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A modelling analysis of drug absorption and administration from the ocular, naso-lacrimal duct, and nasal routes in rabbits

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Abstract

A model is presented to describe drug absorption and administration from the nasal and ocular routes. The advantage of the model is that it considers several physiological processes occurring in the ocular and nasal cavities and that it can incorporate information about the permeability of the nasal mucosa and tissue. The parameters of the model can be calculated from independent experimental studies. Computer simulations of the model were compared with in vitro experimental data to validate the model.

Keywords: Modelling; Ocular route; Naso-lacrimal route; Nasal route; Peanut oil; Enhancer

1. Introduction

Interest in drug delivery of peptides and proteins through non-parenteral routes has increased in recent years. Non-parenteral routes for insulin delivery have been investigated including the nasal (Hirai et al., 1981; Nagai et al., 1984; Gibson and Olanoff, 1987; Björk and Edman, 1990; Farraji et al., 1990) buccal (Nagai and Konishi, 1987), rectal, vaginal (Aungst et al., 1988), pulmonary (Yoshida et al., 1979) and transdermal (Kari, 1986) routes.

In particular, drug administration by the ocular and nasal routes has been discussed by many investigators who have commented on the various parameters that affect drug absorption in the nose from various DDS and related ocular and nasal systems.

We have already reported that peanut oil is an effective vehicle for nasal absorption of insulin whereas insulin is not absorbed without peanut oil and that bioavailability for peanut oil was 6.0% (Yamamoto et al., 1994). The bioavailability of insulin increased when added with a soybean-derived sterol mixture (SS) and its glucoside mixture (SG) as an enhancer (Maitani et al., 1995).

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Unfortunately, very little has been presented up to now on models describing the physiological characteristics of the ocular and nasal routes and their implication for nasal absorption. For this reason, we have now developed a model which incorporates all these physiological and mucociliary characteristics. To elucidate the physiological parameters, the insulin concentration after administration was analyzed by using the newly developed model. The parameters in the model were compared with the already available independent experimental data in vitro.

2. Experimental

Bovine insulin (24.4 IU/mg) was purchased from Sigma Chemicals Co. (St. Louis, MO, USA) and peanut oil was of guaranteed reagent grade from the Japanese Pharmacopoeia 12. Insulin suspensions in oil were prepared by suspending 40 mg of insulin that passed through a 200 mesh sieve in 10 ml of peanut oil with a stirrer. The solubility of insulin in peanut oil was 0.00353 mg/ml.

The oil-based suspensions were applied to the eye surface after ligation of the lacrimal punctum (ocular route), to the eye surface without ligation (naso-lacrimal duct route), or to the nasal mucosa (nasal route). The insulin activity in the blood was measured in rabbits after administration of the insulin incorporated in the oil-based suspensions by the three routes. The precise administration method to Japanese white rabbits and the insulin assay were reported in the previous paper (Yamamoto et al., 1994). Briefly, the ocular route was prepared by inserting a polyethylene tube with a diameter of 1.05 mm for closing the naso-lacrimal ducts of the rabbit. For the ocular route, the dosage forms were loaded in a syringe which was installed with a micro-tube at the top, and the micro-tube was then inserted into the inside of the lower eyelid very carefully. The same method was used for the naso-lacrimal route but without closing the naso-lacrimal ducts. For the nasal route, a polyethylene tube with a diameter of 1.05 mm and a length of 10 cm was installed at the top of a syringe and inserted into the nose of a rabbit. For all three routes, a 250 μl dosage was loaded into the syringe and administered through the tube into either one eye or the nasal cavity of a rabbit (e.g. 10 IU/kg).

3. Results and discussion

3.1. Model

The main compartment associated concentrations are: compartment E, the eye with drug concentration in the ocular formulation, C_E; compartment N, the nose with drug concentration in the nasal formulation, C_N; compartment B, the blood with drug concentration, C_D; compartment G, the GI tract with drug concentration, C_G.

