Physical Model Approach to Taste Studies of Drugs and Pharmaceutical Formulations

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Abstract □ This paper explores the physical model approach in studying the taste of drugs and assessing physical formulation factors for improving the undesirable taste of drugs. Various aspects of physiology relevant to the taste phenomenon have been reviewed to provide the biophysical basis for mathematical modeling. The model involves non-steady-state mass transport across the aqueous boundary layer and buildup of solute concentration at the essentially impermeable tongue surface. The theoretical predictions are consistent with experimental studies on the lag time to taste perception by the electrophysiological method and also with "instantaneous" psychophysical taste perception when solute concentrations much greater than the taste threshold are applied on the tongue. Within the framework of the non-steady-state model, novel experimental studies involving the use of a porous half-diffusion cell placed on the surface of an extended human tongue and the recording of the times for psychophysical taste response are proposed to quantify and provide mechanistic understanding of the taste of drugs and also physical formulation factors in overcoming undesirable taste properties.

Keyphrases □ Taste perception—drugs and pharmaceutical formulations, physical model approach, non-steady-state mass transport □ Physical model—taste perception, drugs and pharmaceutical formulations, non-steady-state mass transport □ Mass transport—non-steady-state, physical model for taste perception, drugs and pharmaceutical formulations

The taste of drugs and the physical and chemical means to overcome or modify undesirable (usually bitter) taste are continuing and nagging problems for the pharmaceutical scientist. Understanding of structure–taste relationships (*i.e.*, taste quality and intensity) remains qualitative as pointed out by Sinkula (1), who reviewed the state of the science in improving taste properties through structural modification. The physicochemical approaches to masking undesirable taste properties remain largely empirical. The purpose of this paper is (*a*) to review the various aspects of physiology relevant to taste stimulation and (*b*) to explore the physical model approach, both theoretically and experimentally, in studying the taste of drugs and formulation factors affecting taste.

BACKGROUND

A rational approach to the understanding of taste and taste stimulation by drugs, among other important considerations relating to the physicochemical properties of the drug molecule and pharmaceutical formulation, requires some degree of knowledge of the tongue: morphology, ultrastructure, organization and functions of the cells, absorption characteristics, and taste reception.

Loci of Taste Quality—Salty, sour, bitter, and sweet sensations are recognized as the four fundamental qualities of taste. Responses to taste are found everywhere in the mouth, which includes the palate, epiglottis, tongue, and buccal area. It is generally stated in textbooks [*e.g.*, Best and Taylor (2)] that the lowest threshold for bitter is located in the back of the tongue; for salty, at the front; for sweet, on the sides near the front; and for sour, on the sides near the back of the tongue. However, it should not be construed that taste quality is confined to these loci of the tongue. Taste buds are not rigidly specific to any one taste quality, but show multiple sensitivity to taste stimulants. Taste buds appear to be differentially sensitive and may be uniquely distributed (3). A recent systematic study (4) using sodium chloride, sucrose, quinine hydrochloride, urea, and citric acid has improved the understanding of taste recognition and psychophysical intensity responses in humans as a function of locus of stimulation on the tongue and soft palate. Collings (4) found the threshold for bitter to be lower for the front of the tongue and soft palate than for the back of the tongue. The combination of the greater intensity of bitter sensation in the back of the tongue and the low threshold of the soft palate for bitter gave the subjective observation of a strong bitter taste in the back of the mouth. Differential responses to a variety of taste stimulants at specific loci were also reported.

Taste Buds and Cells—Associated with the various loci of taste stimulation on the tongue are four kinds of papillary structures (5): vallate papillae in the back of the tongue; foliate papillae on the sides and near the back; fungiform papillae at the front dorsal surface, tips, and sides; and filiform papillae, which are the prevalent type dispersed throughout the tongue surface. A keratin layer covers the surfaces of the papillae and is interrupted by the pores of the taste buds.

Taste buds are most abundant in the vallate and folliate papillae, served by the IX cranial nerve, and the fungiform papillae, served by the chorda tympani of the VII cranial nerve. The filiform papillae, whose keratinized epithelium ends in tapered points, are devoid of taste buds. With respect to the vallate papillae, which is surrounded by a moat, taste buds are dispersed about the sides of the papillae in the depths of the moat. Taste buds of the foliate (leaf-like) papillae are located on the sides, whereas the buds of the fungiform papillae are found on the flat surface portion.

