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RESEARCH PAPER

Application of a Sensorial Response Model to the Design of an Oral Liquid Pharmaceutical Dosage Form

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ABSTRACT

In this paper, we discuss the application of a compartmental model to study the sensorial response, in terms of taste intensity versus time, in an oral solution for pharmaceutical use. The numerical model was developed from sensorial response curves obtained by a panel of three trained individuals. Parameter identification was carried out by means of a least-squares procedure that obtained the linear coefficients in the model by solving an exact linear least-squares problem conditional on the values of the nonlinear parameters for each iteration. Thus, nonlinear estimation was done in terms of the first-order kinetic parameters only, and ill-conditioning of the Hessian matrix present in these models was solved. Results of modeling for a set of formulations were used to determine the effects of various ingredients (sweeteners and an essence) on a baseline unflavored formulation of acetaminophen in a mixture of cosolvents. The first moment of the area under the curve of taste intensity versus time was found to be the best global indicator of taste for the purpose of product design. It was found that a mixture of sweeteners and an essence was the most efficient way of masking the bitter taste of this active ingredient.

Key Words: *Dosage form design; Nonlinear least squares; Parameter identification; Sensorial response model; Taste intensity.*

INTRODUCTION

This work presents a method for analysis of experimental results from time-intensity studies of flavor response that is applicable to the solution of flavoring problems encountered in the design of an oral liquid pharmaceutical dosage form. Data from sensorial response curves, which were obtained on an analog scale by a panel of trained individuals, were fed to a computer and analyzed by converting them to equivalent caffeine concentrations and fitting the measured data points to a mathematical model.

The model is based on first-order kinetics and its response is given as the sum of two exponential functions. These kinds of models have been widely applied in pharmacokinetic and biopharmaceutical studies (1). Application of a model to predict output from different design choices requires model capability to reproduce experimentally observed conditions (substance concentrations or response intensities). The model parameters are adjusted by the procedure of model calibration. This is carried out by processing one or more sets of input and output data with the help of a parameter estimation scheme.

The purpose of this work is to provide a rational basis for designing pharmaceutical products based on a sensorial response of flavor. Parameter estimation in compartmental models, which are given by superposition of exponential decay functions, usually presents severe ill-conditioning in the linear system of normal equations obtained in each iteration of the nonlinear least-squares method. Such strong interaction among parameters leads to failure in standard statistical packages. To overcome this problem, the nonlinear parameters were separated from the linear ones.

By fitting data from a set of formulations, several indicators were computed from the model parameters. The effect of various flavoring agents on global indicators of flavor response was determined. This technique is applicable to obtain an oral liquid dosage form of acetaminophen with a pleasant flavor from an initial bitter, unflavored formulation.

MODEL OF FLAVOR RESPONSE

Although the system of flavor perception is a very complex one, we considered in this work the main aspects that affect unpleasant flavor response in a time-intensity test for the purpose of design of a pharmaceutical oral dosage form. From this point of view, the flavor perception system can be represented schematically by a system of linear compartments. Release from each compartment follows first-order kinetics, that is, the instantaneous rate of release of a substance from the compartment is proportional to the amount of substance present in it. In the proposed model, input is given as a biophysical-chemical stimulus, and response is the neurological-psychological perception of flavor. Between these two end nodes, effects are transmitted first through the mouth cavity zone, in which mechanical and chemical interactions occur between the orally taken sample and the mouth, to a zone in which gustatory and olfactory sensors interact chemically and neurologically with the stimuli, producing the sensorial perception of flavor from the combined input signals. The global response is given as

$$I = b_1 e^{-a_1 t} + b_2 e^{-a_2 t} \tag{1}$$

where t is time, I is flavor intensity, a_1 and a_2 are kinetic rate constants, and b_1 and b_2 are intensity coefficients.

