

IBUPROFEN PEDIATRIC SUSPENSION DESIGNED AND OPTIMIZED BY RESPONSE SURFACE METHODOLOGY

LĂCRĂMIOARA POPA, MIHAELA VIOLETA GHICA*

Physical and Colloidal Chemistry Department, University of Medicine and Pharmacy "Carol Davila", Faculty of Pharmacy, 6 Traian Vuia, 020956, Bucharest, Romania

**corresponding author: mihaelaghica@yahoo.com*

Abstract

Preparation and optimization of an ibuprofen suspension containing pharmaceutically accepted excipients of pediatric use were performed by a 3-factor, 2-level full statistical design completed with four central point replications. The effects of sucrose (sweetener), Tween 20 (surfactant) and methylcellulose (thickener) on the dispersion properties and on its rheological behaviour (sedimentation index, redispersability degree and viscosity at 100 rpm) were investigated. A second order model was evaluated by multiple regression and statistically tested for each of the studied formulation factors. The controlled and response variables were correlated using the three-dimensional response surfaces. To determine the validity of the regression models the optimum formulation was prepared and its properties determined. The experimental design and response surface methodology proved to be a reliable tool for the formulation and optimization of the named suspension.

Rezumat

Prepararea și optimizarea unei suspensii care conține ibuprofen alături de excipienți farmaceutici acceptați pentru utilizare la preparate pediatrice s-a realizat prin utilizarea unui plan factorial de trei variabile la două nivele de variație, completat cu patru replicări în punctul central. Au fost investigate efectul variabilelor: cantitatea de zaharoză (îndulcitor), cantitatea de Tween 20 (surfactant) și respectiv metilceluloză (agent de îngroșare), asupra comportamentului la redispersare și asupra profilului reologic (indicele de sedimentare, gradul redispersabilitate și vâscozitatea la 100 rpm). S-au elaborat, prin regresie multiplă și s-au evaluat statistic modelele regresionale de gradul doi pentru fiecare dintre factorii de formulare studiați. Variabilele controlate și variabilele de răspuns au fost corelate cu ajutorul suprafețelor de răspuns, tridimensionale. Pentru validarea modelelor regresionale, formularea optimă a fost preparată și s-au evaluat proprietățile acesteia. Programarea experimentelor și metodologia suprafețelor de răspuns s-au dovedit a fi instrumente fiabile în formularea și optimizarea suspensiei analizate.

Keywords: ibuprofen, Plackett-Burman factorial design, suspension optimization, response surface methodology.

Introduction

Ibuprofen is one of the most commonly used antipyretics in pediatrics. This drug also provides good postoperative analgesia for the treatment of children's pain and has well-established efficacy and safety

profiles when used in appropriate dosages. Adverse gastrointestinal or renal events for short-term use of ibuprofen appear to be quite rare for children. Patients having extreme ages, like children, often experience difficulty in swallowing solid oral dosage forms. For such patients the drugs are mostly provided in oral liquid dosage forms such as suspensions [1-3].

Due to the low relative stability and lack of solubility in water, it is important to develop an ibuprofen oral suspension by choosing an aqueous medium with appropriate pH in which the active drug can be suspended and remains stable. It is also necessary that the suspension pH is adjusted so that its buffering capacity inhibits the dissolution of ibuprofen in the human saliva, avoiding in this way its subsequent characteristic bitter taste [4]. That is why a formulation stability study of ibuprofen was performed as a preliminary research, to be able to obtain a suspension having the desired requirements – a liquid medium in which the drug has maximum stability. The pH value of such a medium was found to be 4.2.

The influence of various formulation factors in order to achieve an oral pediatric ibuprofen suspension with optimal properties was investigated in this paper. The suspension being a thermodynamically unstable disperse system in which the solid particles of the internal phase tend to aggregate and form sediment, the use of adjuvant agents to improve the moisturizing and dispersion of ibuprofen as well as the increase of viscosity of the continuous media are required. Acting on the characteristics and properties of both the particles and their interaction in the dispersal medium, the obtaining of the product with good stability is expected. The rapid sedimentation of the drug being undesirable, the last aspect of the preparation is related with the relative proportions of the constituents [4]. The modeling and optimization of oral ibuprofen suspensions were realized using an experimental design approach which gives high quality information [5].