Taste buds are intermingled with stratified squamous epithelial cells, and both structures rest on a thick layer of connective tissue called the basement membrane (5, 6). The bud reaches from the basement membrane to the epithelial surface and is 70 μm in length and 50 μm in its widest dimension. The pore of the taste bud, from which "taste hairs" of taste cells are extended, is found at the epithelial surface. The pore diameter is ~5 μm and, therefore, would not be a factor in excluding large molecules from penetrating the pore. The bud contains a single pore and a collection of cells. It has been assumed that the bud contains 4–20 taste cells intermingled with the more numerous supporting cells. A study by Murray (7, 8) however, states that the number of cells within a taste bud varies from 30 to 80. The cells are morphologically characterized as types I (60–80%), II (15–30%), III (3–14%), and IV (basal cells, varying from 3 to 5%). With the exception of basal cells, the others (types I, II, and III) are oblong cells which often extend from the basement membrane to the pit of the pore. The so-called "taste hairs" are microvillous structures which are extensions of the plasma membrane of cells. The membrane is thought to be a typical membrane complex, ~80 Å thick in the microvillous region and ~160 Å in the crypts, consisting of proteins, phospholipids, and lipids. The microvilli are 2-μm long and 0.1–0.2-μm wide. All cells in the vicinity of the pore are joined by tight junctions.

The cells in the taste bud are constantly being replaced. The renewal process is modulated by the activity of taste nerves. The interrelationships between cell types are not yet well understood. It is believed that cell types I, II, and III originate from the basal cells and develop into independent cell lines carrying out unique functions in the bud. On the other hand, there is evidence that the different cells may represent various stages in the metamorphosis of a single cell line. The pit of the pore is filled with a dense substance identified as mucopolysaccharides. Histochemical studies have shown the presence of ATPase, nonspecific esterases, and phosphatases in taste buds (7, 9).

Taste Reception—Taste reception appears to be mechanistically a substrate–receptor reaction, nonenzymic in nature, at the microvillous membrane level, whereby local perturbations of the membrane lead to a cascade of electrophysiological and psychophysical events known as taste perception (10–13). It does not depend on the direct interaction of taste stimulants with free nerve endings in the taste bud for the following reasons. First, the numerous nerve fibers in the underlying connective tissue enter the taste bud and continue upward to a level only a few micrometers from, but never in direct contact with, the microvillous membrane and the pit of the pore. Second, nerve fibers are found between cells, but the intercellular spaces are believed to be inaccessible to the molecular diffusion from the outside due to the presence of tight junctions. The nonpenetrability of the epithelium by sodium cyanide and colchicine is claimed to be supportive evidence of the occlusive properties of the tight junctions. Third, many taste stimulants are highly hydrophilic and yet taste is perceived instantaneously.

The sour taste of inorganic and organic acids is due to the dissociated hydrogen ions, the salty taste to the cations and anions of the dissociated salt. Bitter and sweet are found in a variety of chemicals and are not generally at-

