International Journal of Pharmaceutics, 20 (1984) 107–118
Elsevier

IJP 00683

A theory of molecular diffusion in the intestinal mucus

N.A. Peppas, P.J. Hansen and P.A. Buri

Department of Pharmaceutics, University of Geneva, Geneva 1211 (Switzerland)

(Received September 27th, 1983)
(Modified version received January 31st, 1984)
(Accepted February 8th, 1984)

Summary

Intestinal transport and absorption of drugs is affected by the complex mechanism of diffusional transport through the mucus layer of the small intestine. Evidence is presented that the intestinal mucus gel layer may be described by a macromolecular network model, where the chains are held together by permanent entanglements of a physical and chemical nature. Molecular diffusion of the solute can be described by a topological, free-volume-based model which relates the drug diffusion coefficient to molecular characteristics of the mucus gel network. It is predicted that the diffusion coefficient is affected by the glycoprotein concentration of the mucus, the size of the diffusing species, and the density of the effective macromolecular cross-links of the glycoprotein network.

Introduction

Intestinal absorption of nutrient molecules, drugs and ions is a complex transport phenomenon. From the point of view of physical and mathematical modelling, this problem may be analyzed by taking into consideration both solute dissolution and permeation mechanisms. Thus, several types of lumped parameter models have been proposed and compared with experimental results. For example, Bungay et al. (1981) presented a pharmacokinetic model for enteric transport of chlordecone in the rat intestine.

Correspondence: N.A. Peppas, School of Chemical Engineering, Purdue University, West Lafayette, IN 47907, U.S.A.

Macroscopic analysis of drug absorption has been offered by Amidon et al. (1980) and Elliott et al. (1980), among others. In this analysis, the intestine was considered as a straight cylinder, and drug transport was described in terms of an overall drug permeability coefficient through the intestinal wall. Four types of chyle flow were considered, those of laminar flow, plug flow, flow under radial mixing, or under mixing tank conditions. A similar approach, with lesser emphasis on the flow characteristics of the chyle in the intestine, has concentrated on the importance of the boundary layers formed during drug permeation through the intestinal wall (Goodacre and Murray, 1981; Ho and Higuchi, 1974).

Although these models are of great utility when one attempts to predict the overall transport of drugs in the intestine, by their own nature they fail to consider the effect of molecular structure on the intestinal wall on the permeation process. In fact, drug permeation is the combined result of a diffusive phenomenon characterized and controlled by the structure of the biological membrane, and of the thermodynamic interactions between the diffusing drug and the membrane (Lightfoot, 1974).

Studies by Franz et al. (1980, 1981) using ergot peptide alkaloids and well-characterized intestinal mucus showed that the mucus layer is the rate-limiting barrier for intestinal absorption and transport of these molecules. In our work, we present evidence that the intestinal mucus may be described as a swollen, entangled, macromolecular network, and we provide a new physical model which can be used to correlate the drug diffusion coefficient to structural characteristics of the network.

Intestinal mucus structure

The first physical barrier to transport of solutes through the intestinal wall is the mucus layer, a highly viscous product secreted by the goblet cells of the small intestine (Forstner et al., 1973b). Studies (Debnam and Levin, 1975; Lukie, 1977) have shown that this hydrated goblet cell mucin layer is identical to the 'unstirred layer of fluid' next to the intestinal wall that had been earlier considered to be the primary diffusional barrier (Dietschy et al., 1971; Wilson and Dietschy, 1972a and b; Westergaard and Dietschy, 1974). Indeed, the thickness of these two layers is the same (Lukie, 1977) and in vivo absorption of solutes with different chemical structure has been correlated with solute diffusion through isolated mucus solutions (Nimmerfall and Rosenthaler, 1980). The intestinal mucus is believed to perform important functions, such as binding and transport of solutes; it may also contribute to enzymatic reactions (Kent, 1967).

