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Review

Review on the systemic delivery of insulin via the ocular route

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Abstract

Systemic drug absorption from the ocular route is well known. Although there is some absorption from the conjunctival sac, the nasal meatus is the site where the majority of systemic absorption of instilled drug takes place. This article reviews the principles of systemic absorption of insulin applied topically to the eye. The physiological and pharmaceutical considerations for formulation development and the strategy of improving the systemic absorption and bioavailability of insulin are also discussed.

Keywords: Systemic absorption; Insulin; Ocular route

1. Introduction

Early exploratory work on systemic drug absorption from the ocular route has been reported by numerous research groups. The conjunctival and especially the nasal mucosa are the major systemic absorption sites for drug delivered through this pathway. The absorption of drug from the nasal cavity region is reproducible (Longenecker et al., 1987; Frauman et al., 1987) and comparable to parenteral drug administration (Drejer et al., 1992; Hussain et al., 1979, 1980a,b; Sanchez et al., 1991). This efficient systemic absorption can be utilized as a non-invasive means of delivering drug systemically. It also offers the advantage of by-passing the first-pass gastrointestinal and liver effects which are responsible for the low oral bioavailability of peptides and other drugs (Sanchez et al., 1991).

Despite these advantages, the development of systemic drug delivery via the ophthalmic route is

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restricted by the dynamic of the lachrymal drainage system. This system introduces and rapidly drains tear fluid and any instilled formulation from the precorneal area into the nasal cavity and throat from where it is swallowed into the gastrointestinal tract. This high elimination rate results in a short duration of drug contact with its absorption sites (i.e. conjunctival and nasal mucosa) and consequently, results in a low bioavailability.

In this review, animal data on the ocular insulin delivery is presented. The strategies used to improve the overall efficacy of systemic insulin delivery via the ocular route will be discussed along with some pharmaceutical considerations of ophthalmic drug delivery. Local ophthalmic drug delivery is not discussed in this report, however, several review articles on this topic are available (Aiache et al., 1997; Baeyens et al., 1997; Desai and Blanchard, 1995; Ding, 1998; Keister et al., 1991; Lang, 1995; Sasaki et al., 1999; Shell, 1984).

2. Physiological considerations

Fig. 1 shows a simplified anatomy of the lachrymal system. This system, basically, consists of lachrymal glands, upper and lower eyelids, the conjunctival sac, lachrymal puncta and ducts. After being secreted by the lachrymal glands, tears are distributed over the eye by the blinking action of the eyelids and collected in the lower conjunctival sac. From the lower conjunctival sac, the fluid is drained into the lachrymal sac through the puncta and the lachrymal duct. Blinking also promotes drainage by producing a negative pressure just inside the punctum, while the capillary effect in the lachrymal duct assists this movement into the lachrymal sac. Fluid from the lachrymal sac passes through the nasolachrymal duct which empties into the highly vascularized inferior nasal meatus. The fluid is then transported with the aid of cilia toward the nasopharynx and then swallowed into the gastrointestinal tract.

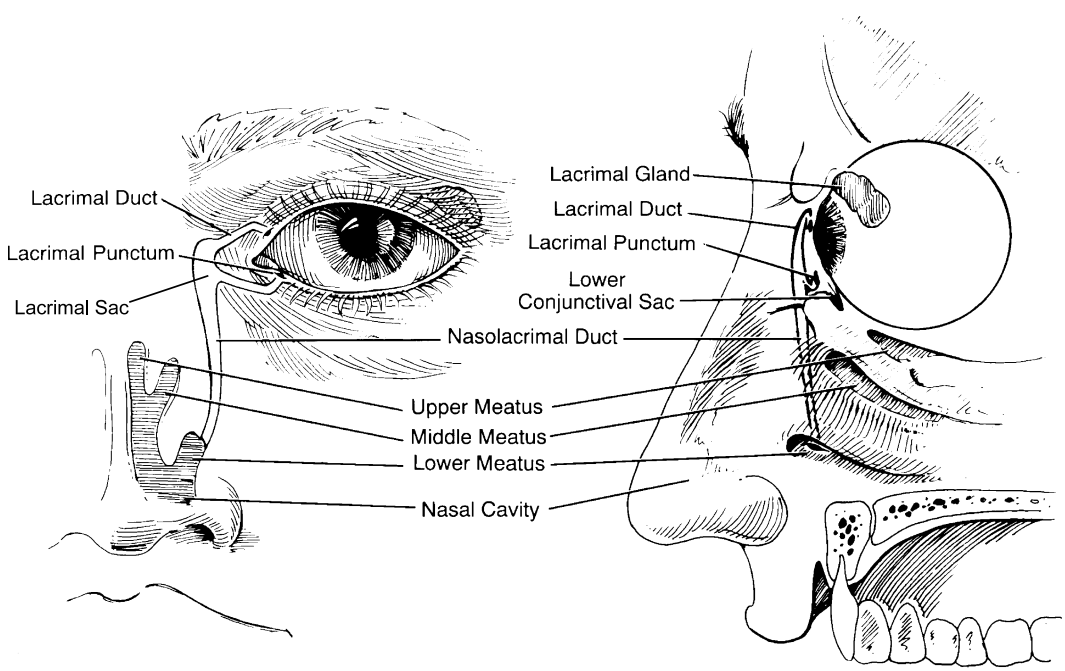
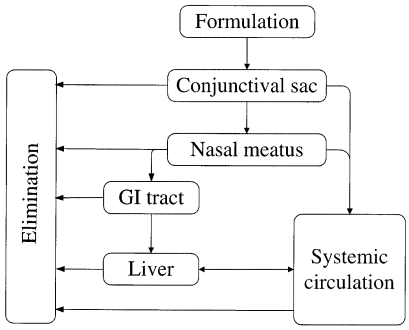


Fig. 1. Anatomy of the lachrimal system.



Scheme 1. Pathway of ocular drug delivery.

Normally, this system produces and drains tears at a constant rate to maintain a constant fluid residence volume in the lower conjunctival sac of approximately 7 μl (Chrai et al., 1973; Lee and Robinson, 1986). The normal turnover rate of tears is approximately constant at 16% per minute (Maurice, 1967). If a foreign substance is instilled into the lower conjunctival sac, the lachrymal system may increase its tear production and clearance rate to wash it into the nasal cavity (Baeyens and Gurny, 1997).

Ocular systemic drug delivery can be accomplished by the simple instillation of formulation into the lower conjunctival sac. The pathway of drug delivery via the ocular route is illustrated by Scheme 1. Upon instillation, the blinking rate of the eye is increased to expel the foreign formulation (Mitra, 1993; Bartlett et al., 1994a). The production rate of tears is also increased to dilute the concentration of formulation and to aid in its removal. There are three possible systemic absorption sites: conjunctival, inferior nasal and gastrointestinal mucosa. In 1993, Urtti and Salminen provided a through review for the pathway of drug delivery ocularly into the systemic circulation.