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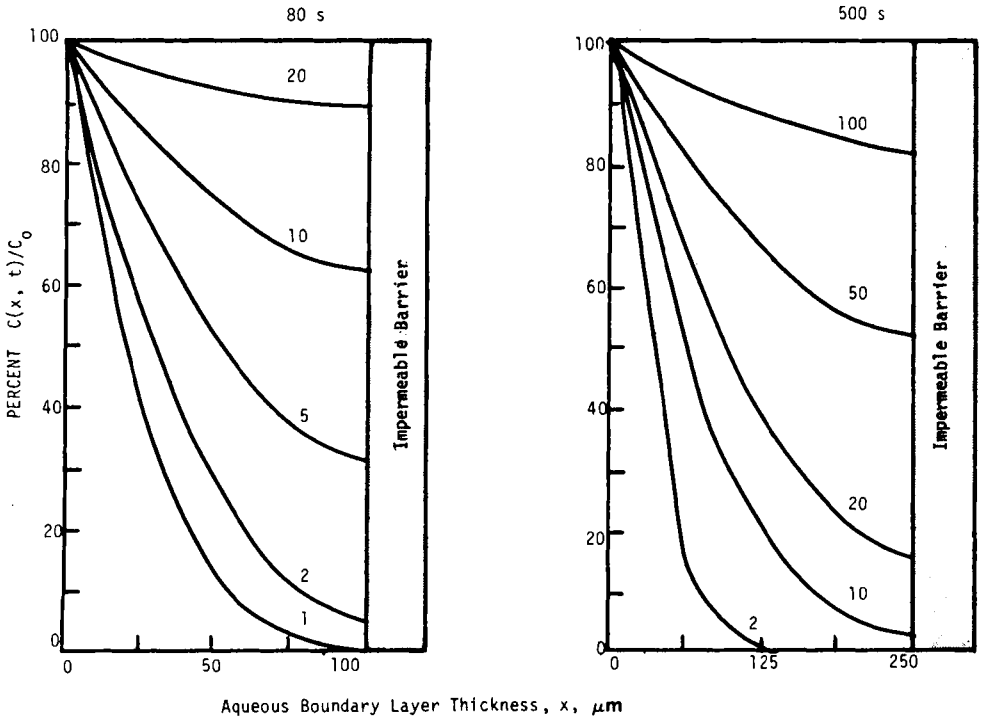


Figure 1—*Percent concentration-distance profile as a function of time for two aqueous boundary thicknesses. Aqueous diffusion coefficient is* 5×10^{-6} *cm²/s.*

tributed to ionic species. Hydrogen bonding is involved at proper geometric sites; often, a small change in configuration will change the sweet taste to bitter and *vice versa*. Beidler and Gross (14) have concluded that each taste cell has many different types of receptor sites and that the number of sites of the same type varies from cell to cell. The Beidler's taste response equation has been applied to all types of taste stimulants with reasonable success:

$$R = \frac{R_m KC}{1 + KC} \qquad \text{(Eq. 1)}$$

where R is the response, R_m is the maximum response, C is the concentration of the stimulus, and K is the binding constant. The binding energy is generally found to be weak, usually a few kilocalories per mole, which supports the reversible nature of taste and the ready removal of stimulants with water and saliva. The taste buds are physiologically rugged to chemical insults, and their sensitivity recovers readily after repeated and long exposures to stimulants.

Permeability of the Tongue—The human tongue appears to be relatively impermeable if the permeability of the rat tongue is a good indicator of the human situation. Mistretta (15) studied the permeability of the rat tongue epithelium in a two-compartment diffusion cell. The surface comprising of fungiform and filiform papillae was highly keratinized. It was estimated that the taste pores (5-μm wide and 1 pore per fungiform papilla) were only 0.0004% of the total surface area. The permeability coefficients of various permeating species are shown in Table I and range from 1.8×10^{-7} to 4.4×10^{-6} cm/s. The progression of the permeability values corresponded roughly with the ether–water partition coefficients. It is conceivable that the tongue, particularly the microvillous membrane of the taste cells, is permeable to more highly lipophilic solutes.

Methods in Studying Taste—Human taste studies are carried out by the psychophysical method. Although the method involves subjective responses on the part of test subjects within well-controlled procedures, it is sensitive and is built around a statistical design to minimize bias and variable responses within and between subjects (3, 16). The electrophysiological method is employed on anesthesized animals, since it involves the surgical implantation of electrodes in the chorda tympani nerve bundle. The response of taste buds is followed by recording neural activity with time (17, 18). The first attempts to record the electrical response in humans undergoing otological surgery under deep anesthesia were made by Diamant *et al.* (19). The electrical taste thresholds of different solutions correlated with subjective values collected from psychophysical experiments.

THEORETICAL

The tongue is a relatively impermeable surface. This important fact provides the rationale for the non-steady-state model for the transport of taste-provoking drugs across the aqueous boundary layer in front of the impermeable tongue surface. In turn, this model lays the foundation for the physical model approach in studying the taste of drugs, and the chemical and physical formulation factors affecting taste, on a quantitative and mechanistically interpretive basis.

