*Pharmaceutical Research, Vol. 7, No. 1, 1990*

*Report*

# Model of Disposition of Drugs Administered into the Human Nasal Cavity

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*Received August 8, 1988; accepted July 11, 1989*

A mathematical model was developed to describe the rate processes involved in the disposition of drugs placed in their delivery systems into the human nasal cavity. The model contains first-order parallel and sequential irreversible rate processes representing the convective drug and carrier transport by fluid flow, mucociliary clearance and peristalsis, drug release and absorption, and decomposition of the drug prior to its appearance in the systemic circulation. The numerical values of the parameters used are based on literature data from clearance studies of nonabsorbable markers deposited in the human nasal cavity, and data obtained under a variety of experimental conditions are consistent with the model. The effect of bioadhesive carriers is successfully simulated by reducing the mucociliary clearance rate constants for the transport from the posterior part of the nose into the gastrointestinal tract. The simulation shows that bioadhesion improves bioavailability and reduces the variability in absorption which might be caused by a variable pattern of deposition in the nose. Variable bioavailability could result from removal of the drug from the nasal cavity by sniffing, blowing, or wiping the nose, leading to different drug residence times in the nose. The model simulations further suggest that drug decomposition in the nose, while lowering bioavailability, also reduces variable absorption due to variable residence times of the drug in the nose.

KEY WORDS: intranasal delivery; nasal absorption; pharmacokinetic models; bioavailability.

## INTRODUCTION

The administration of drugs by the transnasal route has attracted attention in recent years (1,2) because of its potential to improve the systemic delivery of substances with a poor oral bioavailability. An increase in the overall absorption of the active ingredient is, in itself, a desirable goal but it is equally important to achieve reproducibility between and within subjects. A large number of parameters affects the rate of drug absorption from various formulations in the nasal cavity (3–6). It is likely that some of these factors will be important for some drugs and carriers but not for others. A mathematical model would thus be useful in the analysis of existing data and the design of transnasal delivery systems. One may treat the nose simply as a "black box" providing an input function to the systemic circulation. However, such a model would be unable to account for the expected effects of formulation on the disposition of nasally administered drugs. Instead, we propose a model based on the relevant anatomical and physiological features of the nose (e.g., Ref. 7). This organ is interesting from the kinetic point of view because, in addition to the processes of drug release, absorption, and metabolism, it also has a carrier- and drug-translocating mechanism, namely, mucociliary clearance (7). It thus shares some of the features of drug disposition with the human airways (8–10). The rate of mucociliary clearance is not uniform throughout the nasal cavity (7), and it is therefore possible that variations of the sites of drug deposition in the nose cause additional variability in the rate and extent of systemic delivery.

## THEORY

The model of disposition of nasally administered drugs is shown in Scheme I. The model is based on the knowledge of anatomically and physiologically distinct "compartments." Thus, its structural character is restricted and it also prevents arbitary assignment of the values of the rate constants. Indeed, it will become clear that once the model is developed to be consistent with the results for nonabsorbable nonmetabolized markers, the number of adjustable parameters left is substantially reduced.

The amount of drug still contained in its "unreleased" form is represented by uppercase letters, whereas the drug released is in the compartments **a**, **p**, **g**, and **b**. Operationally, **A** and **a** stand for the compartments responsible for the slow clearance phase of nonabsorbed nondegraded liquid and solid substances from the nasal cavity (rate constants $k_1$ and $k_3$), while **P** and **p** represent the compartments from which such substances are cleared rapidly (rate constants $k_5$ and $k_7$). Anatomically, **A** and **a** are probably located mainly in the nonciliated anterior part of the nose, and **P** and **p** in the posterior sections (7). **G** and **g** similarly represent the drug, with and without, its carrier in the gastrointestinal tract, and

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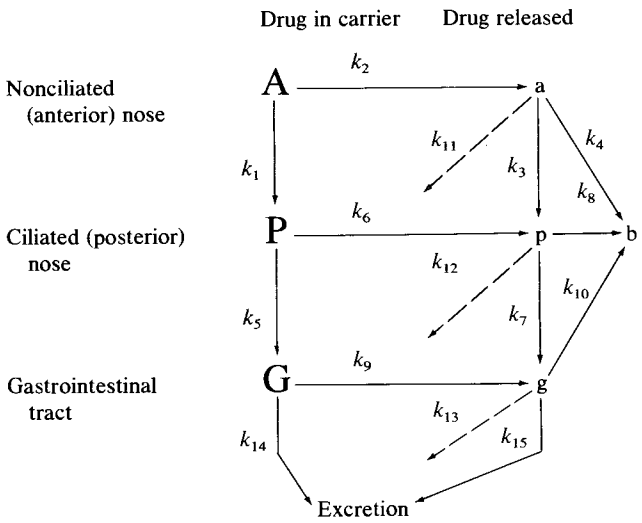


