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Bioadhesive and formulation parameters affecting nasal absorption

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1. Introduction

Recent advances in biotechnology have not only led to the production of therapeutic peptides and proteins, but also provided formidable formulation and delivery challenges to pharmaceutical scientists. Development of suitable delivery systems for these macromolecules is difficult mainly due to the peculiar properties of peptide and protein drugs that include large molecular size, susceptibility to enzymatic degradation, sensitivity to pH and a short in-vivo half-life (Lee and Longenecker, 1988; Zia et al., 1993a). The majority of these drugs are usually administered by injection, a route which is not well accepted by patients, particularly for chronic therapy. Among the non-invasive routes, nasal administration offers promising potential as a viable alternative for the delivery of some peptide drugs. Hence there has been a surge of interest that has led to many investigations involving the nasal cavity as a feasible site for the administration of many therapeutic agents.

Nasal drug delivery offers many advantages that include rapid absorption due to a highly permeable tissue, fast onset of action, avoidance of hepatic first-pass metabolism, utility for chronic medication, ease of administration, and familiarity to the population at large (Chien et al., 1989). However, the limitations of a nasal delivery include: potential local tissue irritation; rapid mucociliary clearance of the therapeutic agent from the site of deposition resulting in a short span of time available for absorption; low permeability of the nasal membrane for the larger macromolecules; presence of proteolytic enzymes that may cause degradation in the nasal cavity; limited formulation manipulation for changing drug delivery profiles; and possible presence of pathological conditions such as colds or allergies which may alter nasal bioavailability. Strategies to overcome these limitations include: the use of bioadhesive polymers that increase residence time of the formulation in the nasal cavity thereby improving absorption; the use of nontoxic enhancers to improve the permeability of the nasal membrane to high molecular weight compounds; and the use of enzyme stabilizers that prevent degradation of peptide drugs in the nasal cavity (Leung and Robinson, 1990; Duchene and Ponchel, 1993).

In this paper, the use of bioadhesive polymers to improve nasal delivery of drugs along with formulation parameters affecting nasal absorption will be reviewed.

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2. Nasal mucociliary clearance mechanism

Under normal conditions, the nasal mucosa is lined with mucus which is arranged in two layers: the external layer which is viscous and dense, and the internal layer which is fluid and serous.

The nasal mucus consists of 95% water, 2.5–3% mucin (a glycoprotein), and the remainder is made up of electrolytes, lipids, enzymes (especially proteolytic enzymes), antibodies, sloughed epithelial cells and bacterial products. It provides a protective barrier against the penetration of various molecules because of the polymeric network constituted by the mucin and the presence of proteolytic enzymes that often degrade the penetrating molecules. The function of the mucus is to protect the nasal mucosa from cold and low humidity; and to trap and remove inhaled substances via mucociliary clearance or sneezing. The mucus moves toward the posterior of the nose by beating of the cilia at a rate of 5–24 mm/min. Thus, the nasal mucus is replaced with a fresh layer every 10–15 min. Under normal conditions, inhaled substances or delivery systems are cleared from the nose within 15 to 20 min. It is important to maintain the mucociliary clearance mechanism for removing dust, allergens and bacteria. However, this mechanism can be influenced by drugs or additives present in the nasal formulation. There are many reports in the literature describing the effect of various chemical entities on mucociliary clearance (Schipper et al., 1991). Thus the design of a delivery system for nasal administration should be considered carefully to avoid irreversible interference with the mucociliary activity.

One of the main reasons for the low bioavailability observed for peptide drugs is the rapid removal of the drug from the site of deposition by the mucociliary clearance mechanism. A potential solution to this problem is the use of a bioadhesive delivery system. Bioadhesives in drug delivery systems have recently received considerable attention by pharmaceutical scientists because they can be used as a means of improving the intimacy of contact between the drug and the absorptive surface and thus extend the residence time of the formulation at the absorption site (Duchene et al., 1988; Harris and Robinson, 1990).

3. Factors influencing nasal absorption

3.1. Formulation variables

Formulation variables such as pH, osmolarity, type and concentration of buffers, viscosity, volume, particle/globule size etc. may alter the nasal bioavailability of drugs. The following is a discussion of particular effects exerted by these factors.

3.1.1. Physicochemical properties of the drug

It has been well established that the absorption process is generally conditioned by the size of the drug molecule, its charge characteristics, solubility, lipophilicity and diffusivity across the biological membrane.

The permeability of the nasal membrane for drugs seems to depend on the size of the drug molecules. The effect of molecular size was investigated in a systematic evaluation of a wide range of drugs with molecular weights varying from 160–34 000 Da (McMartin et al., 1987). The results indicated that nasal absorption decreases exponentially as a function of increasing molecular weight. The same trend was seen for both rats and humans. The nasal rate-limiting molecular weight was found to be 1000 Da compared to 300 Da for the oral route. In other studies, the nasal absorption of a wide range of water-soluble substances with different molecular weights, like *p*-aminohippuric acid, sodium cromolyn, inulin and dextran was investigated in rats (Fisher et al., 1987; Maitani et al., 1989a). The results indicated a good linear correlation between the log of percent absorbed and the log of the molecular weight, suggesting the participation of aqueous channels in the nasal absorption of water-soluble molecules. Donovan et al. (1990) reported the effect of molecular weight on the nasal absorption of the polydisperse polyethylene glycols (PEGs, 600, 1000 and 2000) in rats. These compounds despite their molecular weight differences have similar physicochemical properties such as solubility and partition coefficient. The steepest absorption dependence for nasal mucosa was observed for PEG 600 where the extent of nasal absorption decreased from approximately 60% to 30% over a molecular weight range of less than 300 Da. The mean

absorption for PEG 1000 and PEG 2000 was 14% and 4% respectively.

The nasal membrane seems to be more permeable to lipophilic drugs. Drugs such as propranolol, progesterone and enkephalins appear to be absorbed effectively from the nasal route with bioavailabilities similar to those obtained for an i.v. injection (Chien et al., 1989). Hussain et al. (1985) reported the effect of lipophilicity on the extent of nasal absorption of a series of barbiturates at pH 6.0, where the barbiturates (pKa = 7.6) exist primarily in their unionized form. A forty-fold difference in the partition coefficient of pentobarbital and barbital resulted only in a four-fold increase in the extent of absorption. Furthermore, the nasal absorption of L-tyrosine (Huang et al., 1985a) did not significantly change when the partition coefficient was increased 50 times. Results from nasal studies of a series of progestational steroids with varying hydrophilicity, in ovariectomized rabbits, demonstrated that the octanol/water partition coefficient does not reflect the transport behavior of progesterone and its derivatives through nasal mucosa (Corbo et al., 1988). In these studies systemic bioavailability seemed to correlate well with nasal mucosa/buffer partition coefficient. In another study, the same group (Corbo et al., 1990) reported that nasal membrane permeability decreased as the order of hydrophilicity of the progestins increased.

