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COMMUNICATION

Statistical Optimization of a Sustained-Release Matrix Tablet of Lobenzarit Disodium

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ABSTRACT

The statistical optimization of sustained-release matrix tablets of lobenzarit disodium salt (LDS) was performed using the central composite experiment design 2^3 *for three independent variables: the amount of polymer (Eudragit® RS-PO)* AP, *the total volume of granulation solvent* VS, *and the amount of filler (microcrystalline cellulose)* CE. *The* $t_{90\%}$ *was selected as the response variable. The response surfaces were performed from a statistical mathematical model. The optimal formulation was obtained for the variables (*AP = *15 mg*, VS = *60 μl, and* CE = *0).*
Key Words: *Controlled release; Lobenzarit disodium; Matrix tablets; Optimization.*

INTRODUCTION

The lobenzarit disodium salt (LDS) exerts a prophylactic or therapeutic effect against spontaneously developed arthritis and nephritis, improving immunology abnormalities due to its regulatory effect on the antibody-producing system (1–3). A preformulation study of LDS was carried out and was discussed previously (4). In previous studies, wet granulation using Eudragit® RS-PO as the polymer was selected as the initial technology for the preparation of inert matrices (5,6).

The objective of the present study was to optimize the formulation of a matrix tablet for the controlled release of LDS. The central composite experiment design (7) was used, selecting three independent variables. The time necessary for the dissolution of 90% of the drug dose $t_{90\%}$

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was selected as the response variable. Response surfaces were performed from statistical mathematical models.

EXPERIMENTAL

Materials

Lobenzarit disodium, 2-[(2-carboxyphenyl)amino]-4-chlorobenzoic acid disodium salt, prepared in the Synthesis Laboratory of the Center of Pharmaceutical Chemistry (Havana, Cuba), was employed as the raw material (8). The polymeric matrix-forming material employed was Eudragit RS-PO (Hülls, Barcelona, Spain); microcrystalline cellulose MC-102 was used as filler (Blanver Farmoquímica LTDA, Brazil); and magnesium stearate (Química Sintética S.A., Madrid, Spain) was the lubricant.

Factorial Design

The independent variables for the composite central design 2^3 were the amount of polymer Eudragit RS-PO *AP*, the total volume of granulation solvent (isopropanol:acetone 3:2) *VS*, and the amount of microcrystalline cellulose *CE*. After the dissolution assay, $t_{90\%}$ was used as the response parameter. A second-order model was established for the response variable (see Eq. 1). The model's fit and the coefficient's significance were evaluated by Fisher and Student *t* criteria, respectively (9).

$$t_{90\%} = b_1 AP + b_2 VS + b_3 CE + b_{12} AP \times VS + b_{13} AP \times CE + b_{23} VS \times CE + b_{11} AP^2 + b_{22} VS^2 + b_{33} CE^2 \quad (1)$$

Preparation and Evaluation of the Matrices

The studied formulations (see Table 1) were assayed at least in duplicate, and three replicates were performed in the plane center. The LDS dose was kept constant (150 mg). LDS and filler were mixed for 15 min before the addition of the solution of Eudragit. The granulates were screened, dried at 57°C (15 min), and sieved again adequately. Finally, magnesium stearate was incorporated, and compression was carried out in a rotary machine (Ronchi model MP-8, Milan) with PBR 5/16 punches. The weight (Sartorius model MC), hardness (Monsanto durometer), and thickness (micrometer Ronchi-Milan) were measured, and the disintegration was evaluated (Erweka, type ZT 3-3) using artificial gastric medium without enzymes ($n = 6$).

Table 1

Composition of the Studied Formulations

Lot	*AP* (mg)	*VS* (µl)	*CE* (mg)	Tablet Weight (mg)
1	12	60	0	164
2	18	60	0	170
3	12	144	0	164
4	18	144	0	170
5	12	60	18	182
6	18	60	18	188
7	12	144	18	182
8	18	144	18	188
9	13.5	102	9	174.5
10	16.5	102	9	177.5
11	15	81	9	176
12	15	123	9	176
13	15	102	4.5	171.5
14	15	102	13.5	180.5
15	15	102	9	176

AP = amount of acrylic polymer; *VS* = volume of solvent; *CE* = amount of microcrystalline cellulose.