Mass transport across the aqueous boundary layer in front of the impermeable tongue surface and the buildup with time of the concentration at the tongue surface are essentially non-steady-state diffusional kinetic situations. The model is consistent with the observation that when taste-provoking molecules in solution are applied to the tongue at concentrations much greater than the taste threshold concentration, taste is detected "instantaneously." Moreover, the model will provide the physicochemical framework in designing novel and remarkably simple experiments in studying (*a*) the taste of drugs and molecular modification effects and (*b*) physical formulation factors on a quantitative mechanistic level.

The non-steady-state change in drug concentration in the aqueous boundary layer with distance x and time t is given by Fick's second law:

$$\frac{\partial C(x,t)}{\partial t} = D\frac{\partial^2 C(x,t)}{\partial x^2} \qquad \text{(Eq. 2)}$$

$$(x > 0 \text{ and } t > 0)$$

The boundary conditions are:

$$C(0,t) = C_0$$

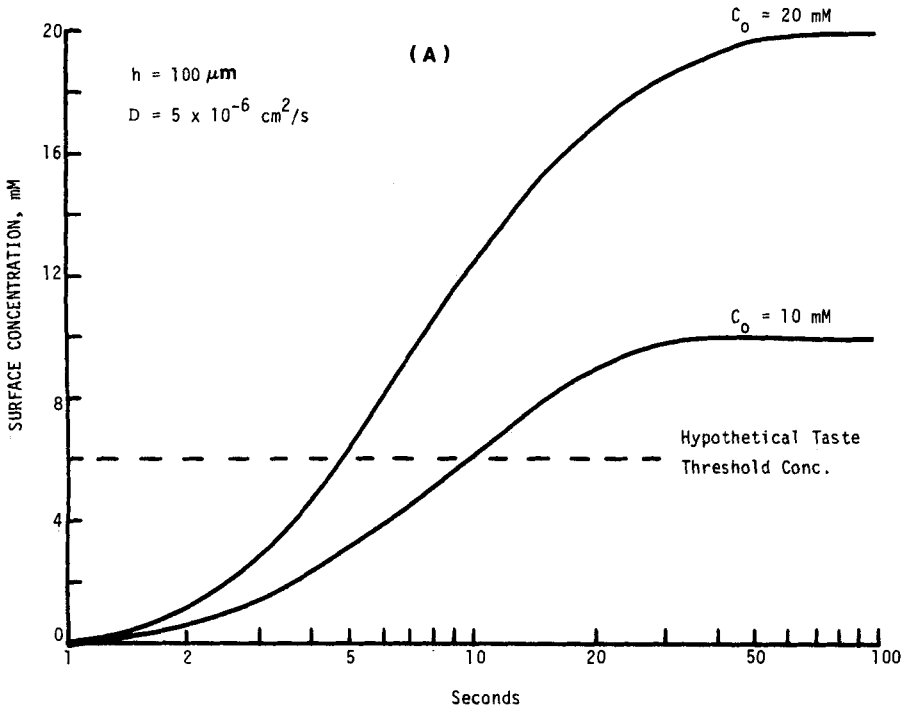
$$C(x,0) = 0$$

$$\left.\frac{\partial C(x,t)}{\partial x}\right|_{x=h} = 0$$

Table I—Permeability Coefficients for Rat Tongue Epithelium [a]

Permeating Species	Permeability Coefficient cm/s × 10^6	Log Partition Coefficient (Ether–Water)
Methanol	4.38	−0.85
Ethyl carbamate	4.15	−0.19
Butanol	3.53	−0.58
Ethanol	3.03	−0.57
Ethylene glycol	2.73	−2.27
Propionamide	2.60	−1.89
Thiourea	1.32	−2.15
Acetamide	1.00	−2.60
Glycerol	0.45	−3.07
Fructose	0.40	—
Sodium butyrate	0.27	—
Glucose	0.18	−5.00
Mannitol	0.18	−5.00

[a] From Ref. 15.



