Design of ocular/lacrimal and nasal systems through analysis of drug administration and absorption

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Abstract

A modeling analysis is presented of drug or peptide absorption and administration via the ocular, naso–lacrimal duct, and nasal routes. This method accounts for the fast absorption and retention of drug in the blood after administration. A key parameter in this process is the ratio of drug absorption rate in the conjunctival mucosa to the drug transfer rate from the naso–lacrimal duct to the nasal mucosa. This ratio depends on the polymer carrier of the formulation. Predicted values of drug concentration in the blood can be used to design new formulations (delivery systems) which will lead to long residence time or fast drug absorption. © 1997 Elsevier Science B.V.

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1. Introduction

Peptide and drug delivery through the ocular [1,2] and nasal [3,4] routes of administration has increased in recent years. Of particular interest is the delivery of peptides and proteins through these routes, as it is known that peptidase activity is reduced or minimized in the nasal cavity or the eyes [5], thus allowing a significant absorption of the bioactive agent. Controlled release formulations for ocular or nasal delivery have been reported [6–8]. Such systems are based on hydrophilic or hydrophobic polymeric carriers, usually in the form of micro- or nanoparticles.

Nasal administration often requires the use of an enhancer that will promote increased absorption [9,10]. Despite the significant interest in this field, little has been proposed in relation to the description of peptide and protein absorption simultaneously by the ocular/lacrimal and nasal routes [1,11,12].

A predictive method was developed to estimate the systemic concentration of absorbed drug or peptide following ocular, naso–lacrimal duct, or nasal administration. This procedure requires the determination of seven kinetic constants. In a previous contribution [13], these constants were calculated based on a first order absorption process in order to fit experimental data with this model.

Although several permeation studies of peptide transport using excised mucosa have been reported, and some studies of in vivo ocular and nasal administration are available, there is no report about the total drug absorption from the eye to the gastro–intestinal (GI) tract. In this work, we evaluated

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such systems.

2. Theoretical analysis

We consider the administration of a peptide or drug in a formulation that may or may not contain a polymeric carrier and is placed in the ocular cul-de-sac. A compartmental model can be defined as shown in Fig. 1. The main compartments of this model are the eye with drug concentration c_E, the nasal cavity with concentration c_N, the GI tract with concentration c_G, and the blood with drug concentration c_D.

Drug absorption can be defined by seven kinetic constants describing various transport processes in the biological system. Direct drug transport from the eye to the circulation is described by k_1. Similarly, transport from the nose and GI tract to the circulation is described by k_2 and k_3, respectively. A relatively high flow-rate is characteristic for transport of a drug from the eye to the nose; it is described by a translocation kinetic constant k_4. An additional kinet-

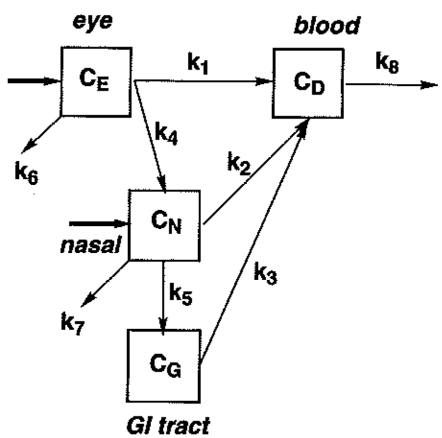

Fig. 1. Schematic representation of a four-compartment pharmacokinetic model for drug administration by the ocular, naso–lacrimal duct and nasal routes.

Ordinary differential equations may describe all the processes using first order kinetic expressions. Thus, the drug concentration in the eye is expressed as

$$-\frac{dc_E}{dt} = k_1 c_E + k_4 c_E + k_6 c_E \qquad (1)$$

The nasal concentration is expressed as

$$-\frac{dc_E}{dt} = -k_4 c_E + k_5 c_N + k_2 c_N + k_7 c_N \qquad (2)$$

The GI tract concentration is

$$-\frac{dc_G}{dt} = -k_5 c_N + k_3 c_G \qquad (3)$$

Finally, the drug concentration in the circulation can be expressed as

$$-\frac{dc_D}{dt} = -k_1 c_E + k_2 c_N - k_3 c_G \qquad (4)$$

Solution of the above four differential equations has been obtained for initial conditions representing the simultaneous drug administration in the ocular and nasal cavities, with initial concentrations c_{E_0} and c_{N_0}, respectively. It is of course assumed that the initial drug concentration in compartment G is $c_{G_0} = 0$.