Scheme I.

b in the systemic circulation. All rate processes in the model are assumed to be first order and unidirectional ("irreversible"). The rates of release of the drug are incorporated into the constants $k_2$, $k_6$, and $k_9$, and the absorption rate constants (for the released drug only) are $k_4$, $k_8$, and $k_{10}$. The possibility of absorption of "unreleased" drug (e.g., still contained in the carrier) is not considered here, as there does not appear to be at present any evidence for such a mechanism. Degradation of the released drug in compartments **a**, **p**, and **g** is governed by rate constants $k_{11}$, $k_{12}$, and $k_{13}$, respectively, and the constants $k_{14}$ and $k_{15}$ are related to the transit time of solid and liquid components through the gastrointestinal tract. The mathematical representation of the model is given in the Appendix, with solutions using conventional integration methods (11).

The model further requires selection of realistic mean values, or ranges of values, of the parameters so that some degree of validation is possible before we use it for predictions. The "translocation" rate constants $k_1$, $k_3$, $k_5$, and $k_7$ are taken from a recently proposed model (12) based on the data with nonabsorbable solid particles (13); we assume for simplicity that the constants for both the "released" and the unreleased drug are the same and that, in the first approximation, there is no distinction in these constants between solids and liquids; as shown below, this assumption is almost certainly invalid for substances that can form rapidly swelling "bioadhesive" gels. Thus, we put $k_1 = k_3 = 0.0625\ hr^{-1}$ and $k_5 = k_7 = 4.167\ hr^{-1}$. The constants $k_2$, $k_6$, and $k_9$ can be varied arbitrarily since a wide range of release rates can be obtained by suitable formulation of the product. Similarly, the rate constants for absorption can vary from near-zero for poorly absorbed substances to, say, $30\ hr^{-1}$ for drugs rapidly absorbed from the nose (14). We would expect that the nasal absorption is generally faster than absorption from the gastrointestinal tract. Although the values of $k_4$ and $k_8$ are probably not equal to each other in reality, little is known at present about the variation of absorption rates from different sites in the nose. The magnitudes of $k_{10}$ and the gastrointestinal transit rate constants $k_{14}$ and $k_{15}$ are not crucial for drugs poorly absorbed upon oral administration; we use here $k_{10} = 0.0001\ hr^{-1}$ and $k_{14} = k_{15} = 0.1\ hr^{-1}$. The decomposition of drugs, particularly peptides, tends to be faster in the gastrointestinal tract than in the nose. Some estimates of the range of values come from the work on drug metabolism using tissue homogenates (15); a variation for $k_{11}$, $k_{12}$, and $k_{13}$ from 0 to about $3\ hr^{-1}$ is probably realistic.

The initial conditions for drugs deliberately administered into the nose can be assumed to be zero for G and g. The initial distribution between the "anterior" and the "posterior" parts depends mainly on the mode of nasal administration. Evidence of differences in the anatomical location of the deposits between different administration methods comes from both *in vivo* experiments in humans (16–18) and the work with nasal casts (19). These experiments have been done with nondegradable nonabsorbable markers, and therefore the kinetics of the clearance of these materials can be readily compared to the model. The initial distribution of the material between the released and the unreleased forms, i.e., between $A_0$ and $a_0$, and between $P_0$ and $p_0$, will depend on the formulation.

## RESULTS AND DISCUSSION

The experimental results from human studies, in which the fate of the nonabsorbable radiolabeled marker, technetium $^{99m}$Tc–human serum albumin ($^{99m}$Tc-HSA) was followed by gamma scintigraphy (16–18) provide a good starting point for estimation of the parameters and validation of the model. These results for the total nasal clearance are shown together with the calculation using the model in Figs. 1 and 2 (the parameters used are listed in Table I). Note that the only adjustable parameter in this part of the model testing is the ratio $A_0/P_0$. The constants $k_1$ and $k_5$ are adopted from a population average obtained from independent studies (12,13); the rest of the rate constants do not affect the results because the behavior of nonabsorbable markers from a very slowly releasing carrier is simulated. As suggested by