Based on the above results one may postulate a simplified mechanism for nasal absorption: (i) nasal aqueous pore pathways (sensitive to variation in molecular weight) play a less rate-limiting role compared to the GI tract in the nasal membrane and are mainly responsible for the transport of water-soluble compounds, providing a slow, but significant route which is dependent on the molecular weight of the polar compounds; (ii) lipoidal pathways are responsible for the transport of lipophilic drugs, with rate dependency based on partitioning.

3.1.2. pH

The pH of a formulation seems to affect the solubility, partition behavior and/or stability of many drugs, especially peptides and proteins. It may also result in damage to the nasal membrane thereby altering nasal absorption of drugs.

Insulin absorption seems to be dependent on pH of the formulation. Hirai et al., 1978 reported that at pH 6.1 only a slight hypoglycemic effect was attained for insulin whereas at pH 3.1 a reduction of about 55% in the glucose level was achieved. The better absorption of insulin at the lower pH was attributed to the fact that insulin at pH 3 is predominantly in a monomeric form. Nagai et al., 1984 observed that the pH effect was more profound when insulin was formulated and administered as a nasal solution. When insulin was administered as a powder, the pH effect was not significant. A similar enhancing effect of nasal absorption at low pH was reported by Ohwaki et al., 1985 for the absorption of secretin in rats. The authors explained their results based on the histological finding that epithelial cells were damaged at the low pH of $\approx$ 3.0.

Similarly, the effect of pH on the nasal absorption of benzoic acid (pKa = 4.19) was studied by Huang et al., 1985a. As the pH of the solution was increased from 2 to 7.19, the amount absorbed was decreased from 44% to 13%, probably due to ionization of the drug. The same group, in another study reported that the absorption of L-tyrosine was pH independent in the range of 4 to 7.4 (Huang et al., 1985b).

Smith et al., 1992 reported that nasal absorption was fast and complete when loperamide hydrochloride was administered in rats at a neutral pH. But when the pH of the solution was reduced to 3.0, the absorption was reduced by half. Machida et al. (1993) studied the effect of pH on nasal absorption of rhG-CSF solutions in rats. The pharmacological bioavailability was found to be maximum (9.7%) at pH 3.0 and minimum (4.7%) at pH 4.0 and about 7–8.7% between pH 5–8.

It was found (Morimoto et al., 1991) that the antidiuretic effects of vasopressin and its analogue after nasal administration in hyaluronate solutions were greater than after administration in buffer solutions at various pH (4.0–7.0). Greater antidiuretic effects were observed with lower pH of both the hyaluronate and buffer solutions.

Pujara et al., 1995 reported that solutions within a pH range of 4–8 caused minimal damage to the nasal mucosa. Solutions with pH above 10

caused significant membrane and intracellular damage. Optimal ciliary beat frequency was observed for pH values between 7 and 10 (Van de Donk et al., 1980; Luk and Dulfano, 1983). Values lower than pH 6 and higher or equal to pH 11 resulted in severe decreases in beat frequency.

Thus, the pH of the formulation seems to play a role in the nasal absorption of drugs especially those administered in solution form. The absence of a clear trend seems to be due to variable pHs in different studies, multitude of effects caused by pH and presumably also the high buffer capacity of the mucus covering the nasal membrane.

3.1.3. Osmolarity

The effect of osmolarity on nasal absorption of secretin in rats was studied by Ohwaki et al., 1987 using sodium chloride and sorbitol in the nasal formulations. Although optimal absorption was obtained with a hypertonic solution containing 0.462 M of sodium chloride, the histological evaluation of the nasal mucosa revealed shrinkage and structural change of the epithelial cells when compared to the control. Interestingly, when the nasal mucosa was treated with 0.924 M of sorbitol having the same osmolarity as the 0.462 M sodium chloride solution, there was neither enhanced absorption nor any structural change of the epithelial cells. Machida et al., 1993 reported that the osmotic pressure of the dosing solution containing rhG-CSF caused slight increases in the pharmacological effects in rats under hypotonic (174 mOsm/kg) and isotonic (285 mOsm/kg) conditions. Pujara et al., 1995 reported that hypertonic and isotonic solutions caused minimal irritation while hypotonic solutions caused extensive leakage of enzyme markers lactate dehydrogenase and 5′-nucleotidase from nasal membrane.

Based on these reports, although hypotonic and/or hypertonic solutions may cause more absorption of drugs than those with isotonic solutions, the integrity of epithelial cells and ciliary beat frequency is best preserved with isotonic solutions.

3.1.4. Type and concentration of buffer

Four different buffers (acetate, adipate, citrate and phosphate) at a concentration of 0.07 M and pH 4.75 were evaluated to determine the effect of buffer type on the integrity of rat nasal mucosa (Pujara et al., 1995). The acetate buffer was found to have the most irritation potential when compared to adipate, citrate and phosphate, probably because of the high lipid partition behavior of unionized acetic acid at pH 4.75. The damaging effect of acetate buffers (pH 4.75) on the nasal mucus was evaluated at three concentrations (0.07 M, 0.14 M and 0.21 M) and found to be concentration dependent with the higher concentration showing the most damaging effect.

Thus, the type and concentration of buffer should be chosen based on the solubility and stability of the drug and safety concerns in maintaining the integrity of the nasal mucosa.

3.1.5. Viscosity

Pennington et al., 1988 compared the clearance of hydroxypropyl methylcellulose (HPMC) solutions (0.6, 0.9 and 1.25% w/v) having kinematic viscosities 36, 120 and 430 mm^2s^{-1}. The solutions were administered as nasal sprays (130 ml) to eight healthy humans. The solutions were labeled with ^{99m}Tc-labeled diethylenetriaminepentaacetic acid. A gamma scintigraphic study showed that the areas of deposition was same for all the solutions. However, the clearance rates decreased with increasing solution viscosity, with the retention half times being 1.0, 1.7 and 2.2 h, respectively. Harris et al., 1988b compared the effects of nasal administration of 100 μl of a solution containing 0, 0.25 and 0.5% w/w methylcellulose delivered by spray or rhinal catheter. The mean particle size delivered by the spray was measured and found to be 51 μm for 0% w/w solution, 81 μm for 0.25% w/w solution and 200 μm for 0.5% w/w solution. The larger particle size gave a more localized deposition in the anterior portion of the vestibule, but optimum retention was provided by 0.25% w/w solution. In contrast, there was no difference in the 50% clearance rates for placebo or 0.5% w/w cellulose solution delivered by rhinal catheter. Lin et al., 1993 studied the correlation between viscoelastic properties of polymeric formulations and nasal residence time. Of the two formulations, 6% HPMC in normal saline and 6% HPMC suspended in a propylene glycol-alcohol

mixture, increased residence time was observed for the latter formulation. However, similar nasal bioavailability was observed for propranolol for both of the formulations.

Thus, increased viscosity prolongs the retention time of drug in the nasal cavity, but whether this will result in improved absorption of drugs or not, remains unclear.

3.1.6. Dose and dosage volume

The site of drug deposition in the nose is highly dependent on the dosage form, dosage volume and delivery device. The volume that can be administered to the nasal cavity is limited.