Mucus secreted in the human small intestine is similar to other epithelial secretions of the body in that it is an aqueous solution of glycoproteins or mucin, inorganic salts, proteins, lipids and mucopolysaccharides. Typical concentrations of its components are 1–1.5 wt% electrolytes, 0.5–1.0 wt% proteins, 0.5–1.0 wt% lipids and glycoproteins, and more than 95 wt% water (Kent, 1967; Labat-Robert and Decaens, 1979). The glycoprotein fraction is the most important component of the mucus, from a macromolecular point of view, since it is responsible for its viscoelas-

tic and gel-forming characteristics. In the mucus glycoproteins, long-chains, branched oligosaccharides are attached to serine and threonine amino acid components of the peptide backbone by O-glycosidic linkages (Pigman, 1977).

Important components of the mucus glycoproteins are the amino acid groups and carbohydrate groups such as fucose, galactose, N-acetylglucosamine, N-acetylgalactosamine, sialic acid and mannose. The protein backbone of the mucus glycoprotein molecules is relatively rich in serine and threonine, and the linkage of carbohydrate chains occurs at these amino acid sites. The arrangement of amino acids is as important as the relative amount of each residue, because the conformation of the macromolecules is determined by information encoded in the sequence of amino acids. The way a protein molecule folds is also affected by the attachment of different oligosaccharide groups (Schwarz and Datema, 1982), which in turn affects the interaction with other glycoproteins of different molecules. All mucins exhibit microheterogeneity both in the peptide backbone and the oligosaccharide portions of their molecules.

Only systems possessing a gel-like structure with some intermolecular cross-linking can control the transport function of the epithelium (King et al., 1974), and the observed rate of transport is markedly dependent on the rheological properties of the gel. Thus, the ability of the mucus to function as a 'molecular sieve' depends on the molecular structure and arrangement of the glycoprotein chains, since these are the macromolecular components of the mucus, capable of forming a gel phase (Edwards, 1978; Morris and Rees, 1978).

When mucus is exposed to an excess of physiological saline it remains as a separate gel phase instead of dispersing (Meyer, 1976). This observation is also consistent with a gel structure of the glycoproteins and it implies that the macromolecules are either heavily entangled, in which case the chains are held together at physical cross-linking points, or chemically cross-linked. In both cases, the chains have lower mobility than free chains and create a topological barrier for diffusion of solutes.

Studies with a variety of mucus samples can provide indications of the molecular weight of the macromolecules involved in the mucus network. For example, Lamblin et al. (1979) reported that the glycoprotein molecules of human bronchial mucus are extended, slightly flexible, rod-like polypeptides, stiffened by the presence of frequent, glycosidically-linked carbohydrate side-chains with a molecular weight of approximately 4×10^5 daltons and length of 1300–1500 Å as determined by electron microscopy. The results of this study are in agreement with values of molecular weight of 1.1×10^5 and 2×10^6 daltons obtained by Allen and Snary (1972) and Forstner et al. (1973a) for the water-soluble fractions of porcine gastric mucus and intestinal rat mucin, respectively.

Allen and Snary (1972) have shown that disulphide bonds serve as intrachain linkages joining glycoprotein subunits. Larger glycoprotein molecules are apparently very closely associated as a gel phase in vivo. Since successive treatment of the water-insoluble mucus gel with solvents capable of disrupting the tertiary structure solubilizes only 70–80% of this phase, Allen and Snary (1972) concluded that it is the difference in molecular structure between the glycoprotein molecules in the

water-insoluble phase and the chains making up the water-soluble phase, which gels reversibly, that may be responsible for this behavior. Further work (Scawen and Allen, 1977) supported this structure and showed that the disulphide bridges may be susceptible to proteolysis. It was shown that the aggregate structure of the gel is due in part to the degree of expansion of the glycoprotein molecules in solution caused by repulsion of negatively charged groups in the carbohydrate side-chains, such as sialic acid terminal groups and ester sulfate groups. At low ionic strength, there is less charge shielding of these negatively charged residues and the molecules occupy a large volume in solution.

Rheological studies of mucus (Lutz et al., 1973; Marriott et al., 1979) showed that the observed mechanical behavior was that of an entangled or cross-linked macromolecular system. Change in the glycoprotein conformation, and presence of divalent ions were responsible for the change of viscoelastic modulus observed in these rheological studies.