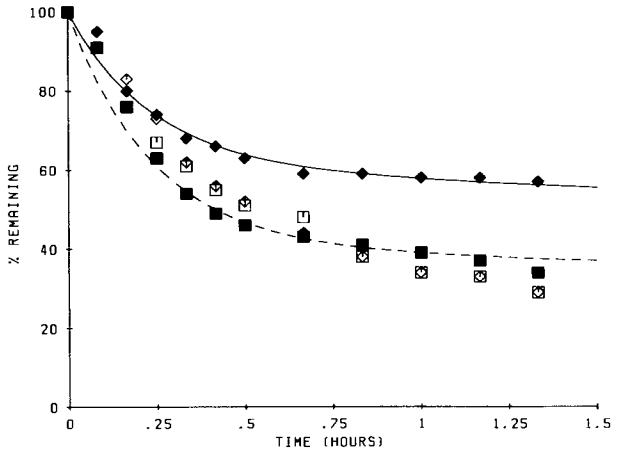


Fig. 1. Clearance of nonabsorbable tracer from the nasal cavity after administration of spray (♦), 1 drop (■ ◇), and 3 drops (□) (Ref. 17). The predictions from the model (Scheme I) for clearance of a marker attached to a nonabsorbable carrier are shown as the solid line for predominantly anterior deposition ($A_0 = 0.6$, $P_0 = 0.4$) and as the dashed line for predominantly posterior deposition ($A_0 = 0.4$, $P_0 = 0.6$).

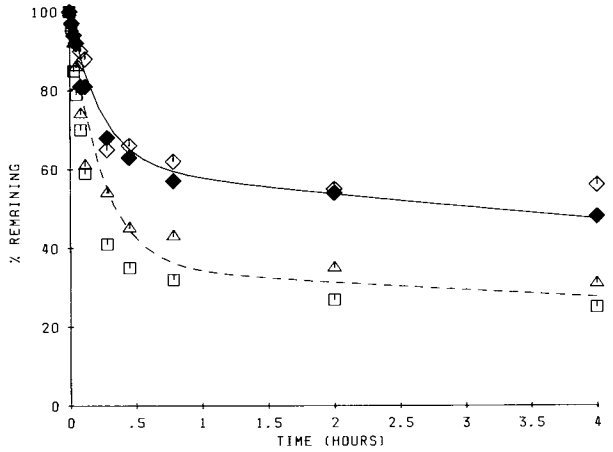


Fig. 2. Clearance of the $^{99m}$Tc-radiolabeled nonabsorbable carrier from the nasal cavity after administration of spray (50 μl × 2, ◇; 100 μl × 2, ◆) or droplets using rhinyle catheter (△) and pipette (□) (Ref. 18). The predictions from the model (Scheme I) for clearance of a nonabsorbable substance are shown as the solid line for predominantly anterior deposition ($A_0$ = 0.6, $P_0$ = 0.4) or the dashed line for $A_0$ = 0.35 and $P_0$ = 0.65.

the scintillation images, the main difference initially between the spray and the droplet applications is that the latter has a lower anterior/posterior ratio than the former. When this is translated into the model calculation in the form of the initial conditions $A_0$ and $P_0$, the model correctly describes the faster initial clearance of the droplets followed by a slower phase similar to the sprays. The quantitative agreement, obtained simply by trial-and-error variation of the proportions of $A_0$ and $P_0$, is very reasonable considering typical standard errors of the means of about ±10% (17,18); further improvement could be readily achieved by small adjustment of the rate constants $k_1$ and $k_5$ to get the best fit.

Table I. Values of the First-Order Rate Constants ($hr^{-1}$) Used in the Computations Based on Scheme I and Presented in Figs. 1–6

| | | a | b | c | d | e |
|---|---|---|---|---|---|---|
| $k_1$ | 0.0625 | | | | | |
| $k_2$ | 30 | | | | 0.001 | |
| $k_3$ | 0.0625 | | | | | |
| $k_4$ | 0.173 | | | | | 0.2 |
| $k_5$ | 4.1667 | 0.41667,1.5 | | | | |
| $k_6$ | 30 | | | | 0.001 | |
| $k_7$ | 4.1667 | 0.41667,1.5 | | | | |
| $k_8$ | 0.173 | | | | | |
| $k_9$ | 30 | | | | 0.001 | |
| $k_{10}$ | 0.0001 | | | | | |
| $k_{11}$ | 0.0001 | | 0.25 | 0.5 | | |
| $k_{12}$ | 0.0001 | | 0.25 | 0.5 | | |
| $k_{13}$ | 0.0001 | | 0.5 | 1.0 | | |
| $k_{14}$ | 0.1 | | | | | |
| $k_{15}$ | 0.1 | | | | | |

The following variations simulate different conditions:

- a Bioadhesion (microspheres in Fig. 3, systems N2, N4 and N5 in Figs. 4–6)
- b Moderate rate of decomposition (systems N3 and N4)
- c Rapid rate of decomposition (system N5)
- d Very slow release rate as used in the imaging experiments (Figs. 1–3 except for the powder and solution of $^{99m}$Tc-DTPA)
- e Absorption rate constants for $^{99m}$Tc-DTPA from the anterior part of nose