Harris et al., 1988a studied the effect of dose volume on the nasal bioavailability of desmopressin. It was found that the bioavailability of desmopressin from 2 × 50 μl dose was 20% which represented a two fold increase over the 11% found with 1 × 50 μl spray or the 9% realized from the 1 × 100 μl dose. This finding suggests that an optimal dosage may be obtained by delivering drug twice into each nostril. In another study, the same group (Harris et al., 1989) reported that greater absorption of desmopressin was observed from 100 μl rather than from 200 μl. The 200 μl spray was cleared in 120 min compared to a 240 min clearance time for the 100 μl spray. By contrast, Newman et al., 1987 observed that a single spray of 100 μl was deposited over a greater area than two sprays of 50 μl, while Bond et al., 1984 could not detect any dependency of the deposition and clearance of ^{99m}Tc-HSA from different volumes of the nasal spray. Similarly, Aoki and Crawley, 1976 reported that no significant difference was found when the volume was varied from 0.1 to 0.75 ml.

Smith et al., 1992 reported that when loperamide hydrochloride was administered nasally in rats with a solution concentration of 0.0012% at dose volumes of 25, 50 and 100 μl, the nasal absorption increased linearly with dose volume. Similar results were observed when different concentrations of drug was administered from a fixed volume.

Dondeti et al., 1994a evaluated spray formulations containing different levels of insulin (1.25, 2.5, 5 and 10 U/kg) in 1% w/v sodium taurocholate in normal rabbits. The maximum hypoglycemic effect was observed for 10 U/kg spray and the minimum effect was seen with 1.25 U/kg spray. However, there was no proportional increase in glucose reduction when compared to increasing dose indicating that the amount of insulin that can be absorbed is limited. In contrast, the nasal absorption of progesterone in women, following the administration (to one nostril) of ointment dosages containing 20, 30 and 40 mg of progesterone showed no significant differences in AUCs among the groups receiving the different dosages (Dalton et al., 1987). However, when 40 mg doses were divided between two nostrils, there was a significant increase in AUC, suggesting that the area of mucosa to which drug is applied is another important determining factor in nasal absorption.

Based on these results it appears that only the applied amount (drug mass) and available absorption surface area determine the nasal absorption of drugs.

3.2. Dosage forms and delivery devices

Drugs are usually administered to the nasal cavity in the form of solutions, suspensions, powders, microspheres, gels or inserts for local or systemic effect (Su, 1993). There are reports in the literature indicating that by choosing a suitable dosage form one can significantly improve the absorption of drugs across the nasal membrane. The mode of administration will also affect the site of deposition and distribution and is therefore important to the efficiency of nasal absorption.

The deposition and clearance of nasal sprays and nose drops of ^{99m}Tc-labeled human serum albumin were compared in humans using gamma scintigraphy (Hardy et al., 1985). The nasal spray was deposited mainly in the anterior part of the nose, whereas the nose drops dispersed more extensively in the nasal cavity. The solution deposited from the nose drops cleared more rapidly than from the nasal spray. In another comparative study (Harris et al., 1986) of nasal sprays and nasal drops, it was shown that the relative bioavailability and biological response to desmopressin was better from a nasal spray than from

nasal drops because of better distribution and larger surface area available with the small droplets of spray.

A comparison was made between solution and suspension dosage forms of human sodium insulin in dogs following nasal administration (Su and Campanale, 1988). The preparation in a suspension form gave a better insulin uptake and blood glucose reduction compared to that from a solution. Nasal absorption was probably improved because of a higher drug concentration on nasal membranes and thereby an increased concentration gradient for drug diffusion. In many investigations, it has been reported that insulin is better absorbed when administered as a powder than as a solution at the same dose (Nagai et al., 1984; Schipper et al., 1993).

Illum et al., 1987 investigated bioadhesive microspheres as a means of prolonging residence time in the nasal cavity and thereby improving the absorption of drugs. They used albumin, starch (Spherex), and DEAE-dextran (DEAE-Sephadex®) microspheres to study loading capacities, release characteristics and nasal clearance. The materials chosen for the microspheres are of as such a nature to take up water and swell to a very large extent when coming in contact with the water in the nasal cavity. Furthermore, they pointed out that the size of microspheres must be above 10 μm for optimum deposition. It was observed that the larger particles will deposit predominantly in the anterior unciliated part of the nasal cavity, which will experience slower clearance. The clearance times were determined by loading and labeling the microspheres with ^{99m}Tc-pertechnetate. The microspheres exhibited a half-life period of 3–4 h when compared to 15 min observed for solutions and powders. Thus particle diameter, swelling, viscosity and bioadhesiveness are important parameters that should be considered while designing a nasal drug delivery system.

Furthermore, to achieve accurate, reproducible and patient acceptable administration of drug to the nasal cavity, a delivery device is essential. A comprehensive review of delivery means and devices for nasal administration of drugs, such as droppers, spray pumps, insufflators, metered-dose nebulizers was written by Chien et al., 1989. The metering accuracy and reproducibility of these systems are critical in obtaining meaningful data for in vivo nasal delivery. Among all the nasal delivery devices, metered dose nebulizers/aerosols are the most preferred form in terms of accuracy, reproducibility and patient acceptability. Metering accuracy is affected by storage conditions and duration, as well as the physical nature of the formulation (in terms of viscosity, surface tension and, in the case of a suspension, homogeneity). Metered dose nebulizers that require manual pressure are preferred to propellant actuated metered dose aerosols because of economic and environmental concerns. However, metered dose nebulizers are often prone to bacterial contamination and should be cleaned regularly and meticulously, and often require inclusion of a preservative in the formulation.

The site of deposition of a nasally administered formulation depends on the delivery system and the technique of administration. A significant difference in drug distribution was observed in the human nose when comparing a variety of delivery devices, such as dropper bottle, plastic bottle nebulizer, automized pump and metered-dose/pressurized aerosol (Mygind, 1979). Hughes et al., 1993 carried out gamma scintigraphic studies to determine the differences in deposition pattern and clearance with the use of four nasal delivery devices: a compressed air nebulizer, a nasal pump sprayer, drops from an instillation catheter and a dry powder insufflator. ^{99m}Tc-labeled colloidal sulfur particles were used as test markers in rhesus monkeys to measure deposition patterns and clearance rates. Deposition patterns were qualitatively similar for all four devices despite the fact that particle size distributions differed considerably. Clearance, when measured 30 min after initial deposition, was also similar for all four devices with a mean retention value of 30%. Thus, the choice of device in these studies did not markedly affect nasal deposition or clearance in monkeys. The compressed air nebulizer would be the device of choice for delivering drugs because a reasonable volume of drug could be delivered with good reproducibility. Newman et al., 1994 compared the effect of four different administration modes from a spray device in humans, in-

volving volumes of 80–160 μl of insulin formulation, and with either gentle or vigorous inhalation while firing the device. Twenty-five to thirty-three percent of the initial dose was retained in the nose after 4 h. A significantly smaller area was covered by the 80 μl dose as compared to 160 μl dose, but the subsequent clearance rates did not vary significantly with mode of administration.