Molecular diffusion in the mucus

There have been virtually no studies on the effect of the cross-linked mucus gel structure on the diffusion of drugs through the mucus. It is only by analogy to other studies with physiological or synthetic macromolecular systems that one can examine the effect of the glycoprotein structure on diffusion. Various studies on diffusion of solutes in hydrophilic gels may provide, by analogy, the general dependence of the solute diffusion coefficient on network properties.

Davis (1974) proposed a simple empirical equation for the description of the normalized diffusion coefficient of a hydrophilic solute through a hydrophilic gel.

$$\frac{D_{ig}}{D_{iw}} = \exp\left[-\left(5 + 10^{-4}M_i\right)c_p\right] \tag{1}$$

where D_{ig} is the diffusion coefficient of solute i through the gel, D_{iw} is the same diffusion coefficient through pure solvent (water), M_i is the molecular weight of the diffusing solute, and c_p is the polymer concentration of the gel (in g of polymer per g of total gel). This equation, although successful in predicting solute diffusion coefficients through highly and moderately swollen polyacrylamide and poly(N-vinyl-2-pyrrolidone) gels, cannot be considered satisfactory for description of drug transport in the mucus, since it does not take into consideration the effect of barrier characteristics of the entangled chains on diffusion. In addition, the effect of solute size is described in terms of the molecular weight of the solute, a parameter that is not necessarily characteristic of the solute structure.

The 'sieving' mechanism of a network in molecular diffusion has been described also by Renkin (1954), who proposed the semi-empirical Eqn. 2, which has become quite popular for description of diffusion in hydrogels and in natural membranes (see e.g. Wisniewski and Kim, 1980).

$$\frac{D_{ig}}{D_{iw}} = (1-\lambda)^2\left[1 - 2.104\,\lambda + 2.09\,\lambda^3 - 0.95\,\lambda^5\right] \tag{2}$$

where λ is the characteristic ratio of the solute diameter, d_i, to the average pore diameter of the membrane, d_p. Although the Renkin equation may have advantages over Eqn. 1, it was developed for macro- and microporous membranes, whereas in networks with pores of 'molecular dimensions' as in the case of the intestinal mucus network, knowledge of the average pore diameter, d_p, is not possible. In addition, the Renkin model does not describe the effect of the polymer concentration on molecular diffusion of the solute.

Other physical models for calculation of the solute diffusion coefficient, and the reasons why they cannot describe accurately the solute diffusion phenomenon in gel networks, are discussed by Peppas and Meadows (1983). Here, we offer a new physical model which may be used for analysis of the dependence of the drug diffusion coefficient on the molecular structure of the intestinal mucus.

Molecular theory of diffusion in intestinal mucus

Theory

We consider the intestinal mucus gel layer as a dilute, entangled network of macromolecular chains, composed of glycoproteins. The network is effectively cross-linked or entangled at different points by permanent physical entanglements, and it is swollen in water up to thermodynamic equilibrium. Supermolecular structure by association of chains in the form of hydrogen bonds, other secondary chemical bonds and aligned chains may also be present; for the purposes of this model, these types of structure are also represented by entanglements. Fig. 1 presents a schematic description of this network.

It is further assumed that these entanglements cannot change or disentangle during the diffusional process, or that, if this happens, an equal number of chains entangles so that statistically there is always a constant number of entanglements, ν_e, per unit volume. Possible enzymatic degradation of glycoproteins during the diffusion process is assumed to be negligible, since it is counterbalanced in vivo by continuous renewal of mucus (Schrager and Oates, 1978). The glycoprotein chains are assumed to behave as long macromolecular chains exhibiting Gaussian distribution (Flory, 1969).

In the swelling medium (water) the chains exhibit high mobility, but on the average a certain percentage of the available volume for diffusion is occupied by chains. It is also assumed that drug diffusion is unidirectional (normal to the surface of the mucus layer) so that diffusional areas may be used for description of the barrier characteristics of the glycoprotein chains. Finally, as shown in Fig. 1, it is assumed that the 'junctions' between chains are of much smaller volume than the chains per se and can be represented by 'points'. In this model, 'ideal' tetrafunctional junctions are used to analyze the network. However, multifunctional junctions may also be considered without alteration of the qualitative results of the model.