Materials and Methods

There were used ibuprofen, methylcellulose, tween 20, sucrose, citric acid, sodium citrate of analytical or pharmaceutical grade obtained from Merck.

The suspensions were prepared as follows: a certain amount of sweetener (sucrose) was dissolved into an appropriate amount of buffer solution (citric acid/sodium citrate). The thickener agent (methylcellulose) was subsequently added and stirred until it was completely hydrated. Ibuprofen (1% for all formulated suspensions) was then dispersed in the presence of a surfactant (tween 20) and added to the previous mixture.

Buffer components were used to adjust the pH of suspension to 4.2 at which ibuprofen is stable and almost insoluble, as our preliminary studies demonstrated. The pH of the suspensions was measured using a digital pH-meter Oakton.

They were stored in measuring glasses at room temperature (25°C) for a week in order to perform the sedimentation analysis.

The rheological properties of the suspensions were studied with a rotational viscometer Multivisc (Fungilab).

Experimental Design

A 2^3 Plackett-Burman factorial design was chosen in order to evaluate the effect of the significant formulation factors and of their interaction on suspension properties and the levels of these factors needed to produce an optimal pediatric suspension. The factorial design was completed with four replications in the center of the design for establishing the experimental errors and validate the model. The three independent variables investigated are the concentrations of sucrose (X_1 %), tween 20 (X_2 %), and methylcellulose (X_3 %) [6-8]. The levels of the factors were selected such as their relative differences have a detectable effect on the response. A guide in choosing these levels is the consideration of the extremes of their useful ranges and their practical application. The effect of the previously mentioned variables was examined on the following system responses: Y_1 (%) – sedimentation index measured 1 week after preparation and determined as the ratio between the volume of sediment and the original volume of the suspension; Y_2 (%) – the easiness of redispersability measured after the same time (the stored suspension in a measuring cylinder was inverted by 180°C and the number of inversion necessary to restore a homogeneous system was determined: one inversion was considered 100% easiness of redispersability and every additional inversion decreased this percentage by 5%); Y_3 (cP) – the viscosity of the suspension 24 h after the preparation, measured at 100 rpm and 25°C [8].

To obtain a suspension with adequate properties (dispersion and viscosity), the sedimentation index must be minimal, but the easiness of redispersability and the viscosity has to be maximal.

A non-linear computer-generated quadratic model corresponding to the following second order equation was built to describe the system responses:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2 \quad (1)$$

where Y is the measured response (dependent variables) associated with each level factor combination, X_1 to X_3 are the independent variables and b – coefficients calculated by multiple regression analysis [9]. The results were computed with Statistica™ Statsoft 6.0 program.

The factorial matrix and the experimental results for all the twelve experiments are presented in Table I.

Table I
Factorial experimental design and the resulting response values

Susp. no.	Coded variable level			System responses		
	X_1	X_2	X_3	Sedimentation index (%)	Easiness of redispersability (%)	Viscosity (cP)
1. (S_1)	-1	-1	-1	12.80	75	14.24
2. (S_2)	+1	-1	-1	7.20	90	14.88
3. (S_3)	-1	+1	-1	16.00	85	12.32
4. (S_4)	-1	-1	+1	16.40	60	13.64
5. (S_5)	+1	+1	-1	8.00	80	8.96
6. (S_6)	+1	-1	+1	15.20	95	24.32
7. (S_7)	-1	+1	+1	11.60	65	46.00
8. (S_8)	+1	+1	+1	18.00	90	24.00
9. (S_9)	0	0	0	11.60	80	26.80
10. (S_{10})	0	0	0	12.40	85	25.00
11. (S_{11})	0	0	0	12.00	80	22.30
12. (S_{12})	0	0	0	11.20	90	23.80

