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COMMUNICATION

Evaluation of Eudragit® RS-PO and Ethocel® 100 Matrices for the Controlled Release of Lobenzarit Disodium

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ABSTRACT

Lobenzarit disodium is a drug for the treatment of rheumatoid arthritis. In this work, inert matrix tablets of lobenzarit disodium were prepared by direct compression using Ethocel® 100 and Eudragit® RS-PO as polymeric materials in different ratios. The obtained powder mixtures and tablets were evaluated from the rheological and technological points of view. The dissolution test was performed to evaluate the in vitro release kinetic of the matrices. The obtained dissolution profiles demonstrated that the matrices containing Eudragit RS-PO showed a slower release rate and therefore were more suitable for controlling the release of drug. The fit to the Higuchi model indicates that the drug release mechanism from these matrices was controlled by the diffusion step.

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INTRODUCTION

The formulation of drugs as inert matrix systems is one of the methods used to achieve the sustained release of drugs. Its main advantages are the simple and fast technology, low cost, and low influence of the physiological variables on its release behavior (1).

Lobenzarit disodium (disodium 4-chloro-2,2′-iminodibenzoate) is a drug conceived for the treatment of rheumatoid arthritis. It exerts a prophylactic or therapeutic effect against spontaneously developed arthritis and nephritis. This drug produces an improvement of immunological abnormalities and has a regulatory effect on the antibody-producing system (2–4). Its pharmacokinetics and dosage characteristics (usually three doses per day), as well as the adverse gastric reactions (anorexia, stomach discomfort, stomachaches, gastritis, nausea), make it a suitable candidate for the design of controlled-release delivery systems (5). A preformulation study of this drug was carried out previously (6,7). The results obtained established that lobenzarit disodium is a good candidate for inclusion in oral sustained-release dosage forms. The differential scanning calorimetry (DSC) technique was used to evaluate the compatibility between lobenzarit disodium and different polymeric materials. Eudragit® RS-PO and Ethocel® were selected as suitable polymeric excipients for preparing inert matrices.

The aim of this work is to investigate the feasibility of controlling the release of lobenzarit disodium using a matrix-type drug delivery system. For this purpose, Ethocel 100 and Eudragit RS-PO were selected as matrix-forming polymeric materials. The influence of the polymer concentration in the tablets was also investigated. The in vitro drug release profiles of the matrices are evaluated, and its release mechanism is studied.

EXPERIMENTAL

Materials

Lobenzarit disodium was employed as the raw material (Synthesis Laboratory of the Center of Pharmaceutical Chemistry, Cuba). The polymeric materials used were Ethocel 100 (Dow Chemical, E-Barcelona) and Eudragit RS-PO (Hüls, E-Barcelona).

Procedures

The dose of lobenzarit disodium to be incorporated in the formulations was calculated using the method described in the literature (8). The following pharmacokinetic parameters were taken into account: C_p = 15.845 μg/ml; V_d = 5.04 L; D_b = 80 mg; $t_{1/2}$ = 9.4 hr; t = 12 hr. The total dose of drug calculated was 150 mg.

Six binary mixtures containing drug and 40%, 50%, and 60% of each polymer (Ethocel 100 and Eudragit RS-PO) were prepared in a V mixer (15 min) (Table 1). The main rheological parameters of these mixtures were calculated to study the rheological properties of the prepared powder mixtures and to predict the possibility of using a direct compression method to obtain the tablets.

To determine the bulk density of the powders, 50.0 g of the mixtures were put into a 100-ml graduated cylinder. The bulk density was calculated from the volume occupied by the solid. The tapped density was calculated from the final volume of the solid after three series of 500 percussion.

The Haussner's index (HI) and the percentage of compressibility (%C) were calculated using equations described in the literature (9). The angle of repose was calculated using 10.0 g of the solid. The funnel was placed 10 cm from the plane surface (9).

Tablets were prepared by direct compression. The mixing time of the tablet components was 15 min. The matrix tablets were formulated to contain 150 mg of lobenzarit disodium. The percentile composition and theoretical tablet weight are also shown in Table 1. Approximately 50 tablets were prepared for each lot in an eccentric machine (Bonals A-300) using the maximum compression force accepted by the formulations.

The weight variation of 10 tablets of each lot was evaluated using an electronic balance (Mettler, type AE-50). Hardness was measured on 5 tablets using a Schleuniger durometer (2E/205). Thickness of 10 tablets was evaluated using a precision micrometer (Export-Pel). Disintegration time was measured for 6 tablets, during 2 hr, in a disintegration apparatus (Erweka DT-6) using artificial gastric medium without enzymes.

The dissolution assay of the formulations was carried out in duplicate in the USP XXIII apparatus (Turu Grau, model D-6) at 37°C ± 0.5°C at 75 rpm and with 900 ml of distilled water as the dissolution medium. The amount of lobenzarit disodium released was detected using a conductivity meter (Crison CM-2201) linked to a chart recorder and a personal computer.