We consider now diffusion of a solute i through this dilute macromolecular network. Any ionic interactions will of course affect the permeation characteristics and should be incorporated in the partition coefficient. Therefore, here we examine only 'barrier effects' on molecular diffusion.

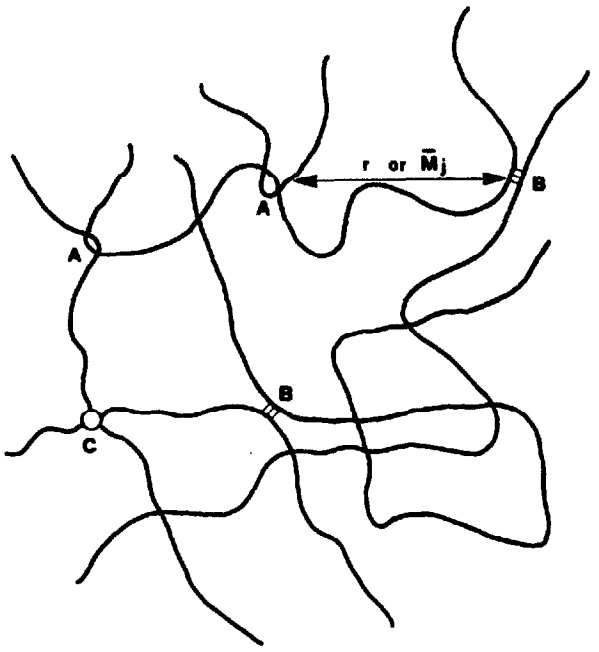

Fig. 1. Schematic representation of intestinal mucus network. Possible junctions include entanglements (A), molecular associations (B) and permanent cross-links (C). An average end-to-end distance between two junctions, r, corresponds to a molecular weight $\bar{M}_j$.

The theory of stochastic processes (McGregor, 1974) suggests that the drug diffusion coefficient through this network, D_{in}, may be written as

$$D_{in} = \frac{\lambda_n^2 \nu}{6} \tag{3}$$

where λ_n is the diffusional jump length, i.e. the average distance traveled every time a drug molecule moves into a new position of the mucus network, and ν is the frequency for this diffusional jump.

According to Eyring's theory of rate processes (Glasstone et al., 1941) this molecular diffusion process evolves through continuous activation of drug molecules into the substrate. Therefore, an expression for the frequency of 'jumps' leads to eqn. 4:

$$D_{in} = \lambda_n^2 \frac{kT}{h} \exp\left(-\frac{\Delta G_n}{RT}\right) = \lambda_n^2 \frac{kT}{h} \exp\left(\frac{\Delta S_n}{R}\right) \exp\left(-\frac{\Delta H_n}{RT}\right) \tag{4}$$

where ΔG_n is the Gibbs free energy for the process of diffusional activation, ΔS_n is the configurational entropy change, and ΔH_n is the associated enthalpy change. Finally k and h are the Boltzmann and Planck constants, respectively, and T is the absolute temperature.

From a topological point of view it is desirable to compare the diffusional process

in the network to that in a medium where macromolecular chain barriers have vanished; for this purpose, one selects diffusion in pure solvent. Then by analogy to Eqn. 4 one can write the following equation for diffusion in water (subscript w).

$$D_{iw} = \lambda_w^2 \frac{kT}{h} \exp\left(-\frac{\Delta G_w}{RT}\right) = \lambda_w^2 \frac{kT}{h} \exp\left(\frac{\Delta S_w}{R}\right) \exp\left(-\frac{\Delta H_w}{RT}\right) \tag{5}$$

Under isothermal diffusional conditions the enthalpic changes for diffusion in the network and diffusion in pure solvent are approximately equal, i.e $\Delta H_n^* \approx \Delta H_w^*$. In addition, since mucus is a *dilute* macromolecular network, one may assume that the diffusional jump lengths are approximately equal, i.e. $\lambda_n \approx \lambda_w$. Under these assumptions eqns. 4 and 5 may be divided to give

$$\frac{D_{in}}{D_{iw}} = \exp\left[\frac{(\Delta S_n - \Delta S_w)}{R}\right] \tag{6}$$

