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RELEASE RATE OF INDOMETHACIN FROM COATED GRANULES

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ABSTRACT

The purpose of this investigation was a study on sustained release coated granules manufactured by means of the air-suspension coating technique. The smoothed 12/20-mesh fractions of indomethacin granulation containing povidone as a binder were coated in a modified air-suspension coater with film of ethylcellulose-glyceryl monostearate mixture at various percents by weight of coat. The kinetics of drug release was determined and appears to conform to the first-order fashion. The relationship between the coating weight and the first-order release rate constant was developed and found to be in the form of exponential function.

INTRODUCTION

The original work that developed the air-suspension coating technique has been reported by Wurster.[1-3] The process later has been utilized to control drug release from coated particles.[4-6] The aim of the present work is to study on the manufacture of sustained release indomethacin granules, coated with ethylcellulose-glyceryl monostearate

mixture by means of the air-suspension coating technique. The kinetics of drug release from such granules is to be investigated as well as the relationship between percentage of coated materials on granules and drug release rate.

MATERIALS

Indomethacin used was obtained from China National Chemicals Import and Export Corporation. Lactose and povidone were from DMV, Veghel, Holland and BASF, Germany, respectively. Ethylcellulose, Dow Chemicals, U.S.A. Glyceryl monostearate, Oleofina, Belgium. All of the materials were B.P., U.S.P., or reagent grades.

METHODS

Preparation of the Coated Granules: Lactose granules containing 19.8%w/w indomethacin were prepared by means of wet granulation using 1%w/w povidone as a binder. The surfaces of moist granules were smoothed for 10 minutes in a coating pan before oven-dried at 50°C for 8 hours. The 12/20-mesh fractions of granulation were coated by using air-suspension coater.[a] Some modifications were made on this machine in order to get an improved systematic fluidization effect by placing a stainless steel cylinder with diameter of 8 cm and 11 cm in length at the center of the settling chamber. The same coating procedure was repeated in triplicate (Lot I, II, and III) for each nearly the same percent coat.

Studies of Drug Release from Coated Granules: A USP XIX dissolution test apparatus 1[b] was used to examine the release characteristics of coated indomethacin granules. A quantity of granules equivalent to 200 mg non-coated granules, containing 39.6 mg of indomethacin, was placed in the basket and immersed in 900 ml of USP phosphate buffer pH 7.2 at 37°C. The basket rotating speed was 100 rpm. The withdrawn samples were analyzed spectrophotometrically for indomethacin. The procedure was carried out in triplicate for coated granules at each percent by weight coated of each lot.

RESULTS AND DISCUSSION

The dissolution of granules coated with ethylcellulose film and releasing their soluble components by diffusive mechanisms has

TABLE 1. Release Rate Constants (k_r^1) and Corresponding Half-lives ($t_{1/2}$) of Indomethacin from Coated Granules Lot II at Various Percent Coated

%w/w Coated	k_r^1 (hr^{-1})	$t_{1/2}$(hr)
0.25	0.18403	3.77
0.57	0.13682	5.07
1.21	0.08545	8.11
2.01	0.02427	28.55
2.79	0.01544	44.88

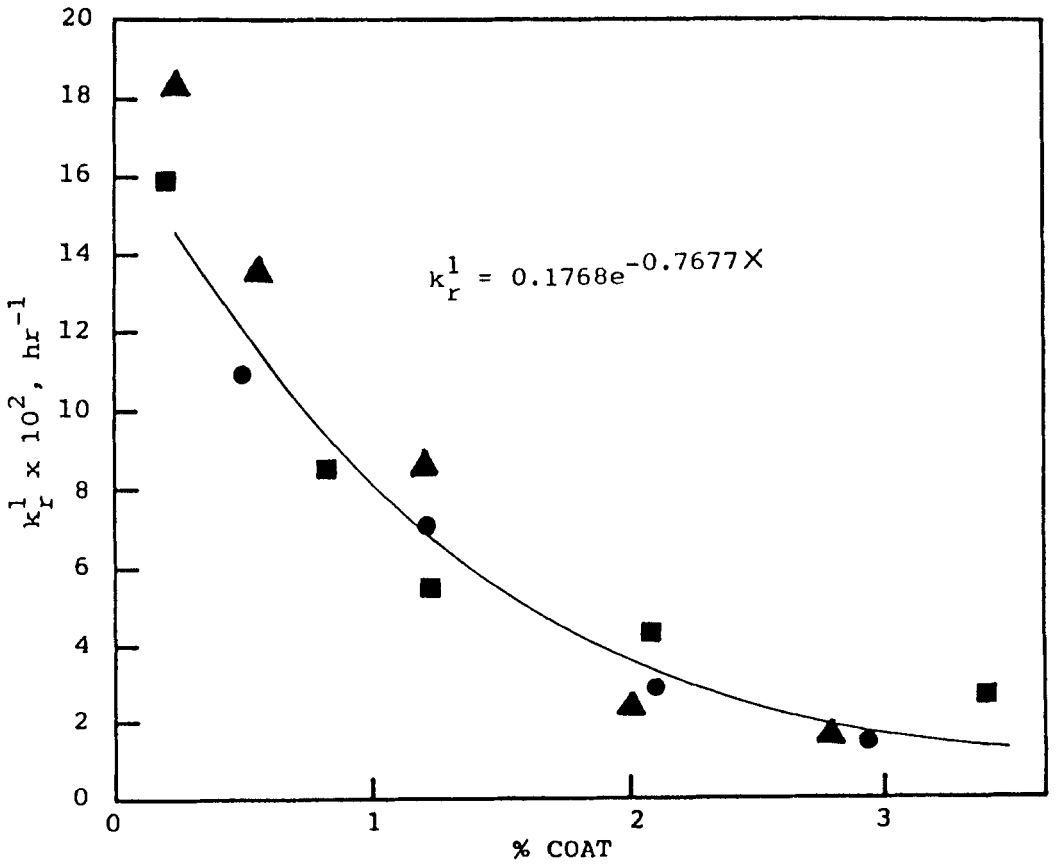

FIGURE 1

Relationship of coating weight (% coat) to the first-order release rate constant (k_r^1) among three lots of coated granules.

Key: ●, Lot I; ▲, Lot II; ■, Lot III.

been treated by first-order kinetics.[6,7] However, the release data of indomethacin from coated granules obtained in this study are independently treated by three release kinetics, i.e., zero-order, first-order, and Higuchi's derivation kinetics, to ascertain which relationship give the best fit. The correlation coefficients for the best statistical lines are used as the principal criteria for evaluation. Comparisons of correlation coefficient values obtained reveal that the first-order kinetics is most applicable. The first-order release rate constants (k_r^1) and the corresponding half-lives ($t_{1/2}$) at various percentages of coat are calculated and presented in TABLE 1. The rank inverse relationship between weight of film coating and k_r^1 suggests that k_r^1 be the fundamental parameter governing the release pattern of the drug. This so-called "k_r^1 - % coat relationship" belonging to coated granules Lot I, II, and III is shown graphically in FIGURE 1 and may be represented by the following empirical function

$$k_r^1 = 0.1768\, e^{-0.7677\, X} \qquad \text{(Eq