To obtain the solutions of these equations, it is helpful to define two kinetic constants k_{10} and k_{11} as:

$$k_{10} = k_1 + k_4 + k_6 \qquad (5)$$

and

$$k_{11} = k_2 + k_5 + k_7 \qquad (6)$$

Then, the drug concentration in the eye is obtained by solution of Eq. (1) with the previous boundary conditions as:

$$c_E = c_{E_0} \exp(-k_{10} t) \qquad (7)$$

Obviously, when the initial nasal concentration is zero, Eq. (8) takes the classic form

$$c_{\mathrm{N}} = \frac{k_4 c_{\mathrm{E}_0}}{(k_{11} - k_{10})}[\exp(-k_{10}t) - \exp(-k_{11}t)] \tag{9}$$

Setting now Eq. (8) into Eq. (3), we obtain the following solution for the drug concentration in the GI tract

$$\begin{aligned} c_{\mathrm{G}} = {} & \frac{k_4 k_5 c_{\mathrm{E}_0}}{(k_{11} - k_{10})(k_3 - k_{10})}\exp(-k_{10}t) \\ & + \frac{k_5}{(k_3 - k_{11})}\left[c_{\mathrm{N}_0} - \frac{k_4 c_{\mathrm{E}_0}}{(k_{11} - k_{10})}\exp(-k_{11}t)\right] \\ & - \left[\frac{k_4 k_5 c_{\mathrm{E}_0}}{(k_{11} - k_{10})(k_3 - k_{10})} + \frac{k_5}{(k_3 - k_{10})} \right. \\ & \left. \times \left[c_{\mathrm{E}_0} - \frac{k_4 c_{\mathrm{E}_0}}{(k_{11} - k_{10})}\right]\right]\exp(-k_3 t) \end{aligned} \tag{10}$$

Finally, from Eqs. (7), (9), (10) the drug concentration in the circulation, c_{D}, can be calculated using Eq. (4). The final expression is as follows

$$\begin{aligned} \frac{c_{\mathrm{D}}}{c_{\mathrm{E}_0}} = {} & -\frac{k_2 k_4 + k_1(k_{11} - k_{10})}{(k_{11} - k_{10})k_{10}}\exp(-k_{10}t) \\ & - \frac{k_2 k_4}{(k_{11} - k_5 - k_{10})(k_{11} - k_5)} \\ & \times \exp[(-k_{11} + k_5)t] + \frac{k_2 k_4 + k_1(k_{11} - k_{10})}{(k_{11} - k_{10})k_{10}} \\ & + \frac{k_2 k_4}{(k_{11} - k_5 - k_{10})(k_{11} - k_5)} - \frac{k_4 t}{(k_2 - k_{10})} \\ = {} & A\exp(-k_{10}t) + B\exp[(-k_{11} + k_5)t] + C \\ & + Dt \end{aligned} \tag{11}$$

where

$$A = -\frac{k_2 k_4 + k_1(k_{11} - k_{10})}{(k_{11} - k_{10})k_{10}} \tag{12}$$

$(k_2 - k_{10})$

This completes the development of the model. The individual kinetic constants take various values depending on whether absorption of peptides or conventional drugs is considered.

3. Model discussion

3.1. Values of kinetic constants

The compartmental model developed above can be used to investigate the influence of various processes on the absorption and distribution of drugs administered by the ocular/lacrimal and nasal routes. In this analysis, use was made of previous experimental studies in order to identify acceptable ranges of values of the kinetic constants.

The kinetic constant of drug transport from the eye to circulation, k_1, usually takes values of 20–50 h^{-1} for fast releasing drugs, although for slowly releasing drugs it may be as low as 1 h^{-1} [14]. Transport from the nasal cavity to the circulation is significantly slower with k_2 of about 0.2 to 0.5 h^{-1} [14]. Poorly absorbed drugs are characterized by very small values of the kinetic constant of transport from the GI tract to the circulation, of the order of $k_3 = 10^{-3}$ to 10^{-4} h^{-1}.