Recalling that for any random process the entropy change is related to the probability, P, by the Boltzmann Eqn. 7:

$$\Delta S_n = R \ln P(v_n) \tag{7}$$

we conclude that it is necessary to determine the probability, $P(v_n)$, that a drug molecule of size v_i will diffuse through a mucus network by finding a 'network space' of size at least v_n, where $v_i \leqslant v_n$. This probability has been calculated by Cohen and Turnbull (1959) for polymer systems and it is given by Eqn. 8.

$$P(v_n) = A(v_n) \exp\left(-\frac{v_i}{V_n}\right) \tag{8}$$

The previous equation suggests that the probability $P(v_n)$ is equal to the probability of having in the network 'spaces' of size at least $v_n \geqslant v_i$, multiplied by the probability that a drug molecule of size v_i will occupy that space. According to the Cohen-Turnbull theory this second probability is described by the exponential term of Eqn. 8, where V_n is the free-volume of the glycoprotein macromolecular chains. For a definition and analysis of the free-volume see Meares (1965).

Similar equations to Eqns. 7 and 8 can be written also for diffusion in pure solvent (subscript w), where it is now realized that since in the solvent there are no macromolecular barriers, the parameter $A(v_w)$ should be equal to one.

$$\Delta S_w = R \ln P(v_w) \tag{9}$$

$$P(v_w) = A(v_w) \exp\left(-\frac{v_i}{V_w}\right) = \exp\left(-\frac{v_i}{V_w}\right) \tag{10}$$

Eqns. 7–10 may be used in Eqn. 6 to obtain

$$\frac{D_{in}}{D_{iw}} = A(v_n) \exp\left[-v_i\left(\frac{1}{V_n} - \frac{1}{V_w}\right)\right] \tag{11}$$

This equation completes the formal derivation of the theory. It predicts that the normalized diffusion coefficient of the drug in the mucus network (left-hand side term) is dependent on topological characteristics of the network (term $A(\upsilon_n)$), geometrical characteristics of the solute (term υ_i), and the glycoprotein (network) concentration in the mucus (term $[(1/V_n) - (1/V_w)]$).

Analysis of theory

Immediate application of Eqn. 11 is not evident. It is therefore necessary to analyze this equation by recasting its parameters in terms of parameters that can be measured readily through physicochemical and biochemical experiments of different mucus samples.

The term associated with the solute requires knowledge of its volume, υ_i. For different drugs where their volume is not immediately known, one may write, for unidirectional diffusion, that:

$$\upsilon_i = \pi r_i^2 \ell \tag{12}$$

where r_i is the characteristic hydrodynamic radius of the drug and ℓ is a characteristic length. The value of r_i may be either the Stokes hydrodynamic radius, or the average size of the molecule as obtained by light scattering experiments. Colton et al. (1971) have tabulated values for r_i for various commonly used small and large molecules.

The term which incorporates the free-volumes of the network, V_n, and water, V_w, may be recast in terms of the degree of swelling, Q_m, of the mucus layer or the concentration, C_m, of the glycoproteins in this gel layer. Indeed, for the free-volume, V_n, one can write

$$V_n = (1 - \upsilon_m)V_w + \upsilon_m V_m \tag{13}$$

where υ_m is the equilibrium swelling volume fraction of glycoprotein in the mucus gel layer, usually less than 0.05. Then,

$$\frac{1}{V_n} - \frac{1}{V_w} = \frac{\upsilon_m(V_w - V_m)}{V_w^2(1 - \upsilon_m) + \upsilon_m V_m V_w} \tag{14}$$

As for most dilute macromolecular systems, the free-volume of pure glycoprotein, V_m, may be assumed to be negligible. Also the volume fraction, υ_m, may be written according to Eqn. 15 in terms of the specific volume of the constituent glycoprotein (in cm^3/g) and the glycoprotein concentration in the gel (in g/cm^3):

$$\upsilon_m = \bar{v}c_m \tag{15}$$

Then, Eqn. 14 can be modified to give:

$$\frac{1}{V_n} - \frac{1}{V_w} = \frac{\upsilon_m}{(1 - \upsilon_m)} \cdot \frac{1}{V_w} = \frac{\bar{v}}{\left(\frac{1}{c_m} - \bar{v}\right)} \cdot \frac{1}{V_w} \tag{16}$$

The term which describes the topological characteristics of the network, $A(\upsilon_n)$, requires understanding of the macromolecular structure of the glycoprotein network for further analysis. The notion of mucus playing the role of a 'molecular filter' was first proposed by Kent (1967). This screening effect can be determined by considering the idealized diagram of Fig. 1.