This model is linear in the parameters b_1 and b_2 and nonlinear in a_1 and a_2. Once the model parameters are estimated, the area under the curve A, the first area moment M, the centroid time t_c, the peak time t_p, and the peak intensity I_p are obtained as follows:

$$A = \frac{b_1}{a_1} + \frac{b_2}{a_2} \tag{2}$$

$$M = \frac{b_1}{a_1^2} + \frac{b_2}{a_2^2} \tag{3}$$

$$t_c = M/A \tag{4}$$

$$t_p = \frac{\ln\left(-\dfrac{b_2 a_2}{b_1 b_1}\right)}{a_2 - a_1} \tag{5}$$

$$I_p = b_1 e^{-a_1 t_p} + b_2 e^{-a_2 t_p} \tag{6}$$

EXPERIMENTAL MEASUREMENT

Sample Preparation

An initial unflavored baseline formulation was prepared with a bitter model drug (acetaminophen, 10% w/v) and a mixture of cosolvents (propyleneglycol 67% w/v, ethyl alcohol 10% w/v, distilled water 13% w/v). Flavored baseline formulations were obtained by adding sweeteners and mixtures of sweeteners as follows (Table 1): (*a*) sucrose 13% w/v, (*b*) sodium saccharin 1.7% w/v, (*c*) aspartame 1.7% w/v, (*d*) sucrose 6.7% w/v plus saccharin 0.8% w/v, (*e*) saccharin 0.8% w/v plus aspartame 0.8% w/v, (*f*) sucrose 6.7% w/v plus aspartame

Table 1

Formulation Ingredients Used in Compartmental Modeling

Formulation Ingredients	Formulations Without Banana Flavor	Formulation with Banana Flavor
Base formula (acetaminophen + cosolvents)	1	1E
Base formula + sucrose	2	2E
Base formula + sodium saccharine	3	3E
Base formula + aspartame	4	4E
Base formula + sucrose + sodium saccharine	5	5E
Base formula + sodium saccharine + aspartame	6	6E
Base formula + sucrose + aspartame	7	7E

0.8% w/v. A banana flavor (0.7% w/v) was added to some of the formulations to evaluate the effect of both ingredients. To account for the concentration of the new ingredient added to each formulation, the weight of water was decreased.

All the formulations were prepared by dissolving the active ingredient in the mixture of cosolvents. Afterward, an aqueous solution of sweeteners or a mixture of sweeteners was added; finally, the banana flavor was added. The final volume of the formulation was adjusted with distilled water. All the materials used in this work were pharmaceutical grade.

Panel Training

For comparative quantification, caffeine solutions were chosen as standard indicator solutions of bitter taste. Different concentrations of caffeine were associated to an analog scale according to the procedure described by Borodkin and Sundberg (2). Three panelists were trained with the above solutions to detect intensity of bitter taste.

Flavor Measurement

Samples with a fixed volume of 1 ml were swallowed immediately by three trained individuals, and time-intensity curves were plotted. The readings were taken immediately and at 12 intervals of 15 sec over a period of 3 min. A washout period with distilled water was used after each sample. A maximum test of four samples was done per session. The readings from the individual curves were averaged, then converted from the analog scale to equivalent caffeine concentrations.

PARAMETER IDENTIFICATION

In the parameter estimation procedure for the proposed model, parameter dependency is considered explicitly. For the sake of better understanding, some basic concepts of parameter estimation are presented in the following paragraphs. In its simplest form, the aim of the linear least-squares method is to fit a set of observed data points $x_{i1}, \cdots x_{im}, y_i$ to a model formed by a linear combination of m independent variables. The general form of this class of models is

$$\hat{Y} = \sum_{j=1}^{m} b_j x_j \tag{7}$$

Agreement between observed data and output from the model is measured by an *objective function*, defined as

$$F(\mathbf{b}) = \frac{1}{2}\|\mathbf{r}\|^2 \tag{8}$$

where $\|\mathbf{r}\|$ is the length of the residual vector $\mathbf{r}$, with n elements that are

$$r_i = y_i - \sum_{j=1}^{m} b_j x_{ij} \tag{9}$$

The solution is given by a system of m normal equations, which is expressed in matrix notation as:

$$\mathbf{Hb} = \mathbf{X}^T\mathbf{Xb} = \mathbf{X}^T\mathbf{y} \tag{10}$$

When the model depends nonlinearly on the set of m parameters, the general form is