Dissolution Assay

The dissolution study ($n = 6$) was carried out using the USP 23 apparatus (Erweka DT-6) at 37°C ± 0.5°C and 75 rpm in 900 ml of distillate water. The aliquots (3 ml) were withdrawn for 12 hr. The samples were diluted and analyzed using a digital spectrophotometer (Kontron type UVIKON 930) at 299 nm. A calibration curve was performed for the determination of LDS using the standard solutions (5, 10, 15, 20, and 25 mg/L) prepared by diluting the stock solution (1 g/L LDS) with water. The precision of the test was evaluated in two samples of LDS (8.5 and 18.5 mg/L). The Cochram test, the standard deviation (SD), and the ponderate coefficients of variation (CV) were calculated. Three mathematical models (zero order, logarithmic, and Higuchi) were used to study the release process. The fitness was estimated by linear regression (10).

RESULTS AND DISCUSSION

Technologica1 Characterization

Table 2 shows the results of the technological characterization of the tablets. The relative error of the measured properties was always below 7%. The studied tab-

Table 2

Technological Properties of the Tablets and $t_{90\%}$ Values Calculated Using the Higuchi Equation

Lot	W ± SD (mg), $n = 10$	H ± SD (mm), $n = 10$	Hd ± SD (kgf), $n = 5$	$t_{90\%}$ (hr)
1	166.62 ± 2.23	2.54 ± 0.01	7.0 ± 0.79	9.87
2	168.60 ± 5.0	2.32 ± 0.06	13.0 ± 1.2	11.24
3	163.90 ± 2.1	2.31 ± 0.05	11.7 ± 4.6	10.82
4	174.35 ± 3.67	2.58 ± 0.10	10.4 ± 1.5	9.11
5	181.63 ± 2.63	2.56 ± 0.03	7.6 ± 1.08	8.08
6	185.20 ± 4.2	2.40 ± 0.16	5.2 ± 0.07	3.39
7	183.80 ± 1.13	2.36 ± 0.06	11.3 ± 1.0	9.45
8	188.73 ± 2.78	2.79 ± 0.08	7.0 ± 1.29	8.18
9	173.10 ± 1.72	2.36 ± 0.06	12.2 ± 1.35	9.94
10	178.70 ± 2.31	2.45 ± 0.05	>15	11.19
11	175.30 ± 1.82	2.35 ± 0.03	12.3 ± 0.08	11.14
12	176.30 ± 0.48	2.42 ± 0.04	13.0 ± 0.9	10.50
13	171.50 ± 3.2	2.30 ± 0.06	13.0 ± 0.3	10.62
14	181.50 ± 0.70	2.49 ± 0.01	12.5 ± 1.23	10.95
15	176.30 ± 1.56	2.42 ± 0.05	13.1 ± 0.52	10.64

W = tablet weight; H = tablet height; Hd = Hardness.

lets exhibited satisfactory technological properties, with the exception of lot 6, which had lower hardness and disintegrated partially in 1 hr.

Dissolution Assays

Regression analysis of the calibration curve [$y = (37.086 \pm 0.936)x - (0.00686 \pm 0.01671)$] for the spectrophotometric analysis of LBD in the studied concentration range gave $r = 0.99936$ as the correlation coefficient ($n = 12$) and a CV (response factors) of 3.32%. The Cochram test showed that the drug concentration does not have a significant influence on the variance of the results ($G_{tab} = 0.975$ and $G_{exp} = 0.6717$), so the pondered SD = 0.009327 and pondered CV = 1.43% have been calculated. The last value, far below the required one (3%), confirms the repeatability of the test (11). The excipients are not soluble in water, ensuring the selectivity of the method.

All the assayed formulations released 90% of LDS during the first 12 hr, indicating an adequate release of the drug. On the other hand, no tablet (except lot 6) disintegrated before the end of the dissolution assay. With respect to the three studied kinetic models, higher correlation values were obtained in all cases for the Higuchi model, indicating a diffusion-controlled release process (12). Therefore, the $t_{90\%}$ were calculated on the basis of the Higuchi model (see Table 1). Equation 2 summarizes the obtained model. The amount of polymer *AP* and filler *CE* have been shown to exert a great influence on the response variable. A correlation coefficient of 0.9938 was been obtained.

$$t_{90\%} = 1.4052\,AP + 0.4076\,CE - 0.0258\,AP \times CE + 0.0019\,VS \times CE + 0.0466\,AP^2 - 0.0206\,CE^2 \quad (2)$$

Influence of the Significant Variables

The influence of the polymer concentration in the formulations without microcrystalline cellulose was analyzed from lots 1 to 4. The $t_{90\%}$ values for lots 1 and 3 were similar, but the fit to the Higuchi model was slightly higher for formulation 1 ($r = 0.99$) than for lot 3 ($r = 0.96$). Technological problems were found for the preparation of lot 3 (high solvent volume), so that an additional drying step was necessary for this lot. Lot 4 did not release the drug dose in 12 hr. On the other hand, lot 2 exhibited the highest $t_{90\%}$ value and showed no technological problems. For lots without filler, the appropriate solvent volume was lower than 144 µl. Furthermore, a polymer concentration of 11% w/w (lot 2) led to better results than 7% w/w (lot 1).