The conjunctiva serves as a protective tissue for the front eye. It consists of a stratified squamous epithelium with a high vascular supply (Sasaki et al., 1999). Watsky et al. (1988) reported that the surface area of human conjunctiva is estimated around 18 cm^2. Huang et al. (1989) found that the conjunctiva is permeable to water soluble drugs having molecular weight up to 20 000 Da, while Hayakawa et al. (1992) suggested that the permeability of this membrane is molecular weight independent. More recently, Prausnitz and Noonan (1998) compiled a comprehensive permeability database of a wide variety of drugs ($n \approx 150$, MW ranged from 18 to 140 000) on the cornea, sclera, and conjunctiva of the eye. Although most drugs delivered by solution only remain in the region for a short period of time, the conjunctival membrane plays an important role in the systemic absorption of pilocarpine (Urtti et al., 1985) and metekephalinamide (Stratford et al., 1988).

The inferior nasal meatus is part of the respiratory region of the nose and normally functions to warm and humidify inhaled air before it reaches the lungs. It is composed of ciliated pseudostratified columnar epithelium that is highly vascularized. Since the tears are drained into this region, it is believed that it is the major systemic absorption site of drug delivered via the ocular route. Chang and Lee (1987) determined that the nasal mucosa is responsible for over 70% of systemic absorption of timolol delivered via ocular route. Several investigators have shown that the onset of the activity of drug absorbed from the nasal cavity is as fast as from an intravenous injection (Illum and Davis, 1992; Quraishi et al., 1997). In 1987, McMartin et al. suggested that the nasal route is suitable for the delivery of drugs with molecular weight less than 1000 Da without the aid of an absorption enhancer and at least 6000 Da with the aid of absorption enhancer.

Since the purpose of systemic drug delivery via the ocular route is to eliminate the first pass effect, the third absorption site, the gastrointestinal mucosa, will not be discussed in this report. However, gastrointestinal absorption of drugs intended for local ocular delivery could be a problem. Lahdes et al. (1990) suggested that scopolamine delivered by eye drop can be absorbed from the gastrointestinal tract. Many drugs are degraded in the GI-tract and by liver. In fact, ocular delivery of systemically acting drugs is only justified if it cannot be given orally.

It is clear that the expelling of tears out of the eyes is responsible for the overall lower local bioavailability of ophthalmic drug delivery because it removes the drug from the delivery pathway. Increased tear production dilutes the concentration of drug and further lowers the local availability. The increased draining rate can cause high systemic

absorption from the nasal meatus and can also cause some unwanted side effects. Therefore, to improve the overall therapeutic efficacy of ocular drug delivery it is necessary to reduce the production of tears, minimize the expelling of tears and maximize the retention time of drug in the conjunctival sac.

3. In vivo experimental considerations

To effectively deliver a biologically active compound into the systemic circulation via the ocular route, factors such as the selection of animal model and the in vivo assessment of the efficacy of the formulation are important. These factors are discussed in this section.

3.1. Animal model

The rabbit is commonly used as an animal model in ophthalmic drug delivery studies because its lachrymal system is relatively close to that of its human counterpart. The lachrymal apparatus of the human and the rabbit are summarized in Table 1 (Lee and Robinson, 1986). As can be seen from the table, the precorneal characteristics of the rabbit eye are similar to those of the human eye. The volume and pH of tear fluid in the rabbit eye are also comparable to those of the human eye. In addition, it has been shown that the nasal mucosa, the major systemic absorption site of ocular drug delivery, of rabbits is structurally similar to that of humans (Corbo et al., 1990; Carstens et al., 1993; Dondeti et al., 1995). On the other hand, the rabbit has a slower tear volume turnover rate and slower blinking rate than the human. Because of this, a topically instilled formulation would be retained somewhat longer in the precorneal area of the rabbit and thus, prolong drug absorption more effectively than in man.

Table 1
The precorneal characteristics of human and rabbit (Lee and Robinson, 1986)

	Human	Rabbit
Normal lacrimal volume	7.0 μl	7.5 μl
pH of tear	7.4	7.4
Turnover rate	1.0 μl/min	~0.5 μl/min
Blinking frequency	15–20 times/min	2–5 times/min

There are several other advantages of using the rabbit as a model animal; rabbits are easy to handle, they have sufficient blood to withdraw for assay, and they have a high survival rate which allows long-term and inexpensive crossover studies. Furthermore, it is mandated by the USP that all insulin preparations must have hypoglycemic tests performed in a conscious rabbit (Insulin Assays, USP 24, US Pharmacopia, 2000). These advantages support the fact that the rabbit is a highly suitable model to use for the investigation of the ocular delivery of drugs, especially insulin.

3.2. In vivo assessment of ocular formulation

Systemic drug delivery via the ocular route can be quantitated by directly measuring the drug remaining in the conjunctival sac. Cotton swabs and capillaries by Ding et al. (1992), porous polyester rods by Jones et al. (1997), and filter paper by Sasaki et al. (1993) were used to collect samples from tears. Sasaki et al. (1993) also used device removal to measure unreleased drug from ophthalmic devices. Lachrymal scintigraphy is another method that can be applied to monitor the disappearance of drug from the low fornix area versus time (Wilson, 1999). Though these methods are easy to perform, they do not provide bioavailability data for the formulations tested. For absolute bioavailability assessment, the assay of drug from urine (Pinsuwan et al., 1997) or plasma (Moses et al., 1983; Pillion et al., 1994b; Sasaki et al., 1996) has to be performed.

Monitoring of the pharmacological response, i.e. blood glucose lowering (Aungst et al., 1988; Li and Mitra, 1994; Lin and Chien, 1995), can sometimes be used to quantitate the efficacy of ocular preparations. This method is easy to perform and it is the most relevant to the therapeutic purpose of giving insulin to patients. Although this approach can potentially be interfered with counter-regulatory hormones, there is a good relationship (Fig. 2, data calculated from Yamamoto et al., 1989) between the bioavailability measured by