A calibration curve was performed for the conductometrical method using the following standard solutions: 5.95×10^{-6} M, 2.97×10^{-5} M, 1.48×10^{-4} M, 2.97×10^{-4} M, 4.52×10^{-4} M, 5.95×10^{-4} M, 7.44×10^{-4} M. and 8.93×10^{-4} M. Accuracy and precision parameters were also evaluated (6,7).

Table 1

Composition (Percentage w/w), Physical Characterization of the Powder Mixtures, and Technological Characteristics of the Prepared Tablets (Mean ± SD)

	Lot 1	Lot 2	Lot 3	Lot 4	Lot 5	Lot 6
LD (%)	40	50	60	40	50	60
E. 100 (%)	60	50	40	—	—	—
E. RS-PO (%)	—	—	00	60	50	40
Th. weight (mg)	375	300	250	375	300	250
Weight (mg	372.2 ± 2.5	298.4 ± 2.3	250.1 ± 1.2	370.8 ± 0.4	288.3 ± 2.2	247.8 ± 2.5
Thickness (mm)	5.0 ± 0.001	3.5 ± 0.008	3.2 ± 0.001	5.1 ± 0.002	3.5 ± 0.004	3.1 ± 0.001
Hardness (kp)	10.5 ± 0.6	7.2 ± 0.6	5.0 ± 0.5	9.3 ± 0.2	7.6 ± 0.3	6.5 ± 0.9
BD (g/cm^3)	0.46 ± 0.005	0.46 ± 0.002	0.50 ± 0.001	0.60 ± 0.003	0.58 ± 0.005	0.58 ± 0.002
TD (g/cm^3)	0.58 ± 0.001	0.60 ± 0.001	0.62 ± 0.002	.08 ± 0.001	0.71 ± 0.003	0.74 ± 0.002
HI	1.26 ± 0.20	1.30 ± 0.25	1.24 ± 0.60	1.33 ± 0.52	1.22 ± 0.30	1.27 ± 0.12
% C	20.7 ± 0.001	23.3 ± 0.002	19.3 ± 0.003	20.0 ± 0.003	18.3 ± 0.005	21.6 ± 0.002
AR (°)	27.2 ± 0.40	28.0 ± 0.30	25.9 ± 0.25	29.7 ± 0.32	30.4 ± 0.26	30.6 ± 0.30

LD = Lobenzarit disodium; E. 100 = Ethocel® 100; E. RS-PO = Eudragit® RS-PO; Th. weight = theoretical weight; BD = bulk density; TD = tapped density; HI = Haussner's index; AR = angle of repose.

Three mathematical models were used to study the drug release process: zero order, first order, and Higuchi (10). Linear regressions were used to study the fitness of the release data.

RESULTS AND DISCUSSION

The results obtained in the physical characterization of the different mixtures are shown in Table 1. Taking into account the strong relationship of the angle of repose, the compressibility, and the Haussner's index with the flow properties of the drug (11,12), it can be concluded that the prepared mixtures have suitable flow properties. On the basis of these results, the direct compression method was selected to prepare the tablets.

The technological characteristics of the prepared tablets are shown in Table 1, which summarizes the values obtained for weight, thickness, and hardness. The tablets presented adequate physical and mechanical properties with low standard deviations. For all the lots, the disintegration time was longer than 2 hr. These results indicate that both polymeric materials are able, in the first instance, to produce true matrices.

Regression analysis of the calibration curve for the conductometrical analysis of lobenzarit disodium in the studied concentration range of $y = (3350.73 \pm 12.54)x - (-0.3168 \pm 3.9181)$ gave $r = .9999$ as the correlation coefficient ($n = 8$) and a Snedecor F value of 71366.8 ($P < .0001$). These data, as well as the results from the previously published validation study of this method (7) that gave precision values of 0.59% ($n = 20$), indicate the adequate linearity, precision, and accuracy of the conductivity assay.

To know if the assayed tablets are true inert matrices, their integrity during the 12-hr release assay was investigated. The release kinetic of lobenzarit disodium from the prepared tablets was studied according to the method indicated previously. Each assay was carried out in duplicate. The amounts of lobenzarit disodium released were calculated using the previously mentioned calibration curve.

Influence of the Type and Concentration of Polymer

Tablets containing Ethocel 100 were disintegrated before the end of the 12-hr release, with the disintegration times of 9 hr, 8 hr, and 5 hr for lots 1, 2, and 3, respectively. These results indicate that, at the assayed concentrations, this polymer does not form a true inert matrix. The tablets prepared with Eudragit RS-PO exhibited different results. The tablets corresponding to lot 6 were disintegrated in 6 hr of dissolution assay. None of the tablets corresponding to lots 4 and 5 were dissolved during the 12-hr dissolution assay. This behavior indicates that, in both cases, true matrices were obtained. Furthermore, these results show that an Eudragit RS-PO content of at least 50% w/w is necessary to obtain true inert matrices with a nonerodible excipient carcass that controls the drug release.