The following kinetic constants are used to express the new pharmacokinetic model presented in Fig. 1: kinetic constant k_1 for drug from the ocular formulation into the circulation; kinetic constant k_2 for drug from the nose into the circulation; kinetic constant k_3 for drug from the GI tract to the blood, which is not crucial for poorly absorbed drugs; kinetic constant k_4, a translocation rate constant which is high due to flow from the eye to the nose; kinetic constant k_5, flow from nose to the GI tract, which is approximately zero because of peptide digestion in the stomach; ki-

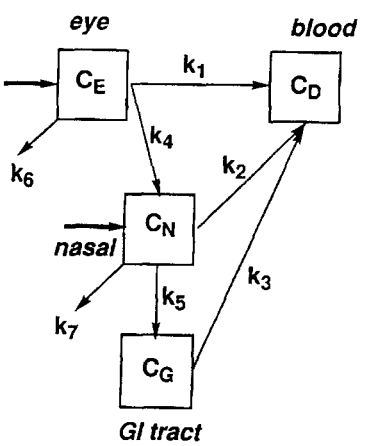

Fig. 1. Schematic representation of a four-compartment pharmacokinetics model for drug administration by the ocular, naso-lacrimal duct and nasal routes.

netic constant k_6 which characterizes the decomposition of drugs and especially peptides on the conjunctival mucosa; kinetic constant k_7 which describes the decomposition of drugs on the nasal mucosa.

In the model, all processes are assumed to be first order, so that the following ordinary differential equations can describe the drug distribution:Drug disappearance from the eye,

$$-dC_E/dt = k_1C_E + k_4C_E + k_6C_E \quad (1)$$

Drug concentration in the blood,

$$-dC_D/dt = -k_1C_E - k_2C_N - k_3C_G \quad (2)$$

Drug concentration in the nasal cavity,

$$-dC_N/dt = -k_4C_E + k_5C_N + k_2C_N + k_7C_N \quad (3)$$

Drug concentration in the GI tract,

$$-dC_G/dt = -k_5C_N + k_3C_G \quad (4)$$

The solution of these four equations is rather simple if the initial conditions are known. For example, from Eq. (1) and assuming that at $t = 0$, $C_E = C_{E0}$ (i.e. the initial concentration), then the solution of Eq. (1) for the eye concentration as a function of time is:

$$C_E = C_{E0}\exp[-(k_1 + k_4 + k_6)t] \quad (5)$$

Then, by placing Eq. (5) into Eq. (3) we obtain:

$$-dC_N/dt = -k_4C_{E0}\exp[-(k_1 + k_4 + k_6)t] + (k_2 + k_5 + k_7)C_N \quad (6)$$

The solution of this equation gives the nasal concentration as a function of time, again under the standard initial conditions at $t = 0$, $C_N = C_{N0}$.

$$C_N = \frac{k_4C_{E0}\exp[-(k_1 + k_4 + k_6)t]}{(k_2 + k_5 + k_7 - k_1 - k_4 - k_6)} + \left[C_{N0}\frac{k_4C_{E0}}{(k_2 + k_5 + k_7 - k_1 - k_4 - k_6)}\right] \times \exp[-(k_2 + k_5 + k_7)t] \quad (7)$$

The solution of Eq. (7) assumes that there is initial drug concentration C_{N0} in the nasal cavity. If this is not so, then $C_{N0} = 0$. Now setting Eq. (7) into Eq. (4), we may solve the resulting equation. Here, we may assume that the initial drug concentration in the gastrointestinal area is zero, i.e. $C_{G0} = 0$. Thus, the drug concentration in the GI tract is expressed by:

$$C_G = \frac{k_4k_5C_{E0}\exp[-(k_1 + k_4 + k_6)t]}{(k_2 + k_5 + k_7 - k_1 - k_4 - k_6)(k_3 - k_1 - k_4 - k_6)} + \frac{k_5}{(k_3 - k_2 - k_5 - k_7)} \times \left[C_{N0} - \frac{k_4C_{E0}}{(k_2 + k_5 + k_7 - k_1 - k_4 - k_6)}\right] \times \exp[-(k_2 + k_5 + k_7)t] - \left[\frac{k_4k_5C_{E0}}{(k_2 + k_5 - k_1 - k_4 - k_6)(k_3 - k_1 - k_4 - k_6)} + \frac{k_5}{(k_3 - k_2 - k_5)} \times \left[C_{N0} - \frac{k_4C_{E0}}{(k_2 + k_5 - k_1 - K_4 - k_6)}\right]\right]\exp(-k_3t) \quad (8)$$

It is then clear that the overall rate of the drug in the blood can be calculated by substituting for Eqs. (5), (7) and (8) in Eq. (2). Similarly, the rate of drug in the blood can be integrated as a function of time to give the total drug concentration (activity).

Several simplifications of the previous equations can be used to provide more realistic evaluation of the drug distribution problem. For example, assuming that the drug is not absorbed from the GI tract, the constants k_3 and k_5 are zero. When a drug formulation is added in the eye, C_{E0}, and the nose, C_{N0}, then Eq. (9) can apply which is of the general form:

$$dC_D/dt = C_{E0}\left[k_1 + \frac{k_2k_4}{(k_2 + k_5 + k_7 - k_1 - k_4 - k_6)} + \frac{k_3k_4k_5}{(k_2 + k_5 + k_7 - k_1 - k_4 - k_6)(k_3 - k_2 - k_5 - k_7)}\right] \times \exp[-(k_1 + k_4 + k_6)t] + \left[k_2 + \frac{k_3k_5}{(k_3 - k_2 - k_5 - k_7)}\right]$$

$$\times\left[C_{N0}-\frac{k_4C_{E0}}{k_2+k_5+k_7-k_1-k_4-k_6}\right]$$
$$\times\exp[-(k_2+k_5+k_7)t]$$
$$-\left[\frac{k_4k_5C_{E0}}{(k_2+k_5-k_1-k_4-k_6)\,(k_3-k_1-k_4-k_6)}\right.$$
$$+\frac{k_5}{(k_3-k_2-k_5)}$$
$$\left.\times\left[C_{N0}-\frac{k_4C_{E0}}{(k_2+k_5-k_1-k_4-k_6)}\right]\right]$$
$$\times\exp(-k_3t)=\alpha\exp(-\beta t)$$
$$+\gamma exp(-\delta t)+\epsilon\exp(-\zeta t) \quad (9)$$

Here, a, β, γ, δ, ϵ and ζ are given by the following expressions:

$$\alpha=\frac{k_2k_4}{(k_2+k_5+k_7-k_1-k_4-k_6)}+k_1 \quad (10)$$

$$\beta=k_1+k_4+k_6 \quad (11)$$

The term γ can be expressed for the naso-lacrimal duct route as

$$\gamma=\gamma_e=-\frac{k_2k_4}{(k_2+k_7-k_1-k_4-k_6)}$$
$$=-\frac{\gamma_n\epsilon(\gamma_n-\beta)}{(\delta-\beta)} \quad (12)$$

and for the nasal route as

$$\gamma=\gamma_n=k_2 \quad (13)$$

Also

$$\delta=k_2+k_7 \quad (14)$$

and

$$\epsilon=\frac{k_4}{(k_2-k_1-k_4-k_6)} \quad (15)$$

For the naso-lacrimal duct route, drugs are absorbed through the conjunctival and nasal mucosae. When the drug formulation is added only in the eye, then $C_{N0}=0$, and we can write:

$$dC_D/dt=C_{E0}\{\alpha\exp(-\beta t)+\gamma_e\exp(-\delta t)+\epsilon\} \quad (16)$$