An inflatable nasal device with its wall constructed from a microporous membrane was developed to provide a long acting and controlled delivery of drug from a suspension (Corbo et al., 1988). When progesterone was administered to ovariectomized rabbits using this device, the plasma drug levels reached a plateau within 20–30 min and remained at an elevated level throughout the course of a 6 h insertion. The oral bioavailability was 72.4% as compared to 82.5% for a nasal spray.

Thus, many factors such as composition of the formulation, mode of administration and the nature of the delivery device can affect the drug distribution in the nasal cavity thereby leading to changes in biopharmaceutics process.

4. Bioadhesive polymers

The nasal membrane is relatively impermeable to large size molecules and often penetration enhancers such as bile salts, chelators or surfactants are included in the formulation to improve the nasal absorption of these drugs. But, due to their possible toxic effects, efforts are being made to find an alternative approach to promote the nasal absorption of larger drugs. Usually drug formulations are rapidly removed from the site of deposition due to the mucociliary clearance mechanism. It has been hypothesized that one might improve the absorption by increasing the retention time of drug in the nasal cavity via bioadhesion (Nagai and Machida, 1990). Recently, a mathematical model was developed (Gonda and Gipps, 1990) describing the rate processes involved in nasal drug delivery. Using this model the effect of bioadhesive carrier systems can be simulated by reducing the mucociliary clearance rate constant for the transport from the posterior part of the nose to the nasopharynx. These simulations predicted that bioadhesion may improve systemic bioavailability and reduce the variability in nasal drug absorption as caused by a variable pattern of drug retention.

Bioadhesion may be defined as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. When applied to mucosal epithelia, a bioadhesive polymer may adhere primarily to the mucus layer in a phenomenon known as mucoadhesion. For drug delivery purposes, the polymer/drug carrier is usually a non-biological macromolecular or hydrocolloid material that adheres primarily to the mucus layer, or alternatively may attach to the underlying epithelium. Many theories have been postulated to describe the mechanisms of bioadhesion (Park and Robinson, 1987; Duchene et al., 1988; Mikos and Peppas, 1990). Pioneering work on the use of bioadhesive polymers in drug delivery was carried out by Robinson and coworkers (Park et al., 1984; Leung and Robinson, 1990; Harris and Robinson, 1990). Peppas, 1985 analyzed the nature of adhesive interface, the surface roughness, the chemical structure of the bioadhesive material, the swelling at the adhesive interface and the dynamic development of bioadhesive bond strength in terms of molecular and surface theories.

Bioadhesives include water-soluble polymers and water-insoluble polymers which are swellable networks joined by cross-linking agents. Bioadhesion is dependent on the nature of the polymer that acts as an adherent to the biological membrane. Bodde et al., 1990 reported that the bioadhesion process requires two criteria: the polymer should possess optimal polarity to make sure it is sufficiently 'wetted' by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. There are several comprehensive reviews available in the literature that describe the requirements that a polymer should possess to have good bioadhesive properties (Park and Robinson, 1985; Gu et al., 1988; Duchene and Ponchel, 1992; Jimenez-Castellanos et al., 1993).

4.1. Nature of bioadhesive polymer

4.1.1. Molecular weight and chain length

It was reported (Chen and Cyr, 1970) that bioadhesive strength increases as the molecular weight of a polymer increases up to 100 000. Also, it was found (Smart et al., 1984) that the molecular weight of NaCMC should exceed 78 600 in order to provide significant bioadhesion. Thus, there appears to be a critical molecular weight requirement for significant bioadhesion. For the majority of polymers, an increase in the molecular weight results in an increase in molecular length, which will in turn influence bioadhesion via its effect on the interpenetration and entanglement of the polymer to the substrate. The bioadhesive property of polyethylene oxide increased from essentially no bioadhesion at a molecular weight of 20 000 to excellent bioadhesion at a molecular weight of 4 000 000. On the other hand, dextrans with molecular weights as high as 19 500 000 have been reported to have similar bioadhesive strength to those with a molecular weight of 200 000 (Chen and Cyr, 1970).

4.1.2. Charges and ionization

Results from various studies (Park et al., 1984; Peppas, 1985; Leung and Robinson, 1988; Duchene and Ponchel, 1993) showed that when both bioadhesiveness and cellular toxicity are considered, polyanionic polymers are preferred over polycationic and neutral polymers. Furthermore, based primarily on limited toxicity data polyanions with carboxyl groups seems to be better candidates than those with sulfate groups.

In studying the bioadhesive strength of poly(-acrylic acid) hydrogels (pKa = 4.75), Park and Robinson, 1987 reported that bioadhesion is favored when carboxylic groups are in an undissociated form and available for formation of hydrogen bonds. Furthermore, polymer chains should be flexible enough to form as many hydrogen bonds as possible. Thus, depending on the pKa of bioadhesive materials, the strength of adhesion can be maximized by controlling the degree of ionization by manipulation of the media pH, or alternatively a bioadhesive with pKa that can provide a low degree of ionization at a chosen pH can be used.

4.1.3. Hydrophilic functional groups and hydration

Bioadhesive polymers have hydrophilic functional groups that can form hydrogen-bonds, e.g., carboxyl, hydroxyl, amide and sulfate groups. Hydrogen-bonding seems to play a dominant role and hence, the amount of water present at the interface between the adhesive polymer and biological membrane and/or mucous is critical for bioadhesion and/or mucoadhesion. When bioadhesives hydrate in aqueous media, they swell and form a gel. The rate and extent of water uptake by the mucoadhesive depends on the type and number of hydrophilic functional groups present in the polymer structure, as well as the pH and ionic strength of the aqueous medium. It was found (Leung and Robinson, 1990) that as the percent composition of charged groups on a polymer decreases, the degree of hydration decreases. Swelling time is an important parameter for assessing bioadhesiveness. The quicker a polymer is hydrated, the faster will be initiation of diffusion, formation of bonds and an entangled interface; and thus the quicker the initiation of the bioadhesion process. The degree of swelling of a polymer is another parameter that contributes to the bioadhesive behavior. It has been reported that excessive swelling results in abrupt drop in the adhesive strength (Gurny et al., 1984).

4.1.4. Chain segment mobility

The ability of the polymer chains to interpenetrate can be approximated by their ability to diffuse. Thus, the chain segment mobility of a polymer, and perhaps mucin, can be related to their viscosity and diffusion coefficients. The diffusion coefficients show an exponential temperature dependency which makes bioadhesion a temperature dependent process (Peppas and Reinhart, 1983). The strength of bioadhesion has been found to decrease with an increase in concentration of the cross-linking agent. An increase in cross-linking density decreases the diffusion coefficient, chain-segment flexibility and mobility, thereby reducing the extent of interpenetration. Bioadhesion is also a time dependent process. As the contact time increases, the depth of interpenetration and thus the strength of adhesion increases.

4.1.5. Expanded nature of the polymer network

The number and size of the pores in the hydrated network will affect the diffusion and interpenetration process. Gu et al., 1988; and Leung and Robinson, 1988 studied the effect of the expanded nature of the mucin network on the shear strength of the mucin-mucin interaction. It was found that mucin-mucin shear strength increased with increased openness of the mucin network. Another factor that affects adhesive strength is the pressure applied to the interacting adhesive-mucin interface. The adhesion strength increases with the applied strength or with the duration of its application, up to an optimum (Duchene and Ponchel, 1992).