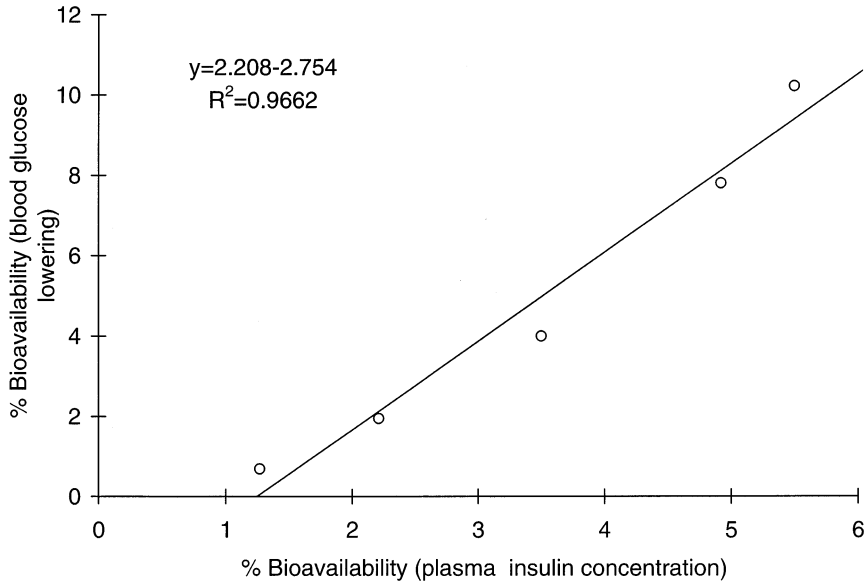


Fig. 2. Correlation of the bioavailability of insulin eye drops calculated from plasma insulin concentration and plasma glucose lowering. (Yamamoto et al., 1989)

blood glucose lowering and plasma insulin elevation. In order to overcome the potential counter-regulatory hormone effects, Nolte et al. (1990) proposed an euglycemic clamp to correlate the pharmacokinetic and pharmacodynamic parameters of non-invasive insulin delivery. This experiment is to infuse the glucose into the blood to maintain the glycemic level within normal range while the experimental animal receives insulin via the nasal route. The bioavailability of the nasal insulin formulation can be calculated by the amount of glucose infused into animal.

4. Ocular delivery of insulin

All currently marketed ophthalmic preparations are used for the treatment of local conditions such as glaucoma or conjunctivitis (McCoy, 1992). In most cases, an aqueous solution is used. Unavoidably, an aqueous solution will produce a rapid and short-lived entry of some drugs into the systemic circulation (Bellot et al., 1992; Jarivinen and Urtti, 1992; Lahdes et al., 1990; Patton and Francoeur, 1978; Salminen, 1990; Tang-Liu et al., 1984; Urtti et al., 1985; Urtti and Salminen, 1993; Vuori et al., 1994.) This pulse mass absorption may produce unwanted systemic side effects such as hypertension, tachycardia, bronchial asthma, etc. (McCoy, 1992; Buskirk, 1980). The most well known case is the fatal side effect of timolol (Nelson et al., 1986). Some experimental pre-clinical systemic drug deliveries via the ocular route are summarized in Table 2. Insulin, because of its high molecular weight, is one of the most challenging drugs to deliver reproducibly via the ocular route (Bartlett et al., 1994a,b; Christie and Hanzal, 1931; Chiou and Chuang, 1989; Morgan and Huntzicker, 1996; Nomura et al., 1989). Rats, rabbits, cats, dogs, and humans have been used to evaluate insulin delivery from solutions, suspensions, and devices. The efficacy of the individual dosage forms is discussed below.

4.1. Solutions

In 1931, Christie and Hanzal performed the first ocular delivery of insulin and demonstrated that insulin can be absorbed via the conjunctiva membrane. In their study, insulin was prepared using a pH 2.5 buffer with 0.2% of phenol. They found that the eye drop could reduce blood sugar

for up to 5 h but the bioavailability was low. Hirai et al. (1978, 1981a,b) studied the effect of pH on the systemic delivery of insulin via the nasal route. They found that systemic insulin absorption is enhanced significantly by using an acidic rather than neutral medium. They suggested that at low pH, insulin exists as a monomer that could more easily be absorbed than the dimer and/or hexamer, which mostly exist in neutral pH. After the pioneering work of Christie and Hanzal (1931), numerous investigations on the systemic delivery of insulin via the ocular route were carried out (Hirai et al., 1981a; Bartlett et al., 1994a,b; Morgan, 1995; Pillion et al., 1991; Sasaki et al., 1994). Not surprisingly, because of their rapid drainage from eyes, these eye drop formulations yielded only low bioavailability. The results of the above studies suggest that the use of absorption enhancers or promoters is necessary. Note that the studies by Bartlett et al. (1994a) showed no adverse reactions on the eye upon 8 weeks insulin eye drop instillation in humans.

Table 2
Systemic drugs delivered via the ocular route

	MW	References
Morphine	285	Chast et al., 1991; Dumortier et al., 1990
Thyrotropin releasing hormone	300	Chiou and Chuang, 1988
Enkephalin derivates	406–630	Chiou et al., 1988a, 1989, 1992a; Stratford et al., 1988
Oxytocin	1000	Chiou et al., 1991
Vasopressin	1080	Chiou et al., 1991
Leuteinizing hormone releasing hormone	1200	Chiou and Chuang, 1988
Melanotan II	1290	Pinsuwan et al., 1997
α-Melanocyte stimulating hormone	1500	Chiou et al., 1992b
Bombecin	1620	Chiou et al., 1992c
Somatostatin	1640	Chiou et al., 1992b
Atrial natriuretic peptides	3240	Chiou et al., 1992c
Vasoactive intestinal peptide	3325	Chiou et al., 1992b
Calcitonin	3420	Li and Chiou, 1992
Glucagon	3500	Chiou and Chuang, 1988; Chuang et al., 1992
β-Endorphin	3465	Rohde and Chiou, 1991
Adrenocorticotropic hormone	4540	Chiou et al., 1992b
Insulin	6000	References cited within the text

A wide variety of absorption enhancers have been evaluated in the delivery of insulin via the ocular route. Some of these are listed in Table 3. As seen in the table, saponin and its derivatives are commonly used as absorption enhancers in the ocular delivery of insulin. The in vivo data indicate that saponin is a strong absorption enhancer. Fig. 3 shows the blood glucose lowering profile of insulin solution containing different concentrations of saponin (Morgan, 1995). From this figure, it is obvious that 0.5% of saponin is required to significantly lower the blood glucose levels on the experimental animals. Unfortunately, saponin is irritating to the eyes (Sasaki et al., 1994, 1995; Morgan, 1995; Morgan and Huntzicker, 1996).