Translation of coded levels in actual units

Coded level	-1(low)	0 (medium)	+1 (high)
X_1 : sucrose (%)	15	22.5	30
X_2 : tween 20 (%)	0.10	0.30	0.50
X_3 : methyl cellulose (%)	0.50	0.75	1.00

Results and discussion

The experimental data obtained (Table I) have been the subject of a multiple regression in view of determining the second order predictor polynomial equation. These equations constituted the full regressional model, but after statistical evaluation (ANOVA), the reduced regressional model was obtained for each dependent variable (equations 2-4).

$$Y_1 = 0.09X_1 + 0.06X_2 + 2.63X_3 + 0.81X_1X_3 - 1.70X_3^2 \quad (2)$$

($r = 0.982$, $p = 0.0011$, $F_{(5,7)} = 38.04$)

$$Y_2 = 0.86X_1 + 3.42X_2 + 3.16X_3 + 2.10X_1X_2 + 1.67X_1X_3 - 5.00X_2X_3 - 2.60X_3^2 \quad (3)$$

($r = 0.998$, $p = 0.004$, $F_{(7,5)} = 32.64$)

$$Y_3 = 0.32X_1 + 0.22X_2 + 1.16X_3 + 0.52X_1X_3 + 0.16X_3^2 \quad (4)$$

($r = 0.957$, $p = 0.0005$, $F_{(5,7)} = 15.35$)

The above equations indicate the quantitative effects of the process variables and their interaction on the system responses. The values of the coefficients X_1 , X_2 and X_3 are associated with the effect of these variables on response. Coefficients with more than one factor represent an interaction effect, whereas those with higher order terms designate quadratic relationships. But compared with the coefficients of X_1 and X_2 , the coefficient for interaction term is quite small, indicating it as a less important factor in affecting the system responses [10]. The greatest number of terms appears in polynomial equation for Y_2 (easiness of redispersability), confirming that this parameter is strongly influenced by all the formulation selected factors. From the quadratic terms of the reduced regression model only the term X_3^2 is retained, this illustrating the quadratic variation of all system responses with methylcellulose as viscosity inductor agent. It must be also mentioned that the interactions between X_1 and X_3 factors appear for all regressional models. The formulation variable X_2 (tween 20) is contained by the final form of the predicting equations in linear terms and has a positive influence on the system responses Y_2 and Y_3 values, and a negative influence on the Y_1 value; the interaction of this variable with the other ones is negligible in system responses Y_1 and Y_3 .

The relationship between the dependent and independent variables is further illustrated using the response surfaces, which enable the visual checking of these effects in the three dimensional space [11-12]. The curvature in the response surfaces represents the contribution of the quadratic terms. Figures 1-4 present some examples of three-dimensional response variables together with the level curves (iso-responses) as functions of two independent variables.

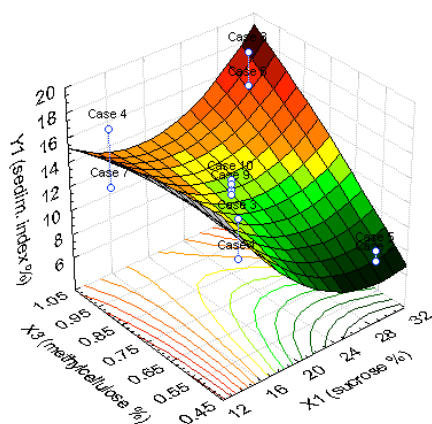


Figure 1

Response 3D surface and levels of iso-response contour for variable Y_1 versus X_1 and X_3