An important parameter of this model is the translocation rate constant, k_4, which characterizes transport from the eye to the nose [15]. Typical values of this constant are from 5 to 10 h^{-1}. The kinetic constant for transport to the GI tract, k_5, is known to be approximately zero for peptides due to peptidase action in the gastric area. However, values of 0.1–1 h^{-1} may be more appropriate for conventional drugs. Finally, the kinetic constants for drug degradation k_6 and k_7, can be calculated from the recent analysis of Lee et al. [16]. Typical values range from 0.5 to 3 h^{-1}.

meability coefficient in the eye, the value of k_1 was calculated as 0.132 h^{-1} for insulin, when $P_E = 4.6 \times 10^{-6}$, the conjunctival area is 8 cm^2 and the volume is 1 ml.

The nasal constants were calculated from recent studies of the insulin permeability in the nasal mucosa, $P_N = 8.56 \times 10^{-6}$ cm s^{-1} according to Maitani et al. [18] with a nasal mucosa area of 61 cm^2 and a volume of 6 ml. Then, the value of k_2 was calculated as 1.88 h^{-1} when the nasal mucosa area is 61 cm^2 and the volume is 1 ml [19]. The value of the drug degradation constant k_7 was determined as 0.832 h^{-1} from the values for 50% of insulin remaining in homogenates of nasal mucosa [20]. Finally, as reported [5] before, $k_6 < k_7$ for insulin and most other peptides.

3.2. Computer simulations

A number of computer simulations were carried out in order to examine the importance of the various transport processes on the overall absorption of drug in the blood. In a first set of experiments, values of $k_1 = 20$ h^{-1}, $k_2 = 0.2$ h^{-1}, $k_3 = 10^{-4}$ h^{-1} and $k_4 = 5$ h^{-1} were selected, and k_5, k_6 and k_7 were varied to examine the effect of drug decomposition on the overall absorption.

All results are expressed as normalized concentration in each compartment with respect to an initial dose in the eye, c_{E_0}. Initial values in the nose and GI tract were assumed zero. Fig. 2(a, b, and c) shows the change of peptide concentration in the blood as a function of time (curve 1). These are typical data for insulin. A relatively fast absorption is observed passing through a maximum at about 20 min when $k_1 = 20$ h^{-1} (Fig. 2b). The ocular insulin concentration is depleted very fast (curve 2), whereas the nasal drug concentration passes through a maximum (curve 3). Finally, the GI tract concentration is virtually zero (curve 4). The values of k_6 were varied

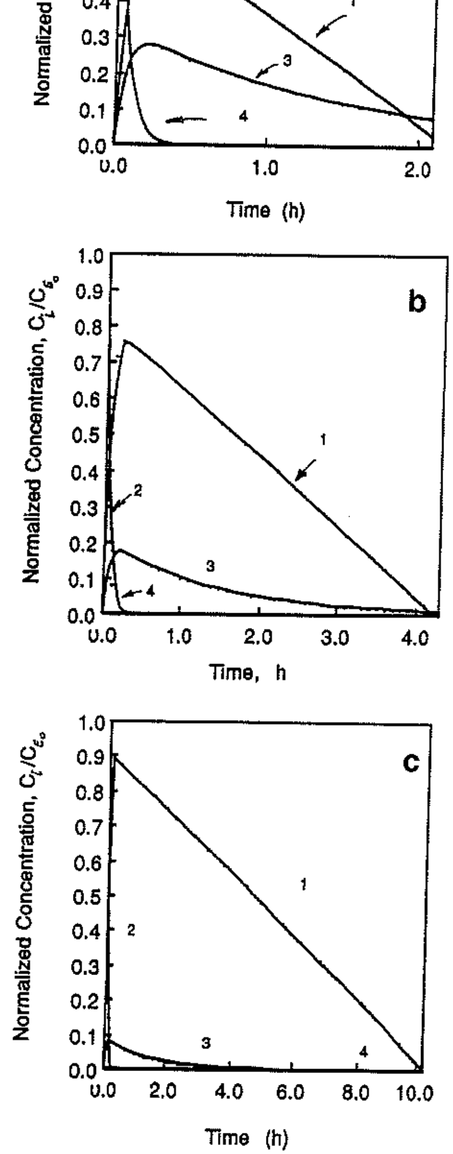

Fig. 2. Normalized drug concentration in the blood (curve 1), eye (curve 2), nasal cavity (curve 3) and GI tract (curve 4) as a function of time for $k_2 = 0.2$ h^{-1}, $k_3 = 10^{-4}$ h^{-1}, $k_4 = 5$ h^{-1}, $k_5 = 0.1$ h^{-1}, $k_6 = 0.1$ h^{-1}, $k_7 = 0.5$ h^{-1}, and $k_1 = 10$ h^{-1} (a), $k_1 = 20$ h^{-1} (b), or $k_1 = 50$ h^{-1} (c).

conjunctival area, k_6. Therefore, these results are in agreement with biological observations.