Other commonly used enhancers are the polyoxyethylene alkyl ethers such as polyoxylethylene-9-lauryl ether (BL-9, HLB = 11.5), polyoxyethylene-20-stearyl ether (Brij-78, HLB = 13.6) and polyoxyethylene-20-oleyl ether (Brij-99, HLB = 15.3). These non-ionic surfactants have been shown to be less irritating to the eyes than the saponins at concentrations below 0.5% (Morgan and Huntzicker, 1996). Fig. 4 displays the blood glucose reduction of cats upon receiving 15 IU regular insulin solutions containing either 0.5% of BL-9, Brij-78, Brij-99, or placebo (Morgan, 1995). As can be seen from this figure, only BL-9 and Brij-78 enhance the systemic absorption of insulin significantly. A similar observation has been reported by Pillion et al. (1994a). It has also been suggested by Chiou et al. (1990) that BL-9 provides a fast T_{max}, while Brij-78 could give a higher C_{max} and larger AUC of either plasma insulin concentration or AAC of blood glucose lowering-time in rabbits. Pillion et al. (1994c) and Morgan (1995) also observed this trend. Hirai et al. (1981a) suggested that the use of polyoxyethylene ether type enhancers with a HLB between 8 and 14 would give an optimal insulin absorption enhancement. This explains why Brij-99 cannot promote the systemic insulin absorption significantly.

Table 3
Absorption enhancers used in the ocular delivery insulin

Enhancer	Concentration (%)	Animal	References
Saponin	0.1–2	Rabbit	Chiou et al., 1988b; Chiou and Chuang, 1989; Chiou et al., 1989; Sasaki et al., 1994, 1995
	0.1–1	Rat	Pillion et al., 1991, 1994c, 1995a,b, 1996
	0.25–0.5	Cat	Morgan, 1995
	0.5	Dog	Morgan and Huntzicker, 1996
Brij-78 (polyoxyethylene-20-stearyl ether)	>0.5	Rabbit	Chiou et al., 1990; Chiou and Li, 1993; Liu and Chiou, 1994; Simamora et al., 1996; Lee et al., 1997a
	0.5	Rat	Pillion et al., 1991, 1994b
	0.5–1	Cat	Morgan, 1995
	0.5	Dog	Morgan and Huntzicker, 1996
BL-9 (polyoxyethylene-9-lauryl ether)	0.5–1	Rabbit	Yamamoto et al., 1989; Chiou and Chuang, 1989; Chiou et al., 1990; Chiou and Li, 1993; Srinivasan and Jain, 1998
	0.5	Rat	
	0.5–2	Cat	Pillion et al., 1991
	0.5–1	Dog	Morgan, 1995; Morgan and Huntzicker, 1996
Brij-99 (polyoxyethylene-20-oleyl ether)	0.5–2	Cat	Morgan, 1995
Cholate derivates	0.1-2	Rabbit	Yamamoto et al., 1989; Chiou et al., 1989; Hayakawa et al., 1992; Srinivasan and Jain, 1998
Fusidic acid	1	Rabbit	Chiou and Chuang, 1989
	0.5	Dog	Morgan and Huntzicker, 1996
Alkylglycosides (C6–14)	0.125–0.5	Rat	Pillion et al., 1994a,c, 1995b
	0.5–1	Dog	Morgan and Huntzicker, 1996
Benzalkonium chloride	0.01	Rabbit	Sasaki et al., 1994, 1995
	0.03–0.1	Cat	Hopper et al., 1991
EDTA	0.05–1	Rabbit	Chiou and Chuang, 1989; Sasaki et al., 1994, 1995
Tween 20	1	Rabbit	Chiou and Chuang, 1989
Decamethonium bromide	1	Rabbit	Chiou and Chuang, 1989
Sorbic acid	0.25	Rabbit	Sasaki et al., 1994, 1995
2-Phenylethanol	0.5	Rabbit	Sasaki et al., 1994, 1995
Benzyl alcohol	0.5	Rabbit	Sasaki et al., 1994, 1995
Parabens	0.04	Rabbit	Sasaki et al., 1994, 1995
Dimethyl sulfoxide	30–45	Cat	Hopper et al., 1991
Proparacaine HCl	0.5	Cat	Hopper et al., 1991

The use of sodium salts of bile acids for promoting the systemic absorption of insulin has been reported by Yamamoto et al. (1989), Chiou and Chuang (1989) and Srinivasan and Jain (1998). Yamamoto et al. (1989) observed that the hydrophobicity of the bile salt is an important determinant of insulin absorption enhancement. Their data indicate that taurocholate is less effective than glycocholate and deoxycholate. Similar observations were reported by Gordon et al. (1985) who used these bile salts to enhance the delivery of insulin via the nasal route. A number of research groups reported that bile salts are irritating to the nasal mucosa and inhibit ciliary movement in experimental animals (Duchateau et al., 1986; Gordon et al., 1985; Marttin et al., 1996). Yamamoto et al. (1989) showed that the bioavailability of insulin eye drop (Fig. 5) is a function of the concentration of sodium glycocholate. As can be seen from the figure, the

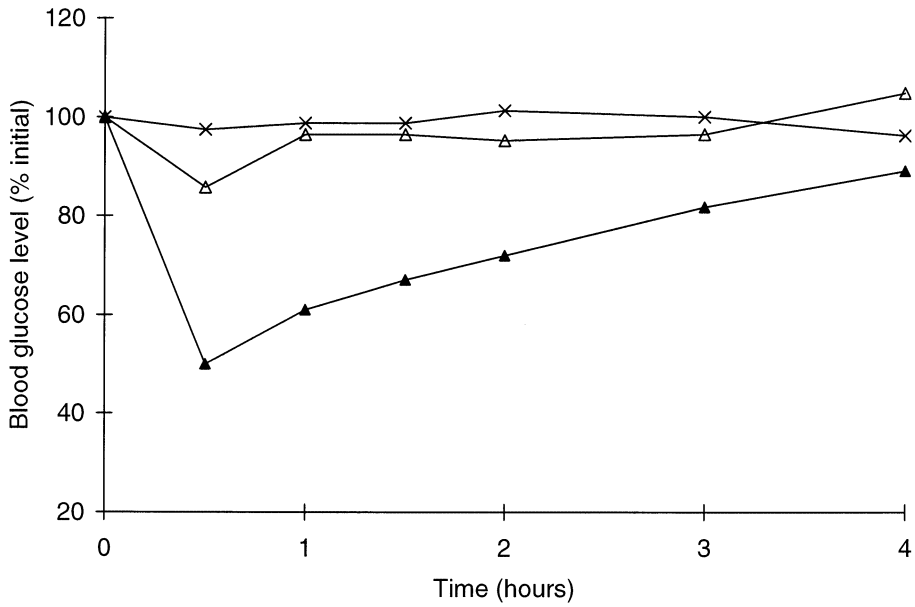


Fig. 3. Percent of initial blood glucose concentrations versus time after ocular instillation of 15 unit insulin eye drop to cats with difference concentration of saponin: 0% (×), 0.25% (△), 0.5% (▲). (Morgan, 1995).