For an ideal 'network space' formed by 4 tetrafunctional junctions, the probability, $A'(\upsilon_n)$, is proportional to the available area, A_n, which may be approximated by r^2, where r is the end-to-end distance of the glycoprotein chain between two junctions.

$$A'(\upsilon_n) = k_2 A_n = k_2 r^2 \tag{17}$$

It is well-known that for any macromolecule in the absence of solvent (i.e. as the unperturbed state), this end-to-end distance is determined by Flory (1969) as

$$r_0^2 = C_n n a^2 \tag{18}$$

where C_n is the characteristic ratio or rigidity factor of the chain, n is the number of links of the chain, and a is the bond length between atoms in the chain. The number of links in a chain, n, is proportional to its molecular weight, which in the case of the entangled glycoprotein network is the average molecular weight between two junctions, $\overline{M}_j$. Therefore

$$n = k_3 \overline{M}_j \tag{19}$$

and

$$r_0^2 = k_3 C_n \overline{M}_j a^2 \tag{20}$$

In reality, the glycoprotein chain is extended over its unperturbed conformation (solvent-free state) by a factor α, the linear expansion coefficient, due to the presence of the solvent.

$$r^2 = \alpha r_0^2 \tag{21}$$

The expansion coefficient is clearly obtained from the equilibrium volume fraction of glycoproteins in the mucus layer, υ_m, since

$$\alpha = \upsilon_m^{-1/3} \tag{22}$$

Therefore, eqns. 17, 20, 21 and 22 give:

$$A'(\upsilon_n) = k_2 k_3 C_n a^2 \upsilon_m^{-1/3} \overline{M}_j \tag{23}$$

One can further combine Eqns. 15 and 23 to obtain:

$$A'(\upsilon_n) = k_1 c_m^{-1/3} \overline{M}_j \tag{24}$$

where the constant k_1 is given by

$$k_1 = k_2 k_3 C_n a^2 \bar{v}^{-1/3} \tag{25}$$

Finally, it must be noted that the probability $A(v_n)$ appearing in Eqn. 11 is 'normalized probability', and that normalization here requires that the right-hand side term of Eqn. 24 be divided by the maximum possible molecular weight of the glycoprotein chain, which is equivalent to the molecular weight of the chain without entanglements, $\overline{M}_n$. Therefore

$$A(v_n) = k_1 c_m^{-1/3} \frac{\overline{M}_j}{\overline{M}_n} \tag{26}$$

With the previous analysis, Eqns. 12, 16 and 26 can be used in Eqn. 11 to yield the final form of the normalized diffusion coefficient of a drug through the mucus, where k_1 is given by Eqn. 25.

$$\frac{D_{in}}{D_{iw}} = k_1 c_m^{-1/3} \frac{\overline{M}_j}{\overline{M}_n} \exp\left[- \frac{\pi r_i^2 \ell \bar{v}}{V_w \left(\frac{1}{c_m} - \bar{v} \right)} \right] \tag{27}$$

Discussion

The previous analysis presented a model for the diffusion of drug through the intestinal mucus. To examine the important conclusions of this work it is interesting to simplify Eqn. 27 by examining the influence of the 3 variables, $\overline{M}_j$, r_i and c_m, and combining all other terms into two constants, k and k', as follows.

$$\frac{D_{in}}{D_{iw}} = k c_m^{1/3} \overline{M}_j \exp\left[- \frac{k' r_i^2}{\left(\frac{1}{c_m} - \bar{v} \right)} \right] \tag{28}$$

The new physical model predicts that as the solute radius, r_i, increases, the solute diffusion coefficient decreases. In addition, the diffusion coefficient depends both on the entangled structure and the concentration of the glycoproteins in the mucus. Indeed, as the concentration, c_m, increases, the diffusion coefficient decreases. Both effects are exponential, so that small changes of the glycoprotein concentration, as in the case of various diseases, and the size of the solute would have a significant effect on the drug diffusion coefficient. The size of the entangled network has a lesser but important effect. Indeed as the mucus layer becomes more cross-linked, the value of

$\overline{M}_j$ becomes smaller, leading to lower diffusion coefficients.