The influence of k_1 was further seen by running simulations for various values of the kinetic constant, k_1 for drug transport from the eye to the blood. Fig. 2(b and c) show the drug absorption for typical values of the kinetic constants with changing time. It is noted that the values of c_N/c_{E_0} and c_D/c_{E_0} depend on the value of k_{10}, as seen in Eqs. (9) and (11). Therefore, an increase of the value of k_1 (appearing in k_{10}) induces the exhibition of maxima in curves 1 and 3 at early times. Also, the maximum value of c_D depends on the third term, C, of Eq. (11). On the other side, the slope of the elimination curves after the peak depends on the fourth term, D, of Eq. (11).

However, the translocation constant, k_4, seems to play a very important role in drug and peptide transport. Fig. 3(a and b) summarize data of drug transport for values of $k_4 = 3$ h^{-1} and 10 h^{-1}, respectively. Clearly, in the first case the peptide concentration in the blood reaches a higher level faster, whereas when $k_4 = 10$ h^{-1} a significant portion of the peptide has passed into the nasal cavity leading to an increased nasal concentration (curve 3).

Further investigation of the effect of the translocation constant on the drug or peptide transport could be obtained by calculating the half-life, $\tau_{1/2}$, of drug in the blood as the time at which the concentration was 50% of the initial concentration. Fig. 4 shows the half-life in the blood as a function of k_4 for different values of k_1. Clearly, fast absorption is achieved as k_4 increases and k_1 decreases, indicating that the nasal route has a great potential for fast transport.

To further analyze this behavior, the half-life was determined as a function of k_1, as shown in Fig. 5. Clearly, as the drug absorption constant, k_1, increased, the half-life increased. The translocation constant, k_4, is important in this process. As shown in Fig. 5, an increase of k_4 led to a significant decrease of the half-life. When k_4 increases, the

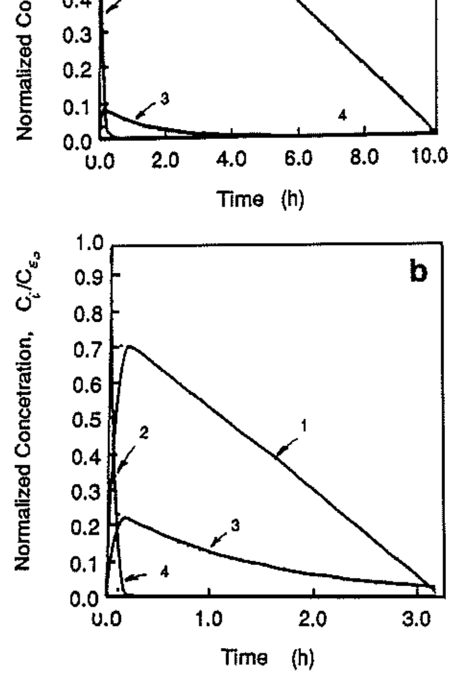

Fig. 3. Normalized drug concentration in the blood (curve 1), eye (curve 2), nasal cavity (curve 3) and GI tract (curve 4) as a function of time for $k_1 = 20$ h^{-1}, $k_2 = 0.2$ h^{-1}, $k_3 = 10^{-4}$ h^{-1}, $k_4 = 5$ h^{-1}, $k_5 = 0.1$ h^{-1}, $k_6 = 0.1$ h^{-1}, $k_7 = 0.5$ h^{-1}, and $k_4 = 3$ h^{-1} (a) or 10 h^{-1} (b).

half-life becomes smaller, i.e., nasal absorption appears to dominate the increase of c_D. This is due to the fact that k_{10} is included in constants k_{10} and D of Eq. (11), whereas the latter has a negative value.

Fig. 6 summarizes the importance of the translocation process (constant k_4) and the nasal drug absorption on the overall drug transport. A maximum in the half-life was observed. This was particularly important in peptides that have low mucosal permeability. A further understanding of the importance of k_2 was obtained from Fig. 7 where the half-life was plotted as a function of k_2 and the ratios of k_1/k_4.

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