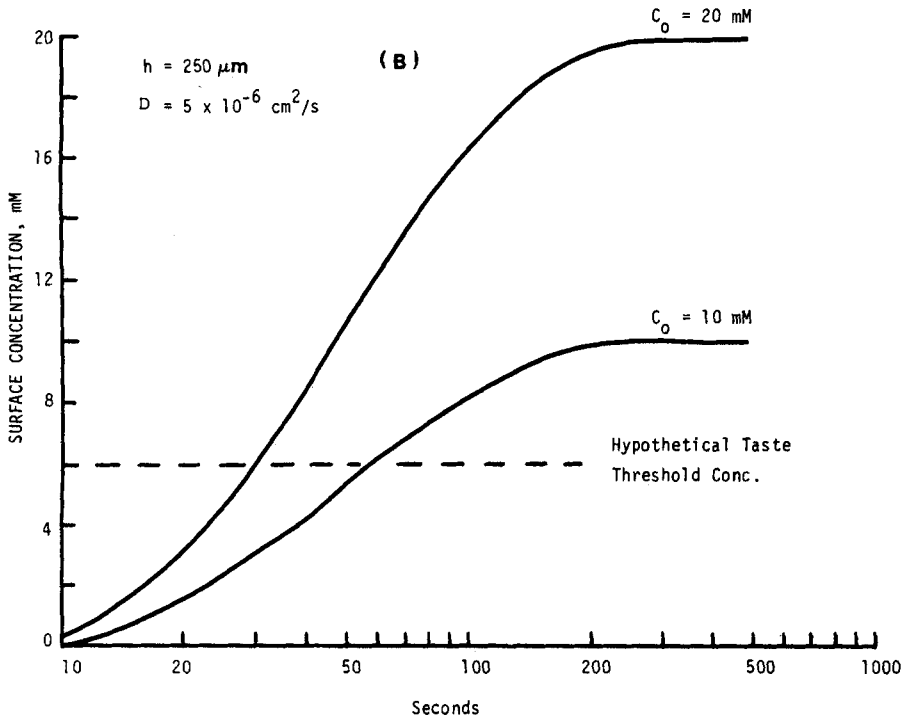


Figure 2—*Surface concentration–distance profiles as a function of time for aqueous boundary layer thicknesses of 100 (A) and 250 μm (B), diffusion coefficient of 5 × 10^{-6} cm^2/s, and bulk aqueous concentrations of 10 and 20 mM.*

The first condition states that the bulk concentration applied on the tongue does not change with time. At time zero, no drug molecules are found within the aqueous layer as described by the second conditions. Because the surface of the tongue is essentially an impermeable barrier, the flux of drug at the membrane surface is effectively zero.

Although the differential equation with its boundary conditions can be readily solved numerically with a computer, one can seek a solution by the Laplace transformation method. It follows that:

$$U(x,s) = C_0 \left[\frac{\cosh (x\sqrt{s/D})}{s} - \frac{\tanh (h\sqrt{s/D}) \cdot \sinh (x\sqrt{s/D})}{s} \right] \quad \text{(Eq. 3)}$$

where $U(x,s)$ is the Laplace transform of $C(x,t)$ and s is a variable of time t. The inverse of the above Laplacian equation is quite complicated. Since one needs only to know the drug concentration at the membrane surface at any time, *i.e.*, $C(h,t)$, with respect to taste response, then Eq. 3 simplifies to:

$$U(h,s) = C_0 \cdot \frac{\operatorname{sech} (h\sqrt{s/D})}{s} \quad \text{(Eq. 4)}$$

In series form:

$$U(h,s) = C_0 \left[2 \sum_{n=0}^{\infty} (-1)^n \cdot \frac{e^{-(2n+1)h\sqrt{s/D}}}{s} \right] \quad \text{(Eq. 5)}$$

whereupon the inverse is:

$$\frac{C(h,t)}{C_0} = 2 \sum_{n=0}^{\infty} (-1)^n \cdot \operatorname{erfc} \left[\frac{(2n+1)h}{2\sqrt{Dt}} \right] \quad \text{(Eq. 6)}$$

As can be seen, the magnitude of the surface concentration at any time t is a fraction of the bulk concentration. After sufficient time, the complementary error function converges to unity so that the surface concentration will finally be equal to the bulk concentration. It is anticipated that whenever