4.1.6. Concentration of bioadhesive polymer

There seems to exist an effective concentration for optimize bioadhesion (Gurny et al., 1984). In highly concentrated systems, the adhesive strength drops significantly. In a concentrated solution, the coiled molecules become solvent-poor, and the available chain length for interfacial penetration decreases significantly. Excessive crosslinking of the polymer does not contribute to bioadhesion for the same reasons. But for solid dosage forms such as tablets, Duchene and Ponchel, 1992 showed that increased concentrations of polymer resulted in higher bioadhesion strengths.

When polymeric adhesive delivery systems are placed in an aqueous medium, the polymer network absorbs a significant amount of water to form a gel. It has been shown (Gu et al., 1988) that the rate of release of drug can be controlled by the hydration rate and crosslinking density of the polymer network, the solubility of the active ingredient, and addition of hydrophilic or lipophilic excipients.

4.2. Methods to study bioadhesion

There are many reported methods in literature that describe and measure the phenomenon of bioadhesion (Park and Park, 1990). The bioadhesive properties of polymers are quantified based on adhesion strength, adhesion number and duration of adhesion. Most of the test methods to study bioadhesion are based on the measurement of either tensile or shear strength and can be classified into two categories: in vitro methods and in vivo methods. The in vitro methods require the use of artificial biological media such as mucus or saliva, whereas the in vivo methods require use of biological tissues such as gingiva, skin or the gastrointestinal mucus layer. There are many comprehensive reviews on these methods available in literature (Duchene et al., 1988; Park and Park, 1990; Jimenez-Castellanos et al., 1993).

Some of the factors that affect the quantitation of bioadhesion include such experimental conditions as initial contact time, applied pressure, speed of testing, nature and concentration of the bioadhesive polymer, pH, ionic strength, osmolality and temperature; and the biological factors such as tissue surface roughness, nature of treatment of the tissues and rate of mucin turnover (Park and Park, 1990).

5. Mechanisms of enhancement of drugs across the nasal membrane

Since nasal membrane permeability for many large size drug molecules is low, it seems to be necessary to consider an absorption enhancement mechanism for co-administration of drugs with either bioadhesive polymers or penetration enhancers or combination of the two. Until now there is no clearly established mechanism by which these components enhance the drug absorption across nasal membrane. In general, these formulation combinations improve the absorption of the drugs by one or several combined mechanisms (Lee, 1990; Lee et al., 1991; Uchida et al., 1991; Su, 1992; Su, 1992; Merkus et al., 1993).

5.1. Bioadhesive polymers

Bioadhesive polymers improve nasal absorption by increasing the residence time of a delivery system in the nasal cavity. The mechanism of adhesion of bioadhesive polymers to soft tissues has been discussed by Peppas and coworkers (Peppas and Reinhart, 1983; Gurny et al., 1984; Peppas, 1985; Park and Robinson, 1987; Mikos and Peppas, 1990) and involves both chemical

and physical binding. Both weak and strong interactions ranging from van der Waals interaction to hydrogen bonding and ionic bonding can develop between certain types of chemical groups on a polymer (e.g. hydroxyl or carboxyl groups) with the glycoprotein network of the mucus layer or the glycoprotein chains attached to the epithelial cells in the nose. It has been suggested that the more promising degradable starch microspheres exert two different effects on the nasal membrane. The bioadhesive effect of the microspheres decreases the rate of clearance of the drug from the nasal cavity and thereby provide a longer contact time with absorptive epithelium. The mechanism of this prolonged clearance may be due to swelling and formation of a mucoadhesive system, thereby providing bonding (hydrogen and ionic, depending on the different materials) between the gel and mucus at a deposition site, the part of the nose which contains fewer ciliary cells and thus minimizing clearance. Furthermore, it has been shown in a study (Edman et al., 1992) employing monolayers of Caco-2 cells that the microsphere formulations promote a transient widening of the tight junctions between cells thereby allowing larger hydrophilic molecules to pass through the membrane. It was also reported (Harris and Robinson, 1990) that a bioadhesive delivery system may be so designed to inhibit the metabolizing enzymes in a localized area when administered to the nasal cavity thereby protecting the drug from degradation and thereby improving the absorption across the nasal membrane.

5.2. Permeation enhancers

There is no one particular mechanism by which the permeation enhancers improve transport of drugs across the nasal membrane. There are many hypotheses provided by various investigators regarding the enhancement mechanism of a variety of penetration enhancers (Lee, 1990; Lee et al., 1991; Uchida et al., 1991; Su, 1992; Su, 1993). Some of these mechanisms by which enhancers improve absorption of drugs across biological membranes include: (i) increasing the membrane fluidity and reducing the viscosity of the mucous layer, thereby increasing membrane permeability; (ii) inhibiting proteolytic enzymes at the absorption site; (iii) transient loosening of the tight junctions between certain epithelial cells; (iv) increasing paracellular or transcellular transport by affecting membrane lipids and proteins; (v) dissociating protein aggregation; (vi) initiating membrane pore formation; (vii) lowering membrane potential during the process of drug transport; (viii) increasing nasal blood flow, thereby raising the concentration gradient across the nasal mucosa and (ix) enhancing the thermodynamic activity of peptides and proteins. Recently, Lee et al., 1991 published a comprehensive review of the different classes of enhancers and their enhancement mechanisms.

6. Use of bioadhesive formulations for nasal absorption of drugs

The poor absorption of drugs across the nasal membrane can be attributed to a number of factors that include: (i) low permeability of the nasal mucosa for large molecules; (ii) quick removal of drug from the site of deposition due to mucociliary clearance and (iii) enzymatic degradation (Lee and Longenecker, 1988; Chien et al., 1989; Leung et al., 1992; Edman and Bjork, 1992; Zia et al., 1993a). These limitations can be overcome by: (i) inclusion of penetration enhancer; (ii) using a bioadhesive drug delivery system that increases the residence time in the nasal cavity and (iii) using an excipient that protects the drug molecule at the site of delivery within the absorbing tissues or addition of enzyme inhibitors in the formulation.

6.1. Use of bioadhesive solutions

Hussain et al., 1980 reported the use of methyl cellulose in the nasal delivery of propranolol in rats and dogs. The results indicated that the blood levels of drug after nasal dosing without methyl cellulose and intravenous administration were identical for propranolol. Sustained release formulations containing methyl cellulose resulted in low initial but prolonged blood levels. The bioavailability of these sustained release formula-

tions was identical to that of i.v. administration. Morimoto et al., 1985 reported that the nasal administration of insulin in 1% w/v carboxymethyl cellulose solution did not result in a hypoglycemic effect in rats.