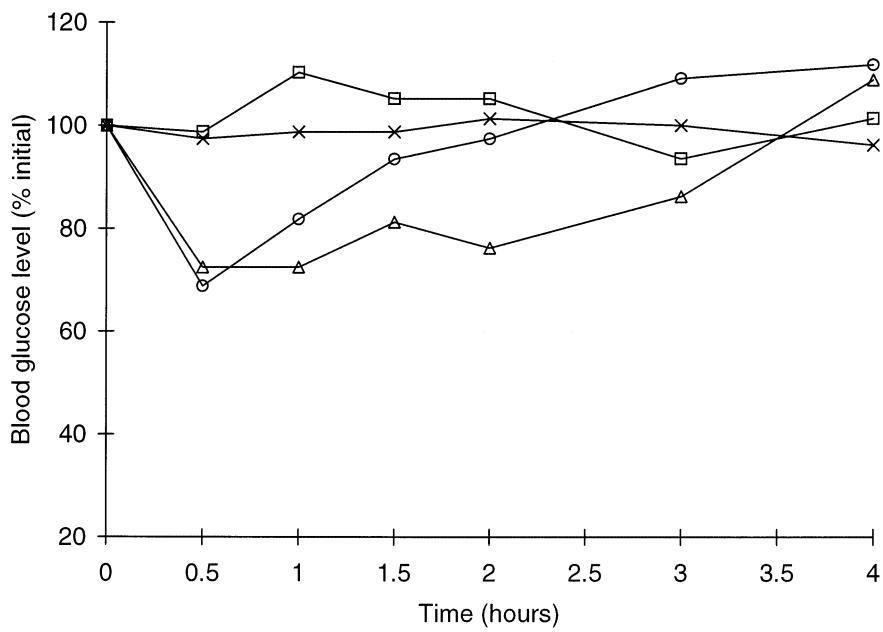


Fig. 4. Percent of initial blood glucose concentrations versus time after ocular instillation of 15 unit insulin eye drop to cats: no enhancer (×), 0.5% Brij-99 (□), 0.5% Brij-78 (△), 0.5% BL-9 (○). (Morgan, 1995).

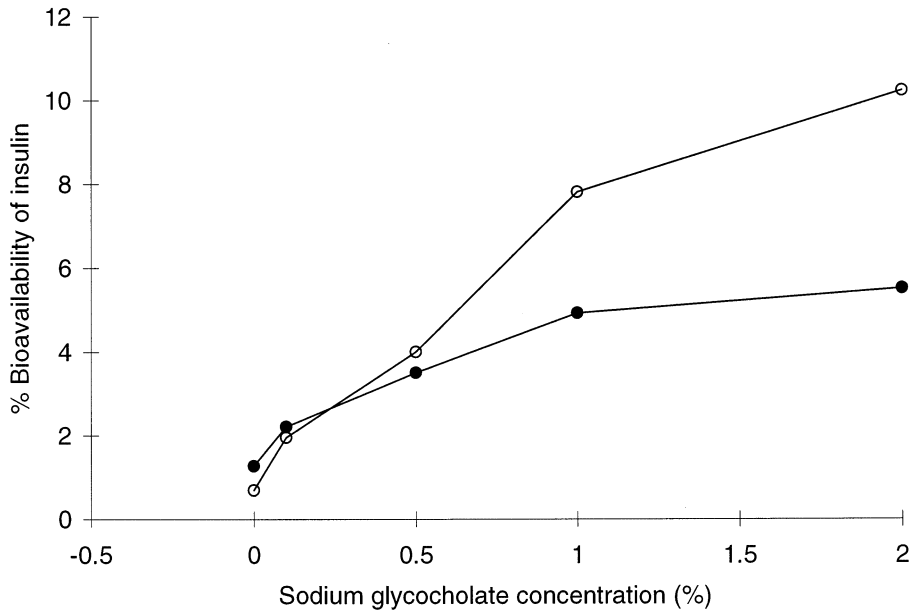


Fig. 5. Percent of bioavailability versus concentration of glycocholate (%) after ocular instillation of 10 unit insulin eye drop to rabbits. Calculated from blood glucose lowering (○), calculated from plasma insulin concentration (●). (Yamamoto et al., 1989).

enhancement produced by sodium glycocholate levels off after 1% of glycocholate in the eye drop solution. Also, the bioavailability, calculated by the blood glucose lowering, tends to be higher than that calculated by plasma insulin concentration.

Fusidic acid and its sodium salt, which are similar in structure (see Fig. 6) to the bile acids and salts, have also been used as enhancers in rabbits by Chiou and Chuang (1989) and dogs by Morgan and Huntzicker (1996). They showed that sodium fusidate is more effective than BL-9 and glycocholate in enhancing the absorption of insulin in rabbits. Interestingly, fusidic acid does not enhance the absorption of insulin in dogs (Morgan and Huntzicker, 1996). Apparently, fusidic acid and its derivatives can only be used in certain animal species and its mechanism of action is not known. The use of other fusidic acid derivatives such as sodium tauro-24,25-dihydrofusidate produced nasal irritation in both humans (Nolte et al., 1990) and rats (Donnelly et al., 1997).

Alkylglycosides were also investigated in enhancing the systemic absorption of insulin (Pillion et al., 1994a,c, 1995b; Morgan and Huntzicker, 1996). These compounds are composed of various hydrocarbons (with chain length ranging from 6 to 14) connected to either a maltose or sucrose unit. Fig. 7 displays the bioavailability of insulin prepared with various alkylglycoside concentrations and chain lengths (Pillion et al., 1994c). As seen in this figure and from the data of Morgan and Huntzicker (1996), the lipophilicity of the carbohydrate tail is a major determinant for the efficacy of the enhancement. This figure also clearly indicates that 0.25% or higher concentration of alkylglycoside is necessary for enhancing the absorption of insulin.

Several other compounds that have been evaluated for their potential as absorption enhancers for insulin are benzalkonium chloride, ethylenediamine tetraacetic acid (EDTA), sorbitan monolaurate (Tween 20), decamethonium bromide, sorbic acid, 2-phenylethanol, benzyl alcohol, methyl paraben, propyl paraben, dimethyl sulfoxide (DMSO) and proparacaine HCl (Chiou and Chuang, 1989; Hopper et al., 1991; Sasaki et al., 1994, 1995). Among these agents, only benzalkonium chloride and EDTA produce a substantial blood glucose reduction in rabbits. In vivo data of Sasaki et al. (1994) indicates that the use of 0.01% of benzalkonium chloride is necessary to alter the