It must be noted that the derivation of the previous theory does not require knowledge of the viscoelastic behavior of the mucus layer. Therefore, Eqn 27 can be used under all conditions, as long as the relaxations of the glycoprotein chain do not interfere with the diffusional process.

The correlative capabilities of the analysis are obvious. One may perform experiments with natural or reconstituted mucus using different size drugs and determine the diffusion coefficient of each drug. Then a plot of $\ln(D_{in}/D_{iw})$ versus r_i^2 should give a straight line.

Acknowledgements

N.A.P. thanks the Zyma Foundation for the Advancement of Medical and Biological Sciences, for a grant that enabled him to conduct this research during his sabbatical leave at the University of Geneva.

References

Allen, A. and Snary, D., The structure and function of gastric mucus. Gut, 13 (1972) 666–672.

Amidon, G.L., Kou, J., Elliott, R.L. and Lightfoot, E.N., Analysis of models for determining intestinal wall permeabilities. J. Pharm. Sci., 69 (1980) 1369–1373.

Bungay, P.M., Dedrick, R.L. and Matthews, H.B., Enteric transport of chlordecone in the rat. J. Pharmacokin. Biopharm., 9 (1981) 309–341.

Clamp, J.R., Allen, A., Gibbons, R.A. and Roberts, G.P., Chemical aspects of mucus. Br. Med. Bull., 34 (1978) 25–27.

Cohen, M.H. and Turnbull, J., Molecular transport in liquids and glasses, J. Chem. Phys., 31 (1959) 1164–1169.

Colton, C.K., Smith, K.A., Merrill, E.W. and Farrell, P.C., Permeability studies with cellulosic membranes. J. Biomed. Mater. Res., 5 (1971) 459–488.

Davis, B.K., Diffusion in polymer gel implants, Proc. Natl. Acad. Sci. U.S.A., 71 (1974) 3120–3123.

Debnam, E.S. and Levin, R.J., Effects of fasting on the kinetics of active and passive sugar absorption across the small intestine in vivo. J. Physiol. (Lond.), 252 (1975) 681–700.

Dietschy, J.M., Sallee, V.L. and Wilson, F.A., Mechanisms for the intestinal absorption. Gastroenterology, 61 (1971) 932–1937.

Edwards, P.A., Is mucus a selective barrier to macromolecules? Br. Med. Bull., 34 (1978) 55–56.

Elliott, R.L., Admidon, G.L. and Lightfoot, E.N., A corrective mass transfer model for determiing intestinal wall permeabilities. J. Theor. Biol., 87 (1980) 757–771.

Flory, P.J., Statistical Mechanics of Chain Molecules. Interscience, New York, 1969.

Forstner, J.F., Jabbal, I. and Forstner, G.G., Goblet cell mucin of rat small intestine: chemical and physical characterization. Can J. Biochem., 51 (1973a) 1154–1166.

Forstner, J.F., Taichman, N., Kalnis, V. and Forstner, G.G., Intestinal goblet cell mucus: isolation and identification by immune fluorescence of a goblet cell glycoprotein. J. Cell. Sci., 12 (1973b) 585–601.

Franz, J.M. and Vonderscher, J.P., Enhancement of the intestinal absorption of ergot peptide alkaloids in the rat by micellar solutions of polyoxyethylene-24-cholesteryl ether. J. Pharm. Pharmacol., 33 (1981) 565–568.

Franz, J.M., Vonderscher, J.P. and Voges, R., Contribution to the intestinal absorption of ergot peptide alkaloids, Int. J. Pharm., 7 (1980) 19–28.