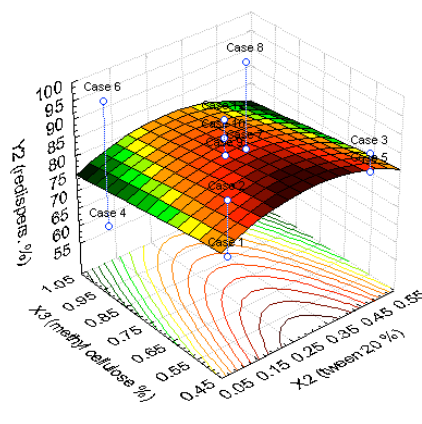
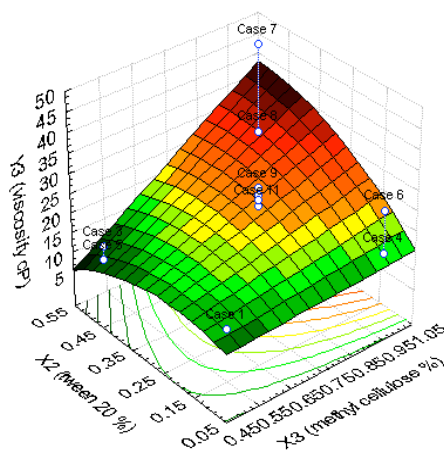
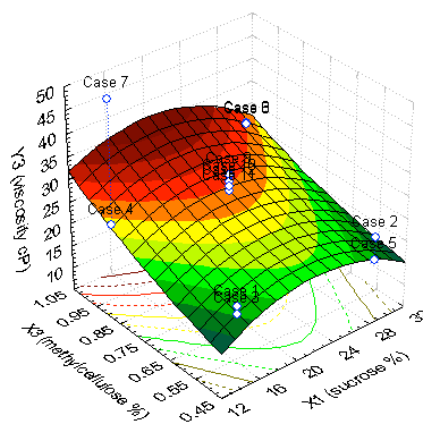


Figure 2

Response 3D surface and levels of iso-response contour plot for variable Y_2 as a function of X_2 and X_3

**Figure 3**

Response 3D surface and levels of iso-response contour plot for variable Y_3 in function of X_2 and X_3

**Figure 4**

Response surface (3D) and levels of iso-response contour plot for variable Y_3 versus X_1 and X_3

Analyzing the response surface model, the variation ranges for each independent variable, respectively their combination having as result the optimal responses can be established.

As it can be seen from the figures, the sedimentation index reaches minimum values for medium and high percentages of sucrose, and low and medium percentage of methylcellulose. The response parameter Y_2 reaches high values for tween 20 medium level, and low and medium content of methylcellulose. The global viscosity of the analyzed suspensions reaches maximum values for high tween 20, medium and high methylcellulose levels and medium sucrose content. A high viscosity for the oral suspensions implies a reduced sedimentation index but a difficult redispersion.

Concluding, the optimal values for the concentrations of independent variables are: sucrose – $22.5 \div 30.0\%$, tween 20 – $0.30 \div 0.50\%$ and methylcellulose – 0.75% .

For the higher extreme values, 30% sucrose and 0.5% tween 20 respectively, and 0.75% methyl cellulose, the application of the predicting polynomial equations gives: $Y_1 = 21.97\%$, $Y_2 = 95.61\%$ and $Y_3 = 22.37$ cP, values considered to be optimal. This theoretically obtained formulation of suspension does not appear in the factorial experimental matrix. The suspension corresponding to this formulation has been prepared and tested in the same conditions as all the other 12 formulations from table I. The values of this optimal formulation of oral pediatric ibuprofen suspension for

the easiness of redispersability, sedimentation index and viscosity determined experimentally are: 22.65%; 95% and 24.52 cP, respectively.

Conclusions

The composition of an oral ibuprofen suspension for pediatric use was designed using as experimental strategy a 2^3 Plackett-Burman factorial matrix with four replications, completed with response surface methodology, considering the main factors affecting its stability and rheological properties: concentrations of sucrose, tween 20 and methylcellulose and their interaction. The validity of the regressional models was verified by the determination of the properties of the suspension having the theoretically obtained optimal composition: easiness of redispersability, sedimentation index and viscosity.

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