Ryden and Edman, 1992 evaluated the effect of polymer solutions which were either viscous (polyacrylic acid and sodium hyaluronate) or showed thermal gelation (poly-*N*-isopropylacrylamide and ethyl hydroxyethyl cellulose) on nasal absorption of insulin in rats. For a 0.5% polyacrylic acid solution, a glucose reduction of 18–19% was observed after nasal administration of 1 and 5 U/kg of insulin. For a sodium hyaluronate solution (0.075%), only the 5 U/kg dose of insulin resulted in maximal decrease of 22% in glucose levels. The acrylate system was comparatively slower in reducing the glucose level than the sodium hyaluronate. Thermoreversible polymer systems are those in which the viscosity depends on whether the temperature is below or above the lower critical solution temperature (LCST). These polymer solutions have low viscosity at room temperature and when the temperature is raised above the LCST, a gel is formed instantly, releasing water and water soluble drugs (Hoffman et al., 1986). Ethyl hydroxyethyl cellulose which has an LCST of 30–32°C when administered along with 1 U/kg of insulin, caused rapid decrease in blood glucose level (12%) after 40 min. Poly-*N*-isopropylacrylamide system with LCST 32–34°C at 1 U/kg insulin dose did not result in a measurable effect whereas at a dose of 5 U/kg, a 20% reduction in glucose level was observed.

Morimoto et al., 1991 reported the use of sodium hyaluronate solution (1% w/v) to enhance nasal bioavailability of vasopressin and its analogue in rats. The nasal absorption was found to be dependent upon the molecular weight of sodium hyaluronates in the range of 55 000–2 000 000. Maximum absorption of vasopressin was observed with hyaluronate of MW of 2 000 000 and no effect was observed with solution containing hyaluronate of low MW (55 000). Greater antidiuretic effects were observed with higher concentrations of hyaluronate (0–1.5% w/v). The improved absorption was due to the high viscosity and the mucoadhesion of the hyaluronate solutions.

Ikeda et al., 1992 studied the effect of hydroxypropyl cellulose (HPC) on the absorption of dopamine in dogs. The presence of HPC increased nasal bioavailability from 11.7% to 20%.

According to Dondeti et al., 1995, when insulin in a microcrystalline cellulose suspension was administered as a spray to diabetic rabbits, a bioavailability of 1.96% was observed with a maximal decrease of 30% in glucose levels after 185 min. In the same study, insulin in a 70% w/w Plastoid L50 formulation resulted in 2.25% absolute bioavailability and a maximal decrease of 17% in glucose levels after 70 min.

It has been reported that chitosan has mucoadhesive properties most likely mediated by ionic interaction between the positively charged amino groups in chitosan and the negatively charged sialic acid residues in mucus. Illum et al., 1994 investigated chitosan as a nasal delivery system for insulin in rats and sheep. The optimum concentration of chitosan for maximal absorption of insulin in rats and sheep was found to be 0.2% and 0.5% respectively. The AUC for chitosan and insulin solution in sheep was found to be 7 times greater than the AUC for insulin alone. The increase in absorption of insulin was attributed to the mucoadhesive properties of chitosan. It was observed that after 30 min, the absorption promoting effect of chitosan decreased rapidly and 60 min after administration very little or no effect remained.

6.2. Use of bioadhesive powders

Nagai et al., 1984 reported the effect of different polymers in powder form on enhancing the nasal bioavailability of insulin in beagle dogs. With the addition of microcrystalline cellulose (MCC) absorption increased significantly and the plasma glucose level decreased to 49% after 30 min with a corresponding increase in serum insulin levels to 455 μU/ml. With the addition of hydroxypropyl cellulose and neutralized Carbopol 934, the powder formulation resulted in reduction of glucose levels to 39% and 42% respectively. The hypoglycemic effect was sustained with the formulation containing neutralized Carbopol and the total effect was one-third the extent of that produced

by i.v. injection. The presence of lactose proved to be least effective in reducing the glucose levels. They also reported that the pH of the insulin solution may have an effect on the absorption process, but such an effect was not clear in the powder dosage forms.

Maitani et al., 1989a examined the effect of Avicel on nasal absorption of human interferon-β in rabbits from a powder dosage form. Avicel did not produce any significant effect on nasal absorption of human interferon-β. Nagai and Machida, 1990 reported the use of hydroxypropyl cellulose (HPC) as a bioadhesive material to enhance the nasal retention of beclomethasone dipropionate in humans. It was found that HPC still remained in the nasal cavity even at 6 h after administration. The study of drug disposition using tritium labeled beclomethasone also showed that the drug remained much longer than that which was observed in the case of sprays. Koochaki, 1993 developed a powder dosage form containing chitosan and HPMC to deliver oxymetazoline nasally. The pharmaceutical composition displayed improved adhesion characteristics and provided a high bioavailability of the active ingredient.

Dondeti, 1994b evaluated different bioadhesive polymers for nasal delivery of insulin in rabbits. The powders were loaded with insulin by freeze-drying and a supercritical fluid method. In all the cases the powders loaded with insulin using the supercritical fluid process resulted in much higher serum insulin levels and glucose reduction than the same formulations prepared by freeze-drying. The increased stability of insulin in carbon dioxide infused powder may be the reason for increased bioavailability as compared to freeze dried powders. The bioadhesive polymers that were evaluated in the decreasing order of efficiency are: polyacrylic acid, crosslinked polyacrylic acid, polyethylene oxide, chitosan and algin.

Supercritical fluid technology using carbon dioxide is a relatively new approach in drug delivery research. Carbon dioxide can be used to infuse small drug molecules into polymers so as to obtain controlled release. Carbon dioxide at high pressure acts as a solvent and dissolves the drug molecule and carries it into the swollen polymer matrix (Debenedetti et al., 1993; Tom et al., 1993; Zia et al., 1993b). This approach provides many advantages over conventional techniques of drug manufacture such as freeze-drying, air drying etc. These include: (i) use of solvent is not necessary thus enhancing the drug stability (such as peptides and proteins which are known to be susceptible to physicochemical degradation); (ii) carbon dioxide is a nontoxic chemical and does not leave any residues because it is in gaseous state at room temperature and (iii) it is relatively very inexpensive and simple process.

6.3. Use of bioadhesive microspheres

It was reported (Illum et al., 1988) that nasal administration of gentamicin in combination with degradable starch microspheres resulted in a bioavailability of 9.7% as compared to $< 1\%$ for a nasal solution.

In another study, Farraj et al., 1990 reported the use of degradable starch microspheres with insulin as model drug for nasal delivery in conscious sheep. The administration of insulin in bioadhesive starch microspheres exhibited a significant change in peak insulin and mean plasma glucose when compared to insulin solutions alone or with L-lysophosphatidylcholine (LPC). However, the administration of insulin in microspheres alone showed low bioavailability and the AUC that was not significantly different from insulin solutions. In another study, Illum et al., 1990 investigated the same system for nasal delivery of biosynthetic hGH in sheep. The bioavailability relative to the s.c. injection was 0.1% for hGH solution alone and 2.7% for hGH in starch microspheres. Critchley et al., 1994 reported that when administered intranasally to sheep as a simple solution, desmopressin was poorly absorbed with a bioavailability of 1.2%. But when administered with starch microspheres as a nasal powder delivery system, the bioavailability of desmopressin was increased to 4.7%.