$$\hat{y} = \hat{y}(\mathbf{x}, \mathbf{c}) \tag{11}$$

and minimization is carried out iteratively. Standard schemes for nonlinear least-squares estimation of param-

eters applied to compartmental models require initial values for all parameters and usually give rise to ill-conditioning of the normal equations. Fortunately, for the present model, it is possible to separate the nonlinear parameters (release constants) from the linear ones. The model takes the following form:

$$\hat{y} = \sum_{j=1}^{t} b_j u_j(t, \mathbf{a}) \tag{12}$$

where **a** is a vector of nonlinear parameters, and the elements of the **b** vector are the l linear parameters b_j. At each iteration of the nonlinear least-squares method, a linear least-squares problem is solved for the **b** vector, which is then expressed as a function of **a**. The objective function is then defined as

$$F(\mathbf{a}) = \frac{1}{2} \sum_{i=1}^{n} \left[y_i - \sum_{j=1}^{l} b_j u_j(t_i, \mathbf{a}) \right]^2 \tag{13}$$

The procedure is carried out as follows. First, initial values are assigned to the elements of the nonlinear parameter vector **a**. For the present case, this vector is formed by the two rate constants. Then, the vector of linear parameters **b** is obtained by linear regression on the nonlinear functions:

$$u_{ij} = u_j(t_i, \mathbf{a}) \tag{14}$$

For the case under study,

$$u_j = e^{-a_j t_i} \tag{15}$$

and

$$\frac{\partial u_{ij}}{\partial a} = -t_i e^{-a_j t_i} \tag{16}$$

A design matrix $\mathbf{U} = \{u_{ij}\}$ is constructed from the above nonlinear functions, and the Hessian matrix with respect to the linear parameters conditional on the nonlinear ones is computed as

$$\mathbf{H} = \mathbf{U}^T \mathbf{U} \tag{17}$$

Then, the normal equations are solved for **b**, and the residual vector **r** is computed. The Jacobian matrix **G** of the linear parameters with respect to the nonlinear ones is computed by the following expression:

$$\frac{\partial \mathbf{b}}{\partial a_k} = \mathbf{H}^{-1} \left[\left(\frac{\partial \mathbf{U}}{\partial a_k} \right)^T \mathbf{r} - \mathbf{U}^T \frac{\partial \mathbf{U}}{\partial a_k} \mathbf{b} \right] \tag{18}$$

The Jacobian matrix $\mathbf{W} = \{w_{ij}\}$ of **r** with respect to **a** is computed next as

$$w_{ij} = \frac{\partial r_i}{\partial a_j} \tag{19}$$

where the derivatives of **r** with respect to the nonlinear parameters are

$$\frac{\partial \mathbf{r}}{\partial a_k} = \frac{\partial \mathbf{U}}{\partial a_k} \mathbf{b} - \mathbf{U} \frac{\partial \mathbf{b}}{\partial a_k} \tag{20}$$

The reduced Hessian of F with respect to the nonlinear parameters is obtained as:

$$\mathbf{D} = \mathbf{W}^T \mathbf{W} \tag{21}$$

and the gradient of F with respect to **a** is

$$\mathbf{q} = \mathbf{W}^T \mathbf{r} \tag{22}$$

Details of the derivation of this scheme have been presented by Saavedra (3). For this work, the iterative nonlinear least-squares method was implemented by coupling the computation of the Hessian matrix **D** and the gradient **q** to the Marquardt algorithm, which has become a standard for these applications (4). Although least-squares minimization is performed by the Marquardt algorithm in terms of the nonlinear parameters only, the procedure as a whole consists of minimizing F with respect to a parameter vector:

$$\mathbf{c} = \begin{pmatrix} \mathbf{b} \\ \mathbf{a} \end{pmatrix} \tag{23}$$

At the minimum point, the joint Hessian matrix of F with respect to the complete vector of parameters **c** is computed as

$$\mathbf{A} - \begin{pmatrix} \mathbf{D} + \mathbf{G}^T \mathbf{H} \mathbf{G} & -\mathbf{G}^T \mathbf{H} \\ -\mathbf{H} \mathbf{G} & \mathbf{H} \end{pmatrix} \tag{24}$$

From the joint Hessian matrix **A**, standard errors of the parameters can be estimated using expressions derived from linear models (5) for approximate goodness-of-fit analysis. The nonlinear least-squares scheme with separation of parameters was successfully applied to parameter estimation for different formulations. For the proposed model, this scheme requires initial values for two nonlinear parameters only and shows faster convergence than widely used least-squares software.