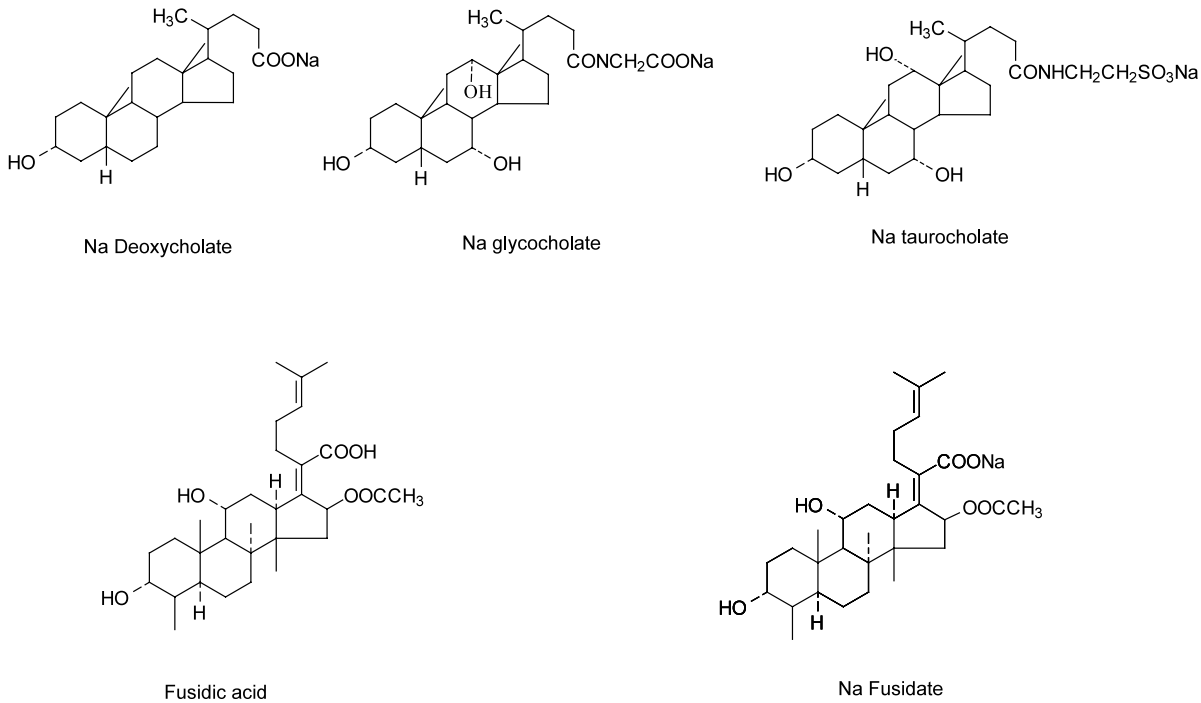


Fig. 6. Chemical structure of cholates and fusidates.

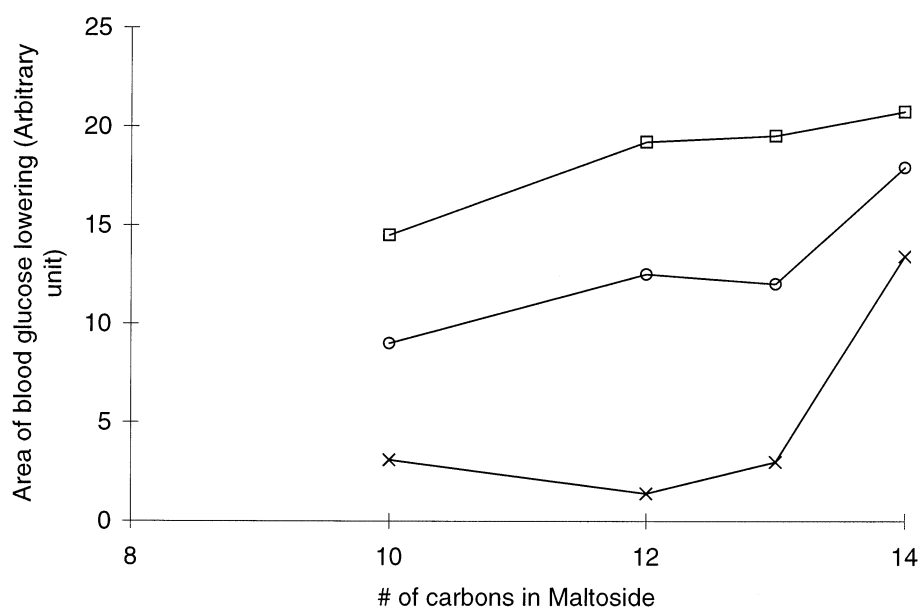


Fig. 7. Area of blood glucose lowering versus number of carbons in maltoside after ocular instillation of 20 μl 0.2% of insulin eye drop to rats with difference concentration of maltoside: 0.125% (×), 0.25% (○), 0.5% (□). (Pillion et al., 1994c).

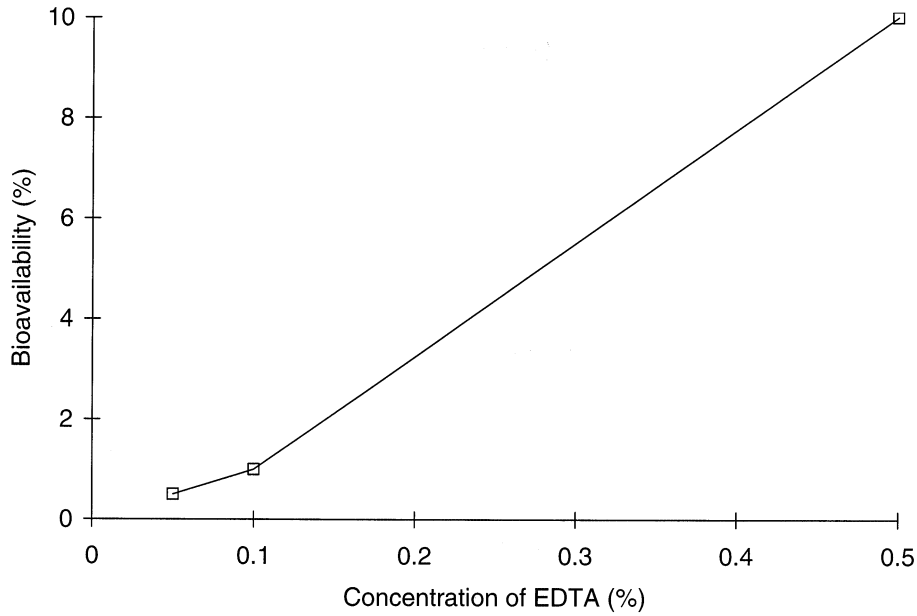


Fig. 8. Bioavailability versus concentrations of DETA after ocular instillation of 10 unit of insulin eye drop to rabbits. (Sasaki et al., 1994).

blood sugar levels of rabbit. Interestingly, this trend was not observed in cats even though the concentration of benzalkonium chloride was in creased ten-fold (Hopper et al., 1991). Marttin et al. (1996) reported that benzalkonium chloride could cause some histological changes in the nasal cavity of the rat. Also, Furrer et al. (2000) reported that this compound causes marked corneal damage in rabbits.