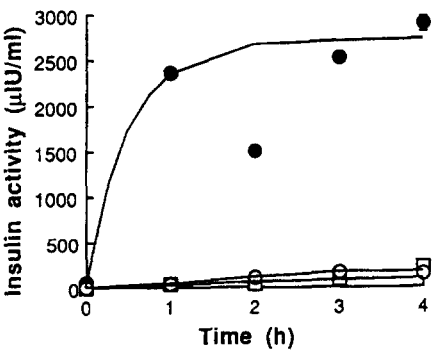

Fig. 2. Plasma insulin level after administration by the ocular, naso-lacrimal duct and nasal routes of an insulin suspension in peanut oil (10 IU/kg). Each value represents the mean ± SD ($n=3$). Data are for the ocular route (conjunctival mucosa) (□), the naso-lacrimal duct route (conjunctival and nasal mucosae) (○) and the nasal route (nasal mucosa) (●). The curves represent calculated values using constants as discussed in the text.

$$C_D=C_{E0}[-\alpha/\beta\{\exp(-\beta t)-1\}$$
$$-(\gamma_e/\delta)\{\exp(-\delta t)-1\}+\epsilon t] \quad (17)$$

For the nasal route, $C_{E0}=0$, and k_1, k_3, k_4, k_5, k_6 are zero. Then,

$$dC_D/dt=C_{N0}\{\gamma_n\exp(-\delta t)\} \quad (18)$$

or

$$C_D=C_{N0}[-(\gamma_n/\delta)\{\exp(-\delta t)-1\}] \quad (19)$$

For the ocular route, k_2, k_3, k_4, k_5, k_7 are zero and $C_{N0}=0$. Then,

$$dC_D/dt=C_{E0}\alpha\exp(-\beta t) \quad (20)$$

or

$$C_D=C_{E0}(-\alpha/\beta)\{\exp(-\beta t)-1\} \quad (21)$$

3.2. Comparison of the in vitro insulin permeation data with the model

From the experimental conditions used here the values of C_{N0} and C_{E0} were, $C_{N0}=C_{E0}=86132$ μIU/ml, i.e. equal to the solubility of insulin in peanut oil. The experimental data of insulin concentration after administration of an insulin suspension through the three routes are summarized in Fig. 2. Several parametric fittings were at-

tempted. For example, using Eqs. (11), (13) and (15), the kinetic constants could be calculated as $k_1 = 3.11 \times 10^{-4}$, $k_2 = 0.0625$, $k_4 = 7.88 \times 10^{-7}$, $k_6 = 0.0568$, $k_7 = 1.923$/h for the simulation curve indicated in Fig. 2, using the multi program described in Yamaoka et al. (1981).

The significantly lower value of insulin of 1498 μIU/ml at 2 h was investigated in order to identify the causes of this discrepancy. First, this unusual behavior may be related to a biphasic behavior of insulin that has also been reported by Okumura et al. (1992) after intratracheal administration. They indicated that the first plasma insulin peak may indicate the absorption of the monomer form, whereas the second one may represent the hexamer form. Alternative fittings of the data of Fig. 2 were attempted.

The permeability coefficients of insulin have been investigated independently in vitro. The conjunctival permeability coefficient of insulin in the albino rabbit has been reported as 4.6×10^{-6} cm/s (Hayakawa et al., 1992) in glutathione bicarbonate Ringer solution (pH 7.4), the conjunctival permeability coefficient of insulin in peanut oil is not known but assuming that the diffusion process of the drug is the rate-limiting step, it should be lower than that in Ringer solution. We have previously reported the nasal permeability coefficient of insulin from peanut oil-based suspensions as 8.56×10^{-6} cm/s (Yamamoto et al., 1994).

One may assume that k_1 and k_2 are constant as a first approximation, or may represent these constants as functions of the permeability coefficient, P, depending on available experimental data, i.e. k_1, $k_2 = f(P)$. The k_1 and k_2 obtained from this model are 3.11×10^{-4} and 0.0625/h, respectively. If the loss of the drug after administration of the three routes is the same, the difference between the k_1 and k_2, and the conjunctival and nasal permeability coefficients should be the conjunctival and nasal areas since the administration volume is the same. The nasal area may be about 100 times larger than the conjunctival one.