According to Bjork and Edman, 1988, the nasal administration of insulin to rats in combination with degradable starch microspheres or with insoluble starch, as a dry powder resulted in a rapid

decrease in plasma glucose. In contrast, insulin with soluble starch had no effect. It is suggested that, when administered intranasally in a dry form, degradable starch microspheres adhere to the mucous membrane, drawing water from the mucus and the underlying epithelial cells and start to swell.

Ryden and Edman, 1992 evaluated dextran microspheres for nasal delivery of insulin in rats. Insulin loaded Sephadex and DEAE-Sephadex microspheres at a dose of 1 U/kg resulted in a maximal glucose reduction of 25% and 9% respectively. When compared to the bioadhesive polymer solutions, the microsphere system resulted in improved absorption of insulin. In another study, the same group reported the use of microspheres of starch and dextran, cross-linked with epichlorohydrin, as an enhancer system for the nasal delivery of insulin in rats (Edman et al., 1992). Starch microspheres are more effective than dextran spheres in inducing a decrease in blood glucose.

Lewis and Kellaway, 1990 reported the preparation and in vitro characterization of microspheres of polyacrylic acid cross-linked with maltose in a w/o emulsification process. It appeared that an increase in curing time of microspheres resulted in an increased release of oxytocin in vitro. This might be due to the fact that an increased curing time leads to a heavily cross-linked polymeric network inside the microspheres which severely limits swelling on hydration. The oxytocin will therefore be surface-associated instead of being uniformly distributed throughout the microsphere. Dondeti, 1994b reports that microspheres of polyacrylic acid prepared in a similar fashion showed significant hypoglycemic activity with a corresponding increase in serum insulin levels following nasal administration. It was also reported that the insulin loading of microspheres via supercritical fluid processing resulted in better absorption as compared to the microspheres loaded by a freeze-drying process.

Vyas et al., 1991 studied human serum albumin based microspheres bearing propranolol hydrochloride for release characteristics, bioadhesion and controlled in vivo absorption following nasal administration. They reported that the release of the drug was dependent on the heat treatment applied for stabilization which in turn was related to the density of the microspheres. The same formulation in dogs resulted in therapeutic plasma levels of drug for 10–12 h and in AUC levels equivalent to that after i.v. administration. The same microspheres containing magnetite, on application of an external magnetic field of 8 kOe produced an additional pulse dosing effect at the magnet application point.

6.4. Use of gel preparations

Morimoto et al., 1985 investigated the enhancement of nasal absorption of insulin and calcitonin using a polyacrylic acid gel. The nasal administration of insulin in 0.1% and 1% w/v polyacrylic acid gels showed maximum hypoglycemic effects at 30 min and 1 h after administration respectively. When calcitonin was administered nasally in a 0.1% polyacrylic acid gel, a significant hypocalcaemic effect was observed during the first 30 min. The same group (Morimoto et al., 1987) in another study, reported nasal absorption of nifedipine from polyethylene glycol 400 (PEG), aqueous Carbopol gel and Carbopol-PEG gel in rats. Nasal administration of nifedipine in PEG resulted in rapid absorption and a high C_{max}. However, the elimination of drug from plasma was very rapid. Nifedepine in aqueous Carbopol gel resulted in low drug plasma concentrations. On the other hand, Carbopol-PEG gel (1:1) showed a relatively high nifedipine plasma concentration and a prolonged action.

Juhasz et al., 1990 performed basic studies on the use of poloxamer 407 solutions for use as a bioadhesive for delivery of atrial natriuretic factor to the nasal mucosa. These solutions show an increase in viscosity with temperature. The bioadhesive properties were characterized and the diffusion of atrial natriuretic factor in the gels was studied. In another study, Chu et al., 1991 reported a novel non-aqueous polymeric formulation that exhibits low-viscosity fluid behavior for ease of spraying with nebulizer. This polymeric formulation when sprayed into the nasal cavity, transforms to a high-viscosity gel for efficient

retention and drug absorption. The study reported the effects of factors such as solvent composition and polymer concentration on the rheological properties of a polyacrylic acid polymer. The viscosity enhancement was correlated with the improved and sustained nasal absorption of propranolol in beagle dogs.

Popovici and Szasz, 1992 developed a nasal mucoadhesive gel formulation containing a 1:1 mixture of 3% pectin and 4% methylcellulose prepared in the presence of preservatives (0.075% nipagine and 0.025% nipasole) with a content of 2.6% w/w magnesium glutamate. This formulation resulted in an enhanced haemostatic effect by reducing the bleeding time in rats by 41.7%. Xi et al., 1992 developed a nasal gel formula by orthogonal design which consisted of glycerine, water, triethanolamine, 1.25% Carbopol 940 as excipients and the drug piroxicam to make a 4% gel. In humans, this formulation resulted in 85% bioavailability as compared with that of the oral tablet in equal dose.

In another study, Dondeti et al., 1994a reported that nasal administration of insulin loaded polyacrylic acid microparticles suspended in 1% w/v polyacrylic acid gel resulted in significant and sustained hypoglycemic effect for 7 h in normal rabbits.

7. Use of bioadhesive polymers and enhancers to improve the nasal absorption of drugs

Using the combination of bioadhesive polymer and penetration enhancer may be a viable alternative for improving the nasal bioavailability of drugs such as high molecular weight peptides.

7.1. Use of bioadhesive solutions and enhancers

Audhya and Goldstein, 1983 reported that addition of 1% sodium glycocholate and 1% methyl cellulose resulted in effective nasal absorption of thymopentin.

Ikeda et al., 1992 reported that with a combination of 2% hydroxypropyl cellulose and 5% azone, the nasal bioavailability of dopamine was increased to almost the same level as with i.v. administration. At the same time, plasma concentrations were maintained at a high level for more than 7 h.

According to Dondeti et al., 1995, insulin spray formulations containing micro-crystalline cellulose along with sodium taurocholate, ammonium glycerrhizinate, glycerrhetinic acid at 1% level resulted in absolute bioavailabilities of 8.4%, 7.8% and 2.2% respectively when administered nasally in diabetic rabbit. The same formulations resulted in total glucose reduction of 39%, 16% and 9% respectively. In the same study, an insulin spray formulation containing the bioadhesive polymer, Plastoid L50 and 1% sodium taurocholate was also evaluated. At 5 U/kg dose, the formulation resulted in 5.9% bioavailability with a total glucose reduction of 17% after nasal administration. The results indicated that the presence of permeation enhancer and a bioadhesive polymer improved insulin absorption when compared to the formulations containing bioadhesive polymer alone or permeation enhancer alone.

7.2. Use of bioadhesive powders and enhancers

Maitani et al., 1989b reported that the presence of bile salts along with Avicel and Human Serum Albumin (HSA) enhanced the nasal absorption of Human Interferon-β in rabbits. Human Interferon-β did not result in any absorption when administered as powder to the nasal cavity without the inclusion of bile salts. The addition of sodium glycocholate at pH 5.2 enhanced the nasal bioavailability to 3%. At pH 8.18, sodium cholate was more effective than sodium glycholate in promoting the nasal absorption of Human Interferon-β.