Fig. 8 shows the relationship observed by Sasaki et al. (1994) that the bioavailability of insulin depends on the concentration of EDTA. Contrary to this finding, Aungst and Rogers (1988) reported that the use of EDTA did not promote the systemic absorption of insulin delivered nasally. It has been reported that EDTA caused nasal mucosa damage and did not enhance the nasal absorption of other small peptides with molecular weight between 450 and 570 (Donnelly et al., 1997). Thus, the effectiveness of both benzalkonium chloride and EDTA is questionable and still needs to be further investigated.

4.2. *Viscous solutions, suspensions and liposomes*

Nomura et al. (1994) increased the viscosity of insulin eye drops with hyaluronic acid in an attempt to enhance the systemic absorption in a diabetic dog. However, their approach did not produce a substantial bioavailability increase. Yamamoto et al. (1994) suspended insulin in a variety of vehicles. They obtained the following insulin bioavailability data: peanut oil (6.0%) > artificial tear ($\approx$ 4.1%) > phosphate buffer with 1% Na glycocholate (2.4%) > liquid paraffin (2.1%) > sesame oil (1.3%). It is interesting to note that artificial tear produced a higher bioavailability than solutions with a surfactant and viscous oily suspensions. The bioavailability of nasal insulin delivery by peanut oil and liquid paraffin suspension was also reported by Maitani et al. (1995) to be low (6.0 and 2.1%, respectively). This finding suggests that the efficacy of ocular insulin delivery is similar to that of nasal delivery. Although the exact mechanism is not clear, it has been reported that peanut oil has a destructive effect on the nasal mucosa of the rabbit (Yamamoto et al., 1995). Nonetheless, the bioavailability produced by the suspension approach is far from being clinically useful.

The encapsulation of insulin into a liposome for systemic delivery via the ocular route has been

explored by Soni et al. (1998) and Srinivasan and Jain (1998). In order to prolong the retention time of the formulation in the precorneal area, a positively charged insulin containing liposome was prepared. This formulation can reduce the blood glucose concentration of rabbits to 65–70% of initial for up to 5 h. Although this preparation can prolong the activity of insulin, the method of preparing the formulation is tedious and time consuming. While this may preclude the use of the formulation tested in ocular insulin delivery, it demonstrates the feasibility of a liposomal product.

4.3. Ocular insert

In 1989, Yamamoto et al. conducted an extensive study on eye drop delivery in rabbits and suggested that an ocular insert would be another feasible approach to prolong and thus enhance the delivery insulin via the ophthalmic route. This is due to the fact that an insert remains in the conjunctival sac much longer than either a solution or an emulsion. It has a distinct potential for producing ocular sustained release of insulin.

The high molecular weight of insulin (≈ 6000 Da) precludes the use of most drug permeable membranes to control the release rate. Simamora et al. (1996) introduced an ocular insert for the delivery of insulin. In their study, Gelfoam® (absorbable gelatin sponge, USP, size 100) was utilized as a drug carrier to deliver sodium insulin with the aid of Brij-78 as an absorption enhancer. The Gelfoam device is ideal for insulin because diffusion takes place in the aqueous region between the gelatin fibers rather than through a membrane. The hypoglycemia versus time profiles obtained in their study are plotted in Fig. 9. As can be seen in the figure, both solution and device formulations give a comparable blood glucose reduction. However, the duration of activity of insulin produced by the eye devices is ten times longer than that produced by an eye drop. It is clear that the therapeutic efficacy of insulin is substantially improved by the use of an eye device. Note that the amount of Brij-78 used in their study is ten times lower than used by other research groups (Chiou et al., 1990; Chiou and Li, 1993; Liu and Chiou, 1994). Lee et al. (1997a) optimized the amount of insulin and Brij-78 in the Gelfoam device. They reported that a device containing 1.0 mg of insulin and 20 μg of Brij-78 can prolong the activity of insulin for up to 12 h without the risk of hypoglycemia in rabbits.

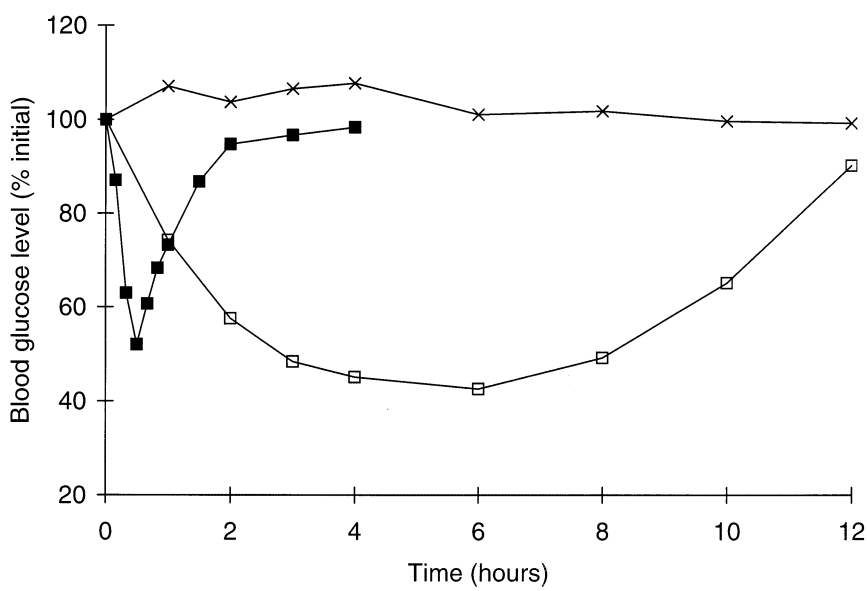


Fig. 9. Percent of initial blood glucose concentrations versus time after ocular instillation placebo eye device (×) and 1 mg insulin eye drop with 20 μg Brij-78 (■), 1 mg insulin device with 20 μg Brij-78 (□) to rabbits. (Simamora et al., 1996).