In the second stage, we examine the likely formulation effects on the clearance of nonabsorbable markers; in principle, there are two adjustable parameters in this part: $k_1$ (= $k_3$) and $k_5$ (= $k_7$). However, the first pair of rate constants can be safely excluded from the considerations because they are known to be already very slow compared to the second pair (12); therefore, reduction of $k_1$ and $k_3$ is not going to affect much the disappearance rate from the nose unless $k_5$ and $k_7$ are also dramatically reduced. Illum (16) reported nasal clearance results using bioadhesive microspheres labeled with bound $^{99m}$Tc. These microspheres were administered by a nasal insufflator and their initial distribution was found to be predominantly in the anterior region. To be consistent, we have assumed in the calculations that $A_0$ = 0.6 and $P_0$ = 0.4, i.e., identical to the values assumed to fit the sprays (Figs. 1 and 2). This is a reasonable assumption because in both modes of application, deposition is very largely due to the same mechanism of inertial impaction (20). Illum found (16) that the microspheres which swelled rapidly, in addition to their good bioadhesive properties, showed the slowest clearance (DEAE-Sephadex microspheres); the starch microspheres, which swelled rather less readily, also showed a slower clearance than the nonbioadhesive carriers used by other authors (17,18). The initial clearance half-lives for the bioadhesive particles are intermediate between the slow clearance from A and the faster clearance from P for the nonbioadhesive carriers. The most straightforward explanation of the "bioadhesion" effect is that this property slows the clearance of the marker from P by reduction of the rate constants $k_5$ and $k_7$. The results calculated on the basis of this assumption are shown in Fig. 3, and the agreement with the experiments using "eyeball"-fitted rate constants $k_5$ and $k_7$ is quite good. The albumin microspheres which have the lowest degree of swelling appear to be cleared at a rate similar to sprays containing solutions (17,18). The best agreement with the model is in fact obtained using the same values of the parameters as for the solid curves in Figs. 1 and 2, which give a good fit for the clearance of sprays. The solution of $^{99m}$Tc-DTPA was found to be dispersed from the atrium to the nasopharynx soon after application, in contrast to the mainly anterior location of the solid particles (16). Accordingly the bottom solid line which fits these solution results the best assumes $A_0$ = 0.3 and $P_0$ = 0.7, i.e., similar deposition pattern to the drops in Figs. 1 and 2. Furthermore, it is assumed that $^{99m}$Tc-DTPA can be absorbed (16) from the anterior part of the nasal cavity ($k_4$ = 0.2 $hr^{-1}$). The mathematical simulation is insensitive to the variation of the absorptive properties of the posterior part because of the high value of the mucociliary clearance constants from this region. Illum (16) observed that the $^{99m}$Tc-DTPA powder had a similar initial deposition pattern to the microspheres. Using, therefore, $A_0$ = 0.6 and $P_0$ = 0.4, relatively rapid release rate constants for the dissolution of this powder ($k_2$ = $k_6$ = $k_9$ = 30 $hr^{-1}$) and $k_4$ = 0.2 $hr^{-1}$ as for the solution of this substance, the dashed line in Fig. 3 was obtained. We cannot at present explain the discrepancy between the theo-

