of an insulin solution administered intranasally affected the plasma glucose level[25,26]. At pH 6.1, only slight hypoglycemic effect was achieved whereas at pH 3.1, a reduction of about 55% in the glucose level was achieved. Insulin has an isoelectric point at pH 5.4 and becomes positively charged at pH lower than its isoelectric point and negatively charged at pH higher than its isoelectric point and is poorly absorbed at higher pH.

Particle size:

It has been reported that particle greater than 10 μm is deposited in the nasal cavity. Particles that are between 2 to 10 μm can be retained in the lungs and particles less than 1 μm are exhaled.

Solubility and dissolution:

Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to be dissolved prior to absorption. It a drug remains as particles or is cleared away no absorption occurs. Thus the drug should have sufficient solubility in the nasal secretion, dissolving at a fast rate and also be able to permeate through the nasal mucosa which depends on its inherent lipophilicity.

NASAL FORMULATIONS:

The nasal formulation along with physicochemical properties of the drug and the anatomical and physiological factors of the nasal cavity affect the nasal absorption of drug molecules, which have been briefly summarized in fig.3. The formulation consists of nasal drops, nasal sprays, gels and powders. Most of the conventional nasal formulations constitute the nasal drops, which is a simple and a convenient system for nasal delivery. The main disadvantage of the drop is the lack of dose precision and therefore may not be suitable for prescription products. Nasal sprays

are systems which can deliver an exact dose because of the availability of metered dose pumps and actuators. Nasal spray can deliver an exact dose from 25 to 200 µl. Both solution and suspensions can be formulated as sprays.

Nasal gels are high viscosity thickened solution or suspensions. They have advantages such as reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulations, reduction of irritation using soothing/ emollient and target delivery to mucosa for better absorption. A vitamin B12 gel has been recently developed for nasal delivery[27]. Nasal powders have the advantage of increased stability, absence of preservative and excipients. However, suitability of powder formulation is dependent on drug solubility, its particle size, aerodynamic properties followed by nasal irritancy of the drug and/or the excipients.

NASAL DELIVERY OF VACCINES

Nasal delivery of vaccines has been reported to not only produces systemic immune response, but also local immune response in the nasal lining, providing additional barrier of protection[9]. Intramuscular injection of a vaccine elicits a strong systemic immune response, characterized by the production of IgG antibodies, which attack the target antigen once it has passed the blood stream. But respiratory diseases enter the body through the mucosal lining of the nose and lungs, when infected droplets are inhaled and microorganism starts to proliferate. Delivering the vaccine to the nasal cavity itself stimulates the production of local secretory IgA antibodies as well as IgG, providing an additional first line of defense, which helps to get rid of the disease before it, can take hold[28]. However, the main problem is that drugs in particular proteins and peptides are poorly absorbed across the nasal mucosa, with less than 1% of the dose enters the bloodstream. Using chitosan boosts absorption to as much as 40 %. It was found that more protein molecules contained in the vaccine reaches the lymphoid tissue when chitosan opens the junction between the cells in the nasal cavity[29]. It has been reported that delivery with chitosan, a nasal vaccine produces the same level of IgG as an injection together with high level of IgA[29]. Evidence is emerging that, as well as stimulating antibody production directly; nasal vaccination also elicits the more powerful cell-mediated immune response in which cytokines stimulate killer cell activity and production of antibodies at cell level. US FDA has granted marketing approval for FluMist™ (http://www.flu-mist.com) for active immunization for prevention of diseases caused by Influenza A and B viruses. It is a live attenuated influenza virus vaccine being proposed for US approval and contains recombinant cold adapted strain of influenza A and B.

Traditional vaccines consist either of inactivated toxins, or of purified preparation of membrane proteins, or as in case of the conventional diphtheria vaccine, of inactivated whole pathogens. Newer vaccines are products of recombinant technology being formulated using novel delivery strategies. ChiSys TM, West's (www.westpharmaceuticals.com) versatile transmucosal delivery technology has been formulated with influenza vaccine for nasal delivery (www.westdrugdelivery.com). It made use of PLSP technology, which are multilayered structures and creates a high surface area for vaccine absorption, enhancing the way the vaccine is delivered to the body. The Innovation project by DanBioSyt (www.emnetco.uk/ highfields/) focuses on a new, genetically detoxified diphtheria vaccine developed by Biocine (http://www.informagen.com/) using recombinant DNA technology.