Glasstone, S., Laidler, K.I. and Eyring, H., The Theory of Rate Processes, McGraw-Hill, New York, 1941.

Goodacre, B.C. and Murray, P.J., A mathematical model of drug absorption. J. Clin. Hosp. Pharm., 6 (1981) 117–133.

Ho, N.F.H. and Higuchi, W.I., Theoretical model studies of intestinal drug absorption. J. Pharm. Sci., 63 (1974) 686–690.

Kent, P.W., Structure and function of glycoproteins. In P.N. Campbell & G.D. Greville (Eds.) Essays in Biochemistry, Vol. 3, New York, N.Y., Academic Press, 1967, pp. 105–151.

King, M., Gilboa, A., Meyer, F.A. and Silberberg, A., Epithelial transport. Amer. Rev. Resp. Dis. 110 (1974) 740.

Labat-Robert, J. & Decaens, C., Glycoprotéines du mucus gastrique: structure, fonctions et Pathologie. Path. Biol., 24 (1979) 241–247.

Lamblin, G., Lhermitte, M., Degand, P., Roussel, P. and Slayter, H., Chemical and physical properties of humans bronchial mucus glycoproteins. Biochimie, 61 (1979) 23–43.

Lightfoot, E.N., Transport Phenomena and Living Systems, Wiley, New York, 1974.

Lukie, B.E., Diffusion in the intestinal wall. Mod. Probl. Paediat., 19 (1977) 46.

Lutz, R.J., Litt, M. and Charkrin, L.W., In H.L. Gabelnick and M. Litt (Eds.), Rheology of Biological Systems, Thomas, Springfield, IL, 1973, p. 119.

Marriott, C., Shih, C.K. and Litt, M., Changes in the gel properties of tracheal mucus induced by divalent cations. Biorheology, 16 (1979) 331–337.

Mc Gregor, R., Diffusion and Sorption in Fibers and Films, Vol. 1, Academic Press, London, 1974.

Meares, P., Polymers, Van Nostrand-Reinhold, New York, 1965.

Meyer, F.A., Mucus structure: relation to biological transport function. Biorheology, 13 (1976) 49–58.

Morris, E.R. and Rees, D.A., Principles of biopolymer gelation: possible models for mucus gel structure. Br. Med. Bull., 34 (1978) 49–53.

Nimmerfall, F. and Rosenthaler, J., Biochem. Biophys. Res. Commun. 94 (1980) 960–965.

Peppas, N.A. and Meadows, D.L., Macromolecular structure and solute diffusion in membranes: An overview of recent theories, J. Membr. Sci. 13 (1983) 361–377.

Pigman, W., Introduction to mucus glycoproteins. In M.I. Horowitz and W. Pigman (eds.), The Glycoconjugates, Vol. 1, Academic Press, New York, 1977, pp. 131–135.

Renkin, E.M., Filtration, diffusion and molecular sieving through porous cellulose membranes. J. Gen. Physiol., 38 (1954) 225–243.

Scawen, M. and Allen, A., The action of proteolytic enzymes on the glycoprotein from pig gastric mucus. Biochem. J., 163 (1977) 363–368.

Schrager, J. and Oates, M.D.G., Relation of human gastrointestinal mucus to disease states. Br. Med. Bull., 34 (1978) 79–82.

Schwarz, R.T. and Datema, R., Inhibition of lipid-dependent glycosylation. In M.I. Horowitz (Ed.), The Glycoconjugates, Vol. 3, Academic Press, New York, 1982, pp. 47–79.

Westergaard, H. and Dietschy, J.M., Delination of the dimensions and permeability characteristics of the two major diffusion barriers to passive mucosal uptake in the rabbit intestine. J. Clin. Invest., 54 (1974) 718–732.

Wilson, F.A. and Dietschy, J.M., Disordered bile acid metabolism. Arch. Int. Med., 10 (1972a) 584–594.

Wilson, F.A. and Dietschy, J.M., Characterization of bile acid absorption across the rat jejunum. J. Clin. Invest., 51 (1972b) 3015–3025.

Wisniewski, S. and Kim, S.W., Permeation of water-soluble solutes through PHEMA. J. Membr. Sci., 8 (1980) 299–315.