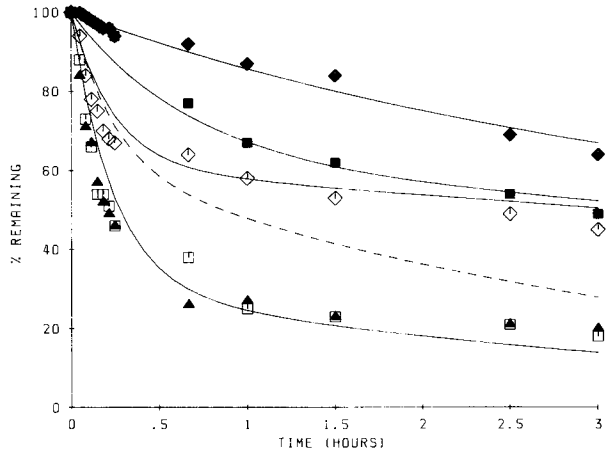


Fig. 3. Clearance of $^{99m}$Tc-labeled microspheres (DEAE-Sephadex, ♦; starch-Spherex, ■; albumin, ◊), $^{99m}$Tc-DTPA solution (□), or powder (▲) (Ref. 16). The solid lines were calculated according to Scheme I assuming (from top to bottom) (i) $A_0 = 0.6$, $P_0 = 0.4$, and markedly reduced mucociliary clearance ($k_5 = k_7 = 0.4167$ hr$^{-1}$); (ii) $A_0 = 0.6$, $P_0 = 0.4$, and moderately reduced mucociliary clearance ($k_5 = k_7 = 1.5$ hr$^{-1}$); (iii) $A_0 = 0.6$, $P_0 = 0.4$, and normal mucociliary clearance ($k_5 = k_7 = 4.167$ hr$^{-1}$); (iv) $A_0 = 0.3$, $P_0 = 0.7$, and normal mucociliary clearance. In i–iii, it is assumed that the tracer is released very slowly from the carrier ($k_2 = k_6 = k_9 = 0.0001$ hr$^{-1}$). The bottom solid line (iv) and the bottom dashed line ($A_0 = 0.6$, $P_0 = 0.4$) assume that the tracer is readily released ($k = 100$ and 30 hr$^{-1}$, respectively). The free tracer can be absorbed from the anterior region with $k_4 = 0.2$ hr$^{-1}$.

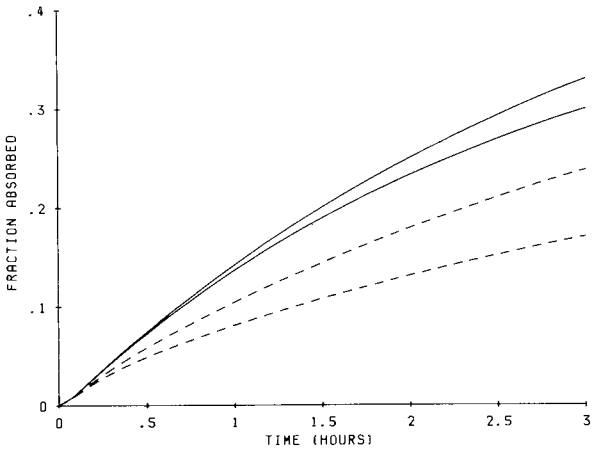


Fig. 4. Fraction of the unchanged drug absorbed into the systemic circulation as a function of the time the drug delivery system resides in the nose, for a drug with a moderate rate of absorption from the nasal cavity and insignificant presystemic decomposition. Dashed line, ordinary formulation N1 with a drug in the form readily available for absorption. Solid line, "bioadhesive" formulation N2 with other properties identical to N1. The upper solid and dashed curves in each apply to $A_0 = 0.6$, $P_0 = 0.4$, and the lower curves to $A_0 = 0.4$, $P_0 = 0.6$.

retical and the experimental results for this formulation. Illum's data for the powder are unusual because the clearance is faster than for solution sprays with the same deposition pattern (17,18); a higher absorption rate constant from the anterior region would improve the agreement of the model calculation with the data for the powder, but it would then give unrealistically fast clearance values for the solution.

As with other dosage forms and routes of administration, the reproducibility of delivery is often even more important than the average value of the bioavailable fraction. There are a number of reasons that might be responsible for intrasubject variability in drug delivery via the nasal route. The two obvious ones are the variation in the proportions delivered to the anterior and posterior regions (12,16–18) and the enhancement of clearance by irregular blowing and wiping of the nose (12). The model is useful to examine the effects of formulation on the variability of systemic delivery. Figure 4 shows the amount absorbed as a function of time for a drug delivery system N1 with a moderate rate of absorption from the nasal mucosa ($k_4 = k_8 = 0.173\ k^{-1}$) and very poor absorption ($k_{10} = 0.0001$ hr$^{-1}$) from the gastrointestinal tract. It is assumed that the "release" is not the rate-determining step and that the compound is not degraded significantly in the nose before it enters the systemic circulation. It is also considered unlikely that the drug delivery system would reside in the nose beyond 3 hr. Figure 4 shows that the amount of drug absorbed from the system N1 will depend crucially on (a) the pattern of initial deposition (cf. the upper and lower curves for $A_0/P_0 = 1.5$ and 0.66, respectively) and (b) the time at which the drug delivery system is removed from the nose (the amount absorbed more than doubles from 1 to 3 hr).

Figure 4 also shows the effect of "bioadhesion" on the drug delivery (system N2). This property is represented by reduction of the rate constant $k_5$ and $k_7$ by a factor of 10 compared to the previous examples. The 10-fold reduction is not arbitrary—it is consistent with the validation part of the model (Fig. 3). There is a marked improvement in "bioavailability." System N2 virtually eliminates sensitivity of delivery to the pattern of initial deposition (there is only a small percentage difference between the curves for $A_0/P_0 = 1.5$ and $A_0/P_0 = 0.66$ for N2) but the amount absorbed is still strongly dependent on the duration of residence of N2 in the nose: the difference between 1 and 3 hr is about 2.5-fold.