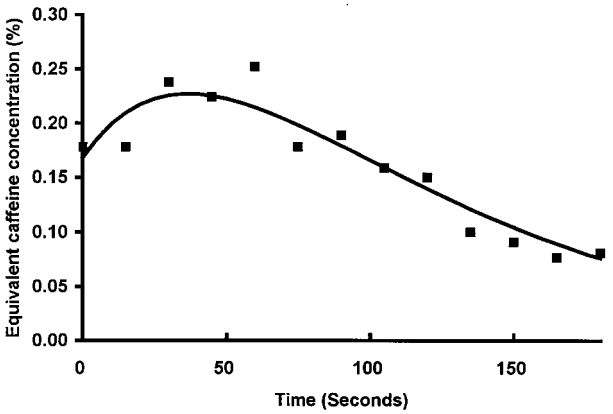

Figure 1. Measured and fitted time-intensity curve for baseline unflavored formulation.

RESULTS

Parameter estimation is applied to the global response of the compartments (i.e., the final response velocity of release [or time intensity]). The above scheme was applied to all of the measured data sets for the liquid formulations. Although convergence of the scheme is still dependent on two initial values of the nonlinear parameters, convergence was considerably faster in applying this scheme instead of commercial packages for nonlinear least squares. Figure 1 shows the measured and fitted data for the baseline unflavored formulation. Figure 2 shows the measured and fitted data for a formulation containing a mixture of sodium saccharine plus aspartame plus banana flavor. Tables 2 and 3 show the parameters in Eqs. 1 through 6 and the standard error S_r resulting from estimation for all tested formulations.

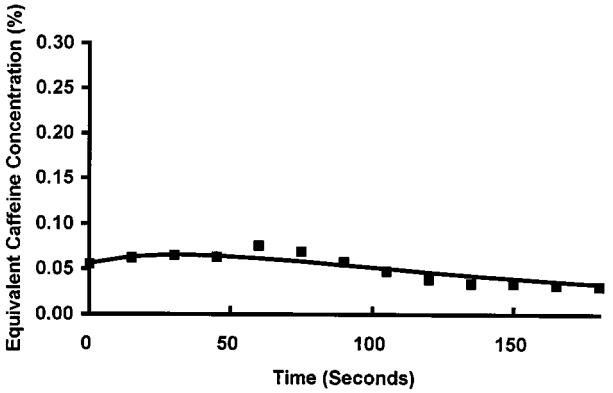

Figure 2. Measured and fitted time-intensity curve for formulation with sodium saccharine plus aspartame plus banana flavor.

In general, the value of a_1 is smaller for the formulations containing sweeteners and flavors. Since separate analysis of the four parameters does not give much information useful for formulation design, the areas, moments, peak intensity, centroid, and peak times were computed to find an indicator of the global effect of taste intensity.

The area under the curve *A* shows the flavoring capacity of several ingredients. In all cases with flavoring ingredients, it is smaller than that of the unflavored baseline formulation. However, there were formulations with relatively small area values that were considered inadequate because of their bitter aftertaste. The centroid time is a global indicator of flavor persistence in time. According to the results in Tables 2 and 3, the largest value belongs to a formulation containing a mixture of sodium saccharine plus banana flavor. This is related to the bitter aftertaste left by both additives. The formulation containing a mixture of sucrose and aspartame gave the smallest centroid time value, although this formulation gave the largest peak intensity value among the flavored formulations. In relation to the peak time, it could have a meaningless negative value, thus making this parameter useless for design purposes. Both time parameters t_c and t_p are related to the extent of bitter unpalatable taste, but do not give information about the intensity of taste by themselves. According to our results, the lower peak intensity was obtained with the formulation containing sodium saccharine plus aspartame plus banana flavor. In the group of formulations without banana flavor, the lowest value was obtained for the formulation containing sucrose as a sweetener.