AlphaVax replicon Vector ArV™ (http://www.alphavax.com) technology presents an opportunity to immunize against new diseases and substantially improve existing vaccines. The technology re-engineers a specially adapted virus to substitute a desired gene for a portion of its original genome, so that the virus produces the protein encoded by the desired gene rather than producing more viruses and thus can be used as a vaccine. It presents an opportunity to immunize against new diseases and substantially improve existing vaccines and has potential for multiple delivery methods such as by nasal, mucosal, subcutaneous and intramuscular routes.

NOSE TO BRAIN DELIVERY

It is well known that the euphoria derived from the sniffing of cocaine in conscious subject occurs rapidly, within 3-5 min[9]. It has been suggested that the reason for such rapid effects, apart from a rapid nasal absorption, is the presence of a direct pathway from the nasal cavity to the CNS and the capacity of the drug to concentrate selectively in the specific regions in the brain. Various studies in animal models have confirmed that, at early time points after nasal administration, the concentration of cocaine in the brain was higher after nasal administration than after intravenous administration, thereby showing the existence of a pathway from the nose to the brain[30,31]. For example, it was shown in the mouse model that (3H)-dopamine reached the olfactory lobe after nasal administration and that at 4 hours after administration the concentration in the tissue after nasal adminis-

tration was 27 times higher than after intravenous injection[32,33]. However, it should be stressed that for, most drugs investigated, the overall quantity appears in the brain tissue amounts to less than 1 % of the dose given to nasal cavity. Evidence of direct nose to brain transport of drug has been gathered in man, mostly in terms of pharmacodynamic effects on the CNS. Fehm[34] reported a significant accumulation of insulin in CSF after a single administration of 40 IU insulin nasally, whereas no increase was seen in insulin plasma levels. Similarly, recent work suggests that apomorphine, when given nasally, reaches the CSF to a higher degree than after subcutaneous injection. Drugs have been shown to reach the CNS from the nasal cavity by a direct transport across the olfactory region situated at the loft of the nasal cavity. The olfactory region is the only site in the human body where the nervous system is in direct contact with the surrounding environment. The drug can cross the olfactory epithelium by one or a combination of mechanisms. There is a transcellular route through the cells as well as the paracellular route between the cells, as is the case of normal epithelium. Furthermore, the drug can be transported through the olfactory neuron cells by intracellular axonal transport primarily to the olfactory bulbs. The intracellular axonal pathway is a slow pathway that can take hours to deliver drugs to the CNS, whereas the two other pathways are fast and enable drug transport to happen within minutes[9].

The nose to brain delivery would be beneficial in therapeutic situations where a rapid and/or specific targeting of drugs to the brain is required. Conditions such as Parkinson's disease, Alzheimer's disease or pain would be befitted from the development of nasal delivery systems which will increase the fraction of drug that will reach the CNS after nasal delivery.

CONCLUSIONS

Considering the advantages of the nasal route for administering systemically active drugs, a wide range of novel nasal products are expected to reach the market in the near future. The market for systemic delivery of drugs is estimated to be growing at around 33 percent per annum with 16 out of the major 20 companies have active nasal drug delivery programs (http://www.iptonline.com/synopsis.asp/cat=4&article137). Ease and convenience coupled with drug delivery to brain in case of Parkinson's disease, Alzheimer's disease and pain are the reasons for the growing interest coupled with systemic delivery of proteins and peptides including vaccines. On a longer term, novel nasal products for treatment of long term illnesses such as diabetes, growth deficiency, osteoporosis, fertility treatment and endometriosis are also expected to be marketed.