Figure 5 makes similar comparisons to Fig. 4 but it is now assumed that the drug can decompose in the nose ($k_{11}$

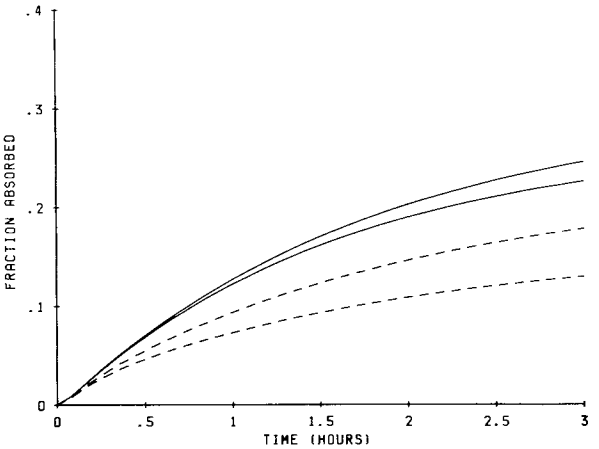


Fig. 5. The same conditions as in Fig. 4, except that the drug is now allowed to decompose in the nose and in the GI tract (system N3 represented by the dashed line, N4 by the solid line).

$= k_{12} = 0.25\ hr^{-1}$) and in the GI tract ($k_{13} = 0.5\ hr^{-1}$). These values are taken to be in the range of the results obtained with tissue homogenates (15). A nonbioadhesive system (N3) shows poor bioavailability compared to N1 and a high degree of dependence on the duration of residence in the nasal cavity. A bioadhesive formulation (N4) shows a significant improvement in bioavailability compared to N3. There is also a marked reduction in variability resulting from different deposition patterns as noted previously with N2. However, compared to the latter system, N4 also shows a smaller dependence of the amount absorbed on the duration of residence of the system in the nose.

Figure 6 compares the effects of different rates of drug decomposition of drugs delivered by bioadhesive systems in the deposition pattern $A_0 = 0.6$, $P_0 = 0.4$. System N2 (bioadhesion, very slow decomposition) shows the highest bioavailability. Increasing the rate constants for decomposition leads, as expected, to reductions in bioavailability. Interestingly, however, it also leads to a substantial reduction in the dependence of the amount absorbed on the duration of residence in the nose: the system N5, which allows relatively rapid drug decomposition in the nose ($k_{11} = k_{12} = 0.5\ hr^{-1}$) and in the GI tract ($k_{13} = 1\ hr^{-1}$), shows the smallest difference between 1- and 3-hr residence in the nose; the difference between 2- and 3-hr residence is only about 13%.

## CONCLUSIONS

The model attempts to reflect the basic functional features of the nose relevant to the clearance of substances from it; additionally, there is a gastrointestinal compartment to allow simulation of the total input of drug into the systemic circulation. A compromise is therefore made between simplicity and the anatomical and physiological reality; further attempts at reductionism would almost certainly preclude the use of the model for any mechanistic explanations of the effect of formulation on mucociliary clearance, metabolism, and absorption in different parts of the nose. In order to minimize arbitrary choice of the numerical parameters for the model, a stepwise approach was taken to constrain the parameter values. Thus, initially the clearance rate constants for nonabsorbable markers were adopted from an independent model (12) and by varying only the ratio of the initial amount of material deposited in the anterior and posterior parts of the nose $A_0/P_0$, a good agreement was found with recent data on the clearance of nonabsorbable nonmetabolized radiolabeled markers deposited in the nose (Figs. 1 and 2). There was also consistency between the fitted $A_0/P_0$ ratio and the reported experimental observations of initial distribution of radioactivity in the nose following different modes of application. Next the effect of "bioadhesive" carriers on radioactive markers was quantified by retaining the previously derived, or adopted, values of the parameters except one: the variation of the rate constants $k_5 = k_7$ was used to simulate the experimental findings (Fig. 3). The fitted values were consistent with the differences in the physical properties of the carriers. Having thus identified the values of the parameters for different modes of administration and different formulations, the model was used to enquire about the extent and variability of systemic drug delivery via the nasal route. Numerical values of rate constants for absorption and metabolism were selected to be in the ranges compatible with out knowledge of the properties of the nasal tissue. It was shown that bioadhesion, as expressed mathematically in the model by reduction of the rate constant $k_5 = k_7$, can lead to a marked improvement in bioavailability and an increased robustness of the drug delivery to variations in the pattern of initial deposition. It was noted that variability in the total amount delivered could result also from sudden removal of the deposited drug delivery system, e.g., by blowing or wiping the nose or as a result of a "sniffing" maneuver. The model predicts this variability to be smaller for drugs which undergo some decomposition before absorption because there is only a little drug left for absorption after 1–2 hr. This raises the question whether the use of enzyme inhibitors to reduce drug metabolism in the nose, particularly that of peptides, is advisable. This study shows that the benefits of such an intervention, i.e., improved bioavailability, should be weighed against the potential reduction of intrasubject reproducibility. However, it should be emphasized that variability in the decomposition rate of the drug in the same subject could also lead to poor reproducibility of delivery (see Fig. 6).