The substances SG and SS increased the bioavailability to 11.6% and 9.4%, respectively, whereas the bioavailability was only 6.9% in peanut oil without enhancers. The insulin nasal permeability coefficients from peanut oil with 1% SG and SS as enhancers in vitro were measured as 8.55×10^{-6} for the control, 13.7×10^{-6} for SG containing oil and 12.2×10^{-6} cm/s for SS containing oil, respectively (Maitani et al., 1995). Peanut oil appeared to have no synergistic effect with SG and SS (Maitani et al., 1995).

The insulin activity is shown in Fig. 3 after nasal administration of an insulin peanut oil based suspension with 1% SG and SS. Using Eq. (13), the parameters, k_2 and k_7 were obtained as $k_2 = 0.0510$ and $k_7 = 1.20$/h for SG or $k_2 = 0.0432$ and $k_7 = 1.05$/h for SS, and $k_2 = 0.0625$, $k_7 = 1.92$/h for the control. From these results of k_7, the effect of enhancer on the nasal absorption is mainly due to the fact that SG and SS prevent insulin degradation on the nasal mucosa. Though the relation between the absorption rate constant, k_2, and the permeability coefficients in peanut oil containing SG and SS in vitro is not clear, the permeability coefficient and k_2 of SG are higher than those of SS but k_2 of the control is higher than that of SS and SG. However, it is possible to estimate the mechanism and the effect of enhancers on the nasal mucosae.

The degradation rates on the conjunctival and nasal mucosae, were estimated as 1.67, and 10/h, respectively, from the data of Yamamoto et al., 1990 who reported the susceptibility of insulin in

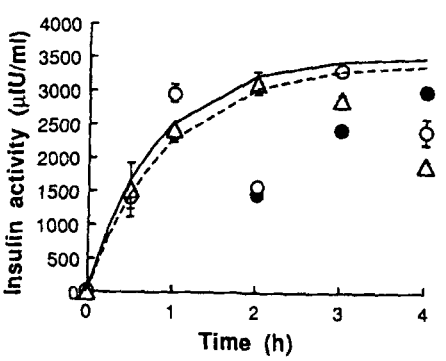

Fig. 3. Plasma insulin level after nasal administration of an insulin suspension in peanut oil with 1% (w/v) of soybean-derived sterylglucosides (SG) and sterol (SS) (10 IU/kg). Each value represents the mean ± SD ($n = 3$). Control (●), SG (○), SS (△). Curves represent calculated values using constants as discussed in the text, SG (————) and SS (- - -).

the homogenate of the conjunctival and nasal mucosae in rabbits. The corresponding values, the k_6 and k_7 obtained from this model are 0.0568 and 1.923/h. The ratio of the kinetic constants of conjunctival degradation rate to the nasal one is lower than that obtained from the degradation rates (Yamamoto et al., 1990). This may be due to the fact that a part of the administered insulin might go down to the GI tract and be inactivated in vivo. In our model, since the GI tract route is neglected, the term k_7 may include this factor and therefore may be overpredicted by the model.

The translocation rate constant, $k_4 = 7.88 \times 10^{-7}$/h is very low. This may be due to the high viscosity of peanut oil. This result may correlate well with the results that the bioavailability of insulin in an artificial tear solution is 1.27 times higher than that in peanut oil after administration in naso-lacrimal duct route neglecting all other parameters (Yamamoto et al., 1994). The following parameters were obtained in each process of drug absorption and administration by using the model on the ocular, naso-lacrimal and nasal routes: $k_1 = 3.11 \times 10^{-4}$, $k_2 = 0.0625$, $k_4 = 7.88 \times 10^{-7}$, $k_6 = 0.0568$ and $k_7 = 1.923$/h.

In future work, it will be very useful to estimate the process of drug administration from the change of such parameters in order to improve and optimize the dosage forms used.

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