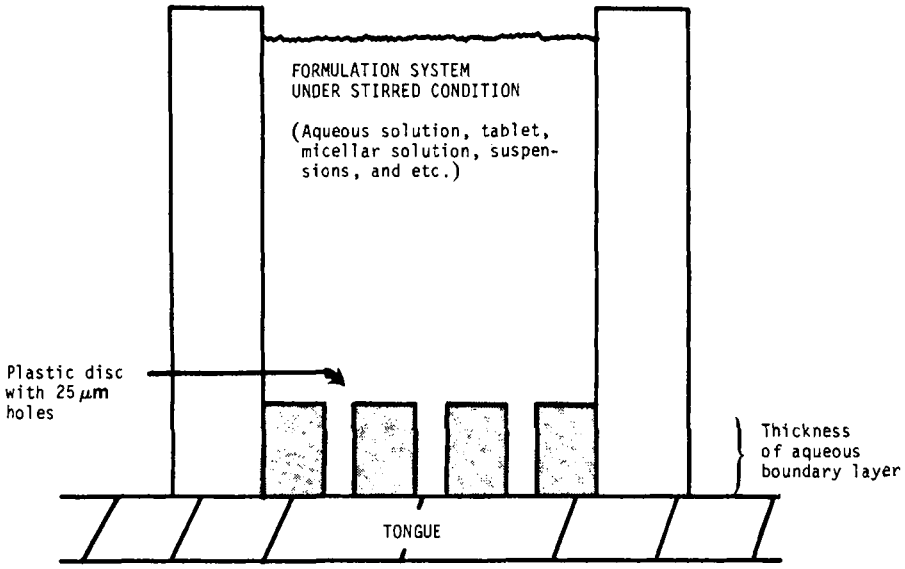


Figure 3—*Schematic diagram of a half-diffusion cell placed over an extended human tongue for psychophysical measurements under non-steady-state transport conditions.*

the concentration buildup at the membrane surface with time equals or exceeds the taste threshold concentration, response to taste occurs. Furthermore, initial taste perception is predicted to occur with high bulk concentrations, C_0, in contrast with lower bulk concentrations, all other factors (diffusion coefficients and aqueous boundary layer thickness) being constant.

DISCUSSION

Figure 1 shows the dimensionless concentration-distance profiles as a function of time for two aqueous boundary layer thicknesses, 100 and 250 μm, as generated from the numerical solution of Eq. 2 and the accompanying boundary conditions. The aqueous diffusion coefficient (D) used was 5×10^{-6} cm^2/s. The influence of the aqueous boundary layer is pronounced. For example, when $h = 100$ μm, the surface concentration is ~0.55% of the bulk concentration within 1 s; in contrast, when $h = 250$ μm, it is only $\sim 4 \times 10^{-6}$% of the bulk concentration. For the 100- and 250-μm boundary layer cases, the surface and bulk concentrations become equal in 80 and 500 s, respectively.

When the non-steady-state surface concentration is plotted against time for various bulk concentrations applied to the tongue, one obtains a family of sigmoidal curves (Fig. 2). Using a hypothetical taste threshold concentration as a point of reference one readily finds interesting relationships between the time at which taste is detected with bulk concentration and aqueous boundary thickness. The higher the bulk concentration, the quicker the detection time for a given diffusion layer thickness. Also, the thinner the diffusion layer, the quicker the detection time for a given bulk concentration. The pattern of the predictions is supportive of the everyday observation that taste is perceived within a fraction of a second after application of taste-provoking solutions at concentrations of at least an order of magnitude larger than the apparent threshold concentration.

In summary, the non-steady-state model provides the basis for the development of a novel experimental design in studying taste problems and for the understanding of the physicochemical factors in overcoming the undesirable taste of drugs *via* pharmaceutical formulations. Figure 3 shows a half-diffusion cell placed over the surface of an extended tongue. The principal feature of the cell is the bottom section which consists of straight cylindrical pores, 50 μm in diameter and of variable length. The pore length fixes the aqueous boundary thickness and may be used to experimentally increase the sensitivity of psychophysical measurements, recorded as the time at which taste is perceived after placing the drug formulation in the previously water-filled pores of the cell. Filling the pores with water before the formulation is placed in the cell fulfills the initial boundary condition for the non-steady-state transport psychophysical taste experiments. It is conceivable that molecular modification and physical formulation factors can be studied within the framework of the proposed experimental design and put on a quantitative and mechanistically interpretive plane. Studies along these lines are being planned.

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