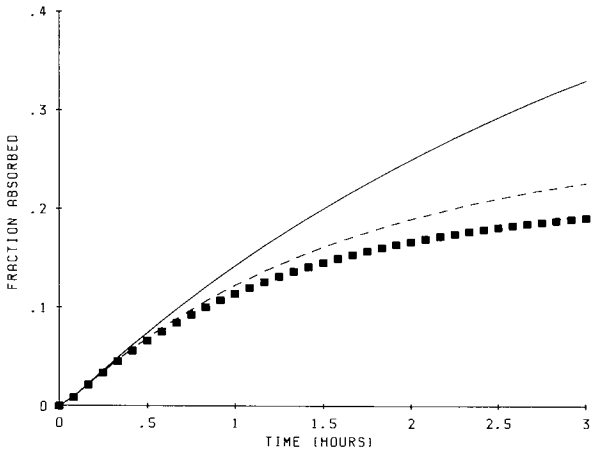


Fig. 6. Systemic absorption of unchanged drug against time for "bioadhesive" systems deposited predominantly in the anterior part of the nasal cavity ($A_0/P_0 = 1.5$) for a drug with a moderate rate of absorption and varying rates of decomposition: N2, almost no decomposition (solid line); N4, intermediate rate of decomposition (dashed line); N5, rapid rate of decomposition (dotted line).

The model predicts also that, in principle, the input rate into the systemic circulation from the nasal route could be a sum of as many as six exponentials. Wilkinson *et al.* (20) concluded that their data on absorption of cocaine from solutions and from crystals placed in the nose are compatible with at least a biexponential input function, even when the drug is administered as a solution. Their results indicate that the distinct absorption surfaces connected via the convective processes (in the model $a \rightarrow p \rightarrow g$) give rise to experimentally detectable separate contributions to absorption. Wilkinson and co-workers' data and computational techniques would not have allowed them to propose a more complicated input function, and indeed, it may be unrealistic to attempt to resolve the input function into more than two or three exponentials. Nevertheless, the present model may facilitate a mechanistic analysis of the complex absorption kinetics and the effect of drug modification or formulation pa-

rameters. However, for the model to be useful, it must be employed judiciously. The number of identifiable parameters depends on the quality, quantity, and variety of experimental results. As shown in this paper, it is possible to constrain the majority of the parameter values on the basis of existing data. The ratio $A_0/P_0$ can be estimated from literature results using the same mode of application and a similar formulation as those used in the study; the rate constants $k_1 \sim k_3$ and $k_5 \sim k_7$ will probably be similar to those investigated in the present work. The deposition pattern and mucociliary clearance rates could also be determined directly (e.g., by a gamma emission method). In many cases, e.g., for peptide delivery, one may ignore any contribution to systemic absorption from the gastrointestinal tract, reducing the input function to a maximum of four exponentials. $k_2 = k_6$ could be obtained from *in vitro* experiments, especially for rate-controlling delivery systems. $k_{11}$ and $k_{12}$ could be obtained by analysis of the kinetics of metabolites and decomposition products. The recent review of the major causes of differences in the bioavailability of peptides and proteins by various routes of administration and in different formulations (21) indicates that the necessary input rates for adequate modeling are becoming rapidly identified for compounds of interest for nasal delivery.

## APPENDIX

Mathematically, the model is defined by the following set of first-order differential equations.

$$-\frac{dA}{dt} = \alpha A \tag{1}$$

$$-\frac{dP}{dt} = -k_1 A + \beta P \tag{2}$$

$$-\frac{dG}{dt} = -k_5 P + \gamma G \tag{3}$$

$$-\frac{da}{dt} = -k_2 A + \delta a \tag{4}$$

$$-\frac{dp}{dt} = -k_6 P - k_3 a + \omega p \tag{5}$$

$$-\frac{dg}{dt} = -k_9 G - k_7 p + \epsilon g \tag{6}$$

where

$$\begin{aligned} \alpha &= k_1 + k_2 \\ \beta &= k_5 + k_6 \\ \gamma &= k_9 + k_{14} \\ \delta &= k_3 + k_4 + k_{11} \\ \omega &= k_7 + k_8 + k_{12} \\ \epsilon &= k_{10} + k_{13} + k_{15} \end{aligned} \tag{7}$$

The total rate of drug input into the systemic circulation is

$$R = k_4 a + k_8 p + k_{10} g \tag{8}$$

The above equations can be solved sequentially in analytical form [11] to give the following algebraic expressions:

$$A = A_0 \exp(-\alpha t) \tag{9}$$

$$P = C_1 \exp(-\alpha t) + C_2 \exp(-\beta t) \tag{10}$$

$$G = C_3 \exp(-\alpha t) + C_4 \exp(-\beta t) + c_1 \exp(-\gamma t) \tag{11}$$

$$a = C_5 \exp(-\alpha t) + C_6 \exp(-\delta t) \tag{12}$$

$$p = C_7 \exp(-\alpha t) + C_8 \exp(-\beta t) + C_9 \exp(-\delta t) + c_2 \exp(-\omega t) \tag{13}$$

$$g = C_{10} \exp(-\alpha t) + C_{11} \exp(-\beta t) + C_{12} \exp(-\gamma t) + C_{13} \exp(-\delta t) + C_{14} \exp(-\omega t) + c_3 \exp(-\epsilon t) \tag{14}$$

where

$$C_1 = k_1 A_0/(\beta - \alpha) \tag{15}$$

$$C_2 = P_0 - k_1 A_0/(\beta - \alpha) \tag{16}$$

$$C_3 = k_5 C_1/(\gamma - \alpha) \tag{17}$$

$$C_4 = k_5 C_2/(\gamma - \beta) \tag{18}$$

$$C_5 = k_2 A_0/(\delta - \alpha) \tag{19}$$

$$C_6 = a_0 - k_2 A_0/(\delta - \alpha) \tag{20}$$

$$C_7 = (k_6 C_1 + k_3 C_5)/(\omega - \alpha) \tag{21}$$

$$C_8 = k_6 C_2/(\omega - \beta) \tag{22}$$

$$C_9 = k_3 C_6/(\omega - \delta) \tag{23}$$

$$C_{10} = (k_7 C_7 + k_9 C_3)/(\epsilon - \alpha) \tag{24}$$

$$C_{11} = (k_7 C_8 + k_9 C_4)/(\epsilon - \beta) \tag{25}$$

$$C_{12} = k_9 c_1/(\epsilon - \delta) \tag{26}$$

$$C_{13} = k_7 C_9/(\epsilon - \delta) \tag{27}$$

$$C_{14} = k_7 c_2/(\epsilon - \omega) \tag{28}$$

$$c_1 = G_0 - C_3 - C_4 \tag{29}$$

$$c_2 = p_0 - C_7 - C_8 - C_9 \tag{30}$$

$$c_3 = g_0 - C_{10} - C_{11} - C_{12} - C_{13} - C_{14} \tag{31}$$

The subscript 0 stands for the intial amounts (at time $t = 0$) in the compartments. The total amount $D(t)$ of intact drug absorbed into the systemic circulation up to time $t$ is obtained by integration of Eq. (8):

$$\begin{aligned} D(t) = {} & k_4[C_5 X(\alpha,t) + C_6 X(\delta,t)] + k_8[C_7 X(\alpha,t) + C_8 X(\beta,t) \\ & + C_9 X(\delta,t) + c_2 X(\omega,t)] + k_{10}[C_{10} X(\alpha,t) \\ & + C_{11} X(\beta,t) + C_{12} X(\gamma,t) + C_{13} X(\delta,t) + C_{14} X(\omega,t) \\ & + c_3 X(\epsilon,t)] \end{aligned} \tag{32}$$

In the above expression, the function $X$ (const,$t$) is

$$X = [1 - \exp(-\text{const} \cdot t)] \cdot \text{const} \tag{33}$$

Absolute bioavailability BA can be then viewed as the ratio of the value of $D$ at $t$ going to infinity, $C(t \rightarrow \infty)$ compared to the administered dose $D_0$:

$$\begin{aligned} BA = {} & [k_4(C_5/\alpha + C_6/\delta) + k_8(C_7/\alpha + C_8/\beta + C_9/\delta + c_2/\omega) \\ & + k_{10}(C_{10}/\alpha + C_{11}/\beta + C_{12}/\gamma + C_{13}/\delta + C_{14}/\omega \\ & + c_3/\epsilon)]/D_0 \end{aligned}$$

## ACKNOWLEDGMENTS

The authors would like to thank Ms. Sandy Butler for typing the manuscript and Ms. Amanda Venables and Messrs. Teck Ting and Andrew McLachlan for supplying information and useful discussions.

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