7.3. Use of bioadhesive microspheres and enhancers

Gentamicin in solution form has a low nasal bioavailability of approximately 1%, but absorption was significantly improved when the drug was administered as a freeze-dried powder in a bioadhesive microsphere system using degradable starch microspheres. When L-lysophosphatidylcholine (LPC) was incorporated as an enhancer,

Table 1
Bioadhesive polymers used in nasal drug delivery studies

Drug	Polymer + enhancer	Dosage form	Species	Bioavailability or pharmacological effect	Reference
Dopamine	4% HPC	Solution	Dog	20% vs IV	Ikeda et al. (1992)
	HPC + 1% HCO	Solution	Dog	25.7% vs IV	
	HPC + 1% SDC	Solution	Dog	37.5% vs IV	
	HPC + 5% Azone	Solution	Dog	63.8% vs IV	
Gentamicin	DSM	Powder	Sheep	9.7% vs IV	Illum et al. (1988)
	DSM + LPC	Powder	Sheep	51.3% vs IV	
Propranolol HCl	1.5% Carbopol 934P PG:GF = 40:60	Gel	Dog	51.8% vs IV	Chu et al. (1991)
Nifedipine	0.5% Carbopol 941 +PEG400 (1:1)	Gel	Rat	Comparable to IV effect	Morimoto et al. (1987)
Vasopressin	1% Na Hyaluronate	Solution	Rat	9.9% vs IV effect	Morimoto et al. (1991)
	+50 mM CM	Solution	Rat	83.6% vs IV effect	
Desmopressin	1% Na Hyaluronate	Solution	Rat	15.9% vs IV effect	Morimoto et al. (1991)
	+50 mM CM	Solution	Rat	39.8% vs IV effect	
Insulin	Carbopol 934	Powder	Dog	25% of IV effect	Nagai et al. (1984)
	HPC	Powder	Dog	20% of IV effect	
	Lactose	Powder	Dog	15% of IV effect	
Insulin	0.1% Carbopol	Solution	Rat	Not determined	Morimoto et al. (1985)
	1% Carbopol	Gel	Rat	Not determined	
Insulin	DSM	Powder	Rat	33% vs IV	Bjork and Edman (1988)
Insulin	DSM	Powder	Sheep	4.5% vs IV; 10.7% vs SC	Farraj et al. (1990)
	DSM + LPC	Powder	Sheep	13.1% vs IV; 31.5% vs SC	
Insulin	DSM	Powder	Rat	26% BG reduction	Edman et al. (1992)
	Sephadex	Powder	Rat	24% BG reduction	
	DEAE-Sephadex	Powder	Rat	8% BG reduction	
Insulin	1.5% MCC	Spray	Rabbit	2.0% vs IV	Dondeti et al. (1994a)
	MCC + ST	Spray	Rabbit	8.4% vs IV	
	MCC + AG	Spray	Rabbit	7.8% vs IV	
	MCC + GA	Spray	Rabbit	2.2% vs IV	
Insulin	70% Plastoid L50	Spray	Rabbit	2.3% vs IV	Dondeti et al. (1994a)
	Plastoid L50 + ST	Spray	Rabbit	5.9% vs IV	
Insulin	PAA (SCF)	Powder	Rabbit	8.1% vs IV	Dondeti (1994b)
	PAA (FD)	Powder	Rabbit	20.4% BG reduction	
	CPAA (SCF)	Powder	Rabbit	3.6% vs IV	
	CPAA (FD)	Powder	Rabbit	1.8% vs IV	
	AG (SCF)	Powder	Rabbit	9.8% vs IV	
	AG (FD)	Powder	Rabbit	2.9% vs IV	
Insulin	0.5% Chitosan	Solution	Sheep	7 times higher AUC	Illum et al. (1994)
hGH	DSM	Powder	Sheep	2.7% vs SC	Illum et al. (1990)
	DSM + LPC	Powder	Sheep	14.4% vs IV	
Interferon-β	MCC + SGC	Powder	Rabbit	3% vs IV	Maitani et al. (1989b)
Calcitonin	0.1% Carbopol	Solution	Rat	Not determined	Morimoto et al. (1985)

AG, Ammonium glycyrrhizinate; BG, blood glucose; CM, camostat mesilate; CPAA, cross-linked polyacrylic acid; DSM, degradable strach microspheres; FD, freeze-drying; GA, glycyrrhetenic acid; GF, glycerol formal; HCO, hydrogenated caster oil; LPC, L-å-lysophosphatidyl choline; MCC, microcrytsalline cellulose; PAA, polyacrylic acid; PG, propylene glycol;SCF, supercritical fluid processing; SDC, sodium deoxycholate; SGC, sodium glycocholate; ST, sodium taurocholate.

nasal bioavailability was further improved to approximately 57% (Illum et al., 1990).

Farraj et al., 1990 reported that with the addition of LPC to a degradable starch microsphere formulation, the nasal bioavailability of insulin was 31.5%. The absorption kinetics of these microspheres were similar to i.v. delivery with a longer duration of action. According to Illum et al., 1990, the addition of LPC to degradable starch microspheres improved the nasal bioavailability of hGH to 14.4% relative to the s.c. injection. In another study, the same group (Critchley et al., 1994) found that the use of delivery system in combination with LPC, had a profound effect on the absorption of desmopressin in sheep, with bioavailabilities reaching nearly 10% as compared to 1.2% for a simple nasal solution of the drug.

7.4. Use of bioadhesive gels and enhancers

Bremecker, 1990 reported that in an attempt to develop a nasal vaccination for tetanus toxoid bioadhesive gels proved to be ineffective, but an aqueous gel of silicic acid in combination with an anionic detergent led to an immunization comparable to that obtained by parenteral administration.

Thus it is evident from the literature that by using bioadhesive polymers alone, either in the form of sprays, powders, microspheres or gels, drug absorption can be improved to some extent. However, by incorporating penetration enhancers in these bioadhesive drug delivery systems a significant improvement is seen in bioavailability. Table 1 shows a summary of the bioadhesive polymers used in the nasal formulations intended for systemic drug delivery.

8. Conclusions

Bioadhesive polymers as drug carriers have received an increased attention following some interesting results especially in improving the delivery of peptide drugs across nasal membrane. Via this paper, we have tried to review some of the latest information relating to the improvement of the nasal delivery of drug molecules with an emphasis on bioadhesive polymers. As evident from the limited toxicological data available, these polymers seem to be relatively nontoxic as compared to other enhancers. Ideally, drugs and additives in nasal preparations should not interfere with the self-cleaning capacity of the nose. The use of bioadhesive polymers as drug delivery systems and their effect on mucociliary clearance mechanism and the possible consequences in humans throughout chronic therapy remains to be studied. The question as to how successful these delivery systems will become in providing consistent, reproducible therapeutic levels still remains to be answered.

So far, nasal administration of drugs especially peptides, along with bioadhesive polymers in combination with a nontoxic enhancer seems to provide a promising potential as an alternative therapy to the injection. If successful, these systems could provide a significant advantage to patients such as those who suffer from diabetes and who often must receive life-long multiple daily injections of insulin for their very survival.

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