It was found that the preference of the panelists corresponded to the smallest values of the area moment. Therefore, the first moment of area under the curve (extrapolated to infinity) was considered as the best global indicator of flavor for the purpose of formulation design.

CONCLUSIONS

Although the system of flavor perception is very complex, for the purpose of pharmaceutical oral dosage form design, we consider in this work, by means of a compartmental model, the main aspects that affect unpleasant flavor response in a time-intensity test.

Although this model does not aim to provide a complete representation of flavor physiology, it provides

Table 2

Best-Fit Parameters in the Compartmental Modeling for Formulations Without Banana Flavor

Formula	a_1	a_2	b_1	b_2	A	M	t_c	t_p	I_p	S_r
1	0.0135	0.0191	1.2765	−1.1086	36.31	3931.7	108.3	36.6	0.227	0.02126
2	0.0089	0.0266	0.1697	−0.0868	15.82	2023.8	127.9	24.0	0.091	0.00752
3	0.0097	0.0816	0.1978	−0.0863	19.35	2091.9	108.1	18.1	0.146	0.00923
4	0.0081	0.2148	0.1496	−0.0586	18.27	2297.7	125.7	11.3	0.131	0.01028
5	0.0098	0.0235	0.1874	−0.0653	16.32	1827.6	112.0	−13.2	0.124	0.01366
6	0.0100	0.0267	0.1240	−0.0177	11.71	1210.1	103.3	−58.0	0.138	0.00707
7	0.0125	0.0384	0.2894	−0.1473	19.28	1747.8	90.6	17.2	0.157	0.01256

Table 3

Best-Fit Parameters in the Compartmental Modeling for Formulations With Banana Flavor

Formula	a_1	a_2	b_1	b_2	A	M	t_c	t_p	I_p	S_r
1E	0.0135	0.0170	1.1531	−1.0921	21.20	2556.4	120.6	50.4	0.120	0.00760
2E	0.0089	0.0226	0.3279	−0.2263	26.73	3675.2	137.5	40.8	0.138	0.03155
3E	0.0051	0.0468	0.0961	−0.0541	17.76	3697.5	208.2	39.4	0.070	0.00960
4E	0.0089	0.0379	0.1499	−0.1012	14.09	1802.7	128.0	36.3	0.083	0.00987
5E	0.0066	0.0501	0.1157	−0.0553	16.54	2668.8	161.4	29.8	0.083	0.01309
6E	0.0057	0.0342	0.0942	−0.0380	15.32	2833.1	184.9	30.8	0.066	0.00759
7E	0.0076	0.0506	0.1490	−0.0778	18.11	2561.3	141.4	29.0	0.102	0.00973

some insight into relative time effects of flavoring ingredients. According to the model fit, an agreement was found between the tendency given by this model with the numerical values found for the kinetic rate constant a_1, which has a low value that corresponds to a first zone in which the chemical and physical interactions of the formulation vehicle with the oral cavity are produced, with a time scale in the order of usual taste intensity tests (i.e., about 3 min). In the case of the kinetic rate constant a_2, its larger value corresponds to a sensorial perception zone with combined gustatory and olfactory papillae, which has a response that has a shorter timescale.

The estimation procedure applied to this type of model provides a rational basis for evaluating the effects of flavoring ingredients. Extrapolation of the experimental time-intensity curves has been found adequate to represent the global effect of flavor, thus overcoming the problem of long and repetitive tests for a measurement using a panel of trained individuals as a data source.

The first area moment under the fitted time-intensity curve of bitter flavor, computed from the estimated parameters, is a valuable indicator for use in designing pharmaceutical oral dosage forms. It was found that formulations with small area moment values correspond to those formulations with a more palatable global flavor. The use of the area moment is encouraged for the procedure of optimizing the taste of formulations. To do so, it is necessary to take into account a balance between sweeteners and essences. For the presented case, banana flavor proved to be an efficient flavoring agent to be taken into account in the taste-masking process.

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