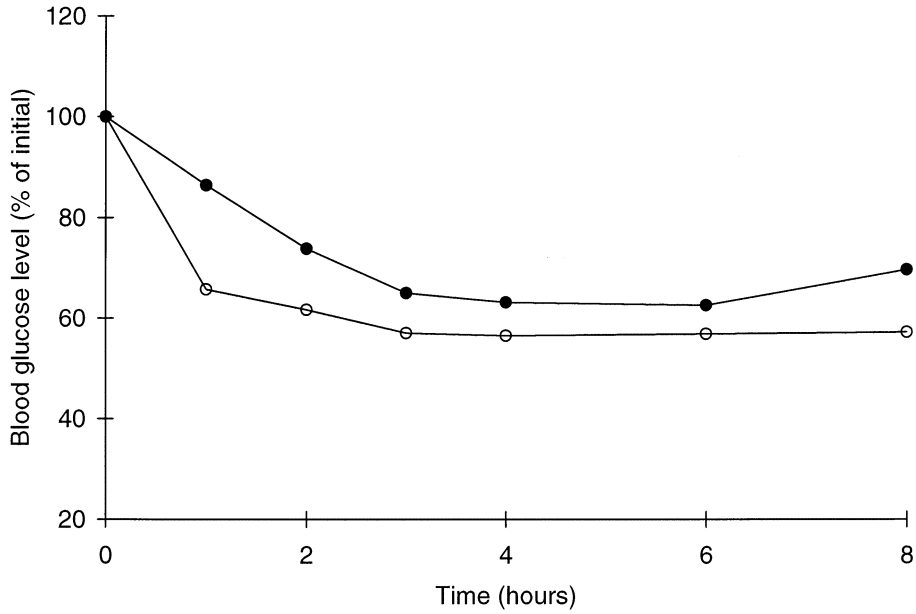


Fig. 10. Percent of initial blood glucose concentrations versus time after ocular instillation 0.2 mg insulin eye device treated with 1% HCl (●) and 5% acetic acid (○) to rabbits. (Lee and Yalkowsky, 1999b).

The need for Brij-78 in the insulin eye device can be eliminated if the delivery system is treated with dilute acetic acid or aqueous hydrochloric acid (Lee et al., 1997b; Lee and Yalkowsky, 1999a,b). The blood glucose lowering versus time profiles produced by the dilute acid treated 0.2 mg insulin device are plotted in Fig. 10. It is clear from the figure that both acetic acid and hydrochloric acid (HCl) treated devices give virtually identical blood sugar reduction. From this data, it is clear that insulin delivery is greatly improved by acid treatment. These improvements include elimination of the need for an enhancer and the reduction of the dose of insulin up to five-fold with comparable efficacy to that of devices containing the absorption enhancers described by Simamora et al. (1996).

This surfactant-free enhancement was further investigated by Lee and Yalkowsky (1999c). They proposed that the acid hydrolyzed gelatin could serve as an absorption enhancer to promote the systemic absorption of insulin delivered via ocular route. This is in agreement with the studies by Imai et al. (1989) and Kimura et al. (1990, 1991) who used hydrolyzed gelatin fragments (mean molecular weight 6000) to promote the absorption of some poorly water soluble drugs after oral or rectal administration. Although neither the chemical composition nor the mechanism by which it acts are known, it is clear that the interaction of gelatin with dilute acid produces an enhancer that promotes the systemic absorption of insulin delivered via the ocular route. From these reports, there is no doubt that the gelatin based eye device outperforms the solution formulation for ocular insulin delivery. Most importantly, the reduced blood glucose levels of rabbits were well maintained in a uniform fashion over 8 h.

4.4. Mechanism of absorption enhancement

Based upon the previous discussions, both the enhancer and the type of dosage form play an important role in the systemic absorption of insulin via the ocular route. It is believed that insulin can be absorbed into the systemic circulation from the paracellular pathway (tight junction) of both the conjunctival and the nasal mucosa (Carstens et al., 1993; Donnelly et al., 1997; Donovan et al., 1990; Hirai et al., 1981b).

The conjunctival pathway has been suggested to be molecular weight independent and the permeability of insulin from the conjunctival mucosa is very small (Hayakawa et al., 1992). The absorption of drug through the nasal mucosa is molecular weight dependent with a cut-off of approximately 1000 Da. It is generally believed that the use of an absorption enhancer is necessary if the target compound has a molecular weight higher than 1000 (McMartin et al., 1987). While the use of an enhancer is considered a requirement for the efficient absorption of insulin, the exact mechanism of the enhancement is not well understood. There are several enhancement mechanisms that have been proposed. These include (1) enlargement of the paracellular channel, (2) inhibition of the aggregation of insulin from monomer to diamer or hexamer, (3) micelle formation between insulin and enhancer, (4) inhibition of the enzyme degradation and prolong the half-life of insulin in the absorption site, (5) modification of the polarity of the surface of the mucosa, and (6) inhibition of the clearance rate of mucus on the nasal mucosa and prolong the contact time of insulin to its absorption site (Aungst et al., 1988; Aungst, 1994; Carstens et al., 1993; Donovan et al., 1990; Gizurarson and Bechgaard, 1991; Hirai et al., 1981a; Longenecker et al., 1987; McMartin et al., 1987; Behl et al., 1998). While these mechanisms are reasonable, they cannot be used as a general rule in different animal models.

Unlike the complexity of absorption enhancers, an ocular insert simply prolongs the residence time of the drug in the precorneal area and thus prolongs the contact time of the drug with its absorption site. According to McMartin et al. (1987), systemic drug absorption in the nasal cavity could follow two phases, a fast absorption phase which depends on the lipophilicity of the chemical and a slow absorption phase which depends on the molecular weight and the rate of transport of the chemical through the nasal cavity. The former mechanism can be improved by the use of absorption enhancers and the latter mechanism can be achieved by prolonging the contact time of drug to its absorption site.

These two mechanisms can be used to explain the superiority of eye devices to the eye drops discussed previously. A small amount of enhancer (20 μg of Brij-78 per device) can enhance the absorption of insulin in the fast absorption phase while the slow release of insulin from the device fits into the second absorption phase since the contact time of insulin on its absorption site is prolonged. In addition to insulin delivery, Pinsuwan et al. (1997) successfully delivered melanotan II, a cyclic heptapeptide with a molecular weight of 1290, by an enhancer-free Gelform device. They found the bioavailability of melanotan II to be 67 and 25%, respectively, for the ocular device and eye drop. These observations, again, suggest that the prolongation of the contact time of drug to its absorption site is the most important factor in both ocular and nasal drug delivery (Chang and Lee, 1987; Harris and Robinson, 1990; Maitani et al., 1997).

5. Conclusions

There are a larger number of factors that must be considered in formulating a drug for systemic delivery via the ocular route. Among the most important is the desired systemic concentration–time profile. If a rapid onset and a short duration are desired, eye drops will usually be most effective. However, if a prolonged blood level is needed, some sort of device must be used. Viscous aqueous solutions, oil solutions, and emulsions can be drained from the eye by the lachrymal system and therefore can only provide minimal prolongation of drug release.

While all ocular preparations must be compatible with iris, corneal, and conjunctival tissues, these factors are more important for devices. Because it must remain in one place for several hours, irritation of local tissue can be more problematic for an eye device than for an eye drop, which is eliminated within seconds. Also a device must be comfortable and designed so that it does not fall out during sleep. Most importantly, the device must release the drug in a constant and reproducible manner. Finally, all of the pre-clinical studies suggest the feasibility of delivering

insulin systemically via the ocular route. No toxic effects were observed in several preliminary human studies. The application of this approach, however, still needs further investigation in order to be clinically useful.

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