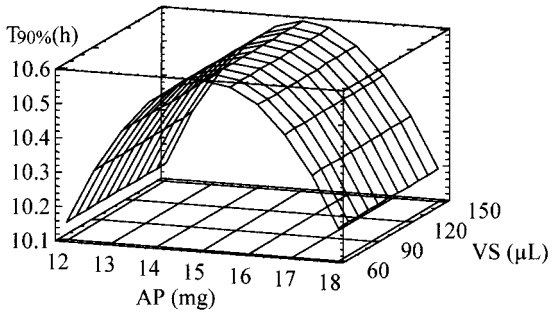

Figure 1. Response surface for $t_{90\%}$ as a function of the amount of polymer Eudragit RS-PO *AP* and the volume of solvent *VS* employed.

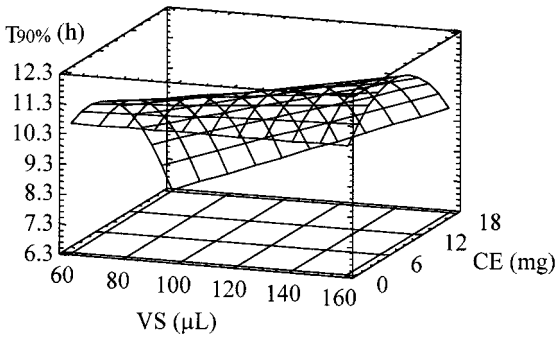

Figure 3. Response surface for $t_{90\%}$ as a function of the volume of solvent *VS* and the amount of microcrystalline cellulose *CE* employed.

The influence of the polymer concentration in formulations with filler was analyzed in lots 5 to 8. A similar release behavior was found for lots 5, 7, and 8; nevertheless, the drug release rate was significantly higher for lot 6, showing the lowest $t_{90\%}$ value. The low volume of solvent employed (60 μl) was not sufficient for wetting the high amount of solid (≅190 mg). For this reason, an optimum grade of agglutination was not achieved, and the tablets showed bad technological properties (low hardness, high friability, fast disintegration) and not controlled drug release.

Generally, lower $t_{90\%}$ values were obtained from the matrices containing cellulose. This fact can be attributed to the high porosity of this material, which can lead to faster water uptake (13).

On the other hand, Figs. 1 to 3 show the response surfaces for $t_{90\%}$ as a function of *AP* and *VS* (Fig. 1), *AP* and *CE* (Fig. 2), and *VS* and *CE* (Fig. 3). From the analysis of the response surfaces and taking into account the total cost of raw materials in a tablet, the optimal formulation contains 15 mg of polymer and was prepared with 60 μl of solvent without cellulose. This formulation has $t_{90\%}$ = 10.6 hr, and its total cost is 1.6 times lower than the cost of the formulation with higher $t_{90\%}$ (11.5 hr).

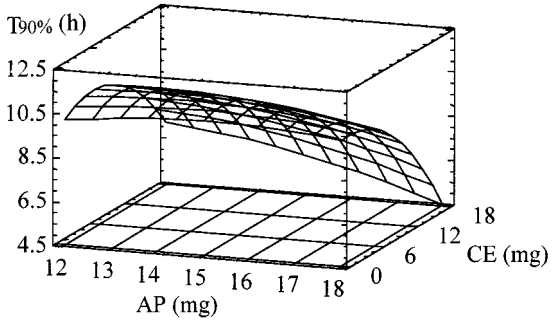

Figure 2. Response surface for $t_{90\%}$ as a function of the amount of polymer Eudragit RS-PO *AP* and microcrystalline cellulose *CE* employed.

CONCLUSIONS

Greater $t_{90\%}$ values were achieved for the formulations without microcrystalline cellulose. Therefore, this filler must be suppressed or used in a lower concentration. The statistical study and response surfaces showed that the optimal formulation, according to its $t_{90\%}$ value and its cost, corresponds to the following values of the independent variables: *AP* = 15 mg, *VS* = 60 μl, and *CE* = 0.

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