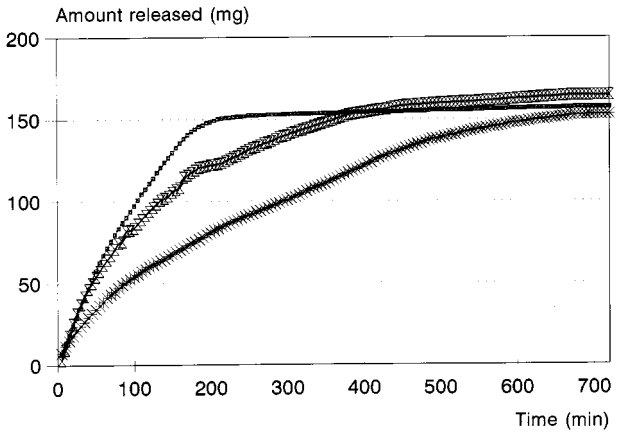

Figure 1. Release profiles of lobenzarit disodium–Ethocel 100 matrices.

From the point of view of percolation theory (12,13), this behavior can be attributed to the existence of a percolation threshold of the polymer between 40% and 50% w/w of Eudragit RS-PO, that is, below these concentrations, only finite clusters of the insoluble excipient are obtained. Therefore, when the drug is dissolved, the excipient does not form a coherent structure, and the tablet disintegrates.

The amounts of lobenzarit disodium released as a function of time for lots containing Ethocel 100 (lots 1–3) are shown in Fig. 1. As expected, an increase in the concentration of the polymer produces a more-extended drug release period. As Fig. 2 shows, slower drug release

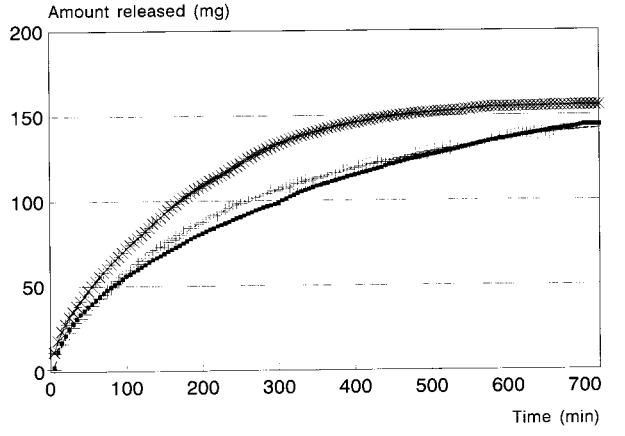

Figure 2. Release profiles of lobenzarit disodium–Eudragit RS-PO matrices.

rates were obtained from matrices containing Eudragit RS-PO compared to those with Ethocel 100.

The study of the release behavior as a function of the type of polymer allows the conclusion that Eudragit RS-PO is more suitable than Ethocel 100 for the controlled release of lobenzarit disodium during an extended period of time. This result can be explained on the basis of the chemical structure of the polymers. Ethocel 100 has hydroxyl groups in the anhydroglucose units, as well as ethoxyl groups, and both hydrophilic groups make the matrix water sensitive. Consequently, it is more difficult to control the release of lobenzarit disodium, a hydrophilic drug. On the other hand, Eudragit RS-PO is only slightly permeable to water due to its low content of quaternary ammonium groups, so it is more suitable for controlling the release of this hydrophilic drug.

Considering the lots with the same drug and polymer concentrations (lot 1 vs. lot 4; lot 2 vs. lot 5, and lot 3 vs. lot 6), it can be concluded that smaller amounts of Eudragit RS-PO than Ethocel 100 are necessary for achieving the release of the drug for an extended period of time. On the other hand, with respect to the polymer content of the matrices, the same behavior was observed for all lots. An increase in the polymer content results in a decrease in the drug release rates due to a decrease in the total porosity of the matrices (initial porosity plus porosity due to the dissolution of the drug) (14).

Kinetic Studies

The kinetic studies of the release data were performed using the equations corresponding to zero-order, first-order, and Higuchi models. For all the formulations, the best fit corresponded to the Higuchi model. Taking into account the whole release process, it can be considered diffusion-controlled release, that is, the diffusion of the drug through the matrix is the rate-determining step. The best fits to the diffusion model were obtained for lots 4 ($r = .997$) and 5 ($r = .987$), which contain an excipient infinite cluster that controls the drug release.

CONCLUSION

The physical characterization of the powder mixtures containing lobenzarit disodium and Ethocel 100 or Eudragit RS-PO demonstrated adequate properties for tablet compression. The prepared formulations presented good physical and mechanical characteristics. According to results of disintegration and dissolution tests, the tablets containing 40% and 60% w/w of Eudragit RS-PO

were able to produce true matrices. The correlation values obtained when the Higuchi equation was applied to release data suggest that the release of drug from these tablets is preferentially a diffusion-controlled process.

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