REFERENCES

1. Chien, Y.W., Su, S.E. and Chang, S.F., In: Nasal Systemic Drug Delivery, Dekker, New York, 1989
2. Chien, Y.W. and Chang, S.F., **Crit. Rev. Ther. Drug Carrier Syst.,** 1987, 4, 67
3. Chien, Y.W. and Chang, S.F., In; Chien Y.W., Eds., Transnasal Systemic Medications: Fundamental Concepts and Biomedical Assessment, Elsevier Science Publishers, Amsterdam, 1985, 1
4. Chang, S.F. and Chien, Y.W., **Pharm. Int.,** 1984, 5, 287
5. Illum, L., **J. Control. Release,** 2003, 1-3,187
6. Dominique, D. and Gilles, P., **Drug Develop. Ind. Pharm.,** 1993,19, 122
7. McMartin, C., Hutchinson, L.E.F., Hyde, R. and Peters, G.E., **J. Pharm. Sci.,** 1987, 76, 535
8. Madara, J.L. and Dharmsathaphm, K., **J. Cell Biol.,** 1985, 101, 2124
9. Illum, L., **Drug Discovery Today,** 2002, 7, 1184
10. Soane, R.J., Frier, M., Perkins, A.C., Jones, N.S., Davis, S.S. and Illum, L., **Int. J. Pharm.**, 1999, 178, 55
11. Illum, L., In: Mathiowitz, E., Eds., Drug Delivery Issues in Fundamentals, Novel Approaches and Development Marcel Decker, New York, 1998, 507.
12. Moore, K.H., Hussey, E.K., Shwaw, S., Fureau, E., Duguesnoy, C. and Pakes, G.E., **Cephalagia,** 1997, 17, 541
13. Illum, L., Farraj, F. and Davis, S.S., **Pharm. Res.,** 1994, 11, 1186
14. Kotze, A.F., Lue Ben, H.L., De Boer, A.G., Verhoef, J.C. and Junginger, H.E., **Eur. J. Pharm. Sci.,** 1999, 7, 145.
15. Hilsted, J., Madsbad, S., Hvidberg, A., Rasmussen, M.H., Krarup, T., Ipsen, H., Hansen, B., Pederrsen, M., Djurup, R. and Oxen Boll, B., **Diabetologia,** 38, 680
16. Dodane, V., Amin Khan, M. and Mervin, J.R., **Int. J. Pharm.,**1999, 182,21
17. Schipper, N.G.M., Olsson, S., Hoogstraete, J.A., De Boer, A.G., Varum, K.M., Artursson, P., **Pharm Res.,** 1997, 14,923
18. Roon, K.I., Soons, U, De Beukelar and Ferran, **Brit. J. Clin. Pharmacol.,** 1988, 47, 285.
19. Davis, S.S., **Pharm. Science and Tech.,** 1999, 2, 450
20. Fisher, A.N., Brown, K., Davis, S.S., Parr, G.D. and Smith, D.F., **J. Pharm. Pharmacol.,** 1987, 39, 357
21. Huang, C., Kimura, R., Nassar, A. and Hussain, A., **J. Pharm. Sci.,** 1985, 74, 1298
22. Hussain, A.A., Bawarshi, R and Huang, C.H. In; Chien, Y.W., Eds., Transnasal Systemic Medications, Elsevier, Amsterdam, 1985, 12.
23. Kaneo, Y., **Acta Pharm. Suec.,** 1983, 20, 379
24. Gibson, R.E. and Olanoff, L.S., **J. Control. Release,** 1987, 6, 36
25. Hirai, S., Ikenaga, R. and Matsuzawa, T., **Diabetes,** 1978, 27, 296
26. Hirai, S., Yashiki, T., Matsuzawa, and Mima, H., **Int. J. Pharm.,** 1981, 1, 317
27. Behl, C.R., Pimplaskar, H.K. and Sileno, J., **Adv. Drug Delivery Rev.,** 1998, 29, 89.

28. Davis, S., **Adv. Drug Deliv. Rev.,** 2001, 41, 21
29. Illum, L., Jabbat-Gill, Hinchcliffi, M., Fisher, A.N., and Davis, S.S., **Adv. Drug Deliv. Rev.**, 2001, 51, 81
30. Illum, L., **Eur. J. Pharm. Sci.,** 2000, 11, 1
31. Chow, H. and Chen Zhi, Matseura, T., **J. Pharm. Sci.,** 1999, 88, 754
32. Dahlin, M., Bergmen, U., Junssjon, B., Bjork, E. and Brittebo, E., **Pharm. Res.,** 2000, 17, 737
33. Dahlin, M., Janssen, B. and Bjork, E., **Eur. J. Pharm. Sci.,** 2001, 14,75
34. Fehm, H.L., Perras, B., Surolnik, R., Kern, W. and Born, J., **Eur. J. Pharm, Sci.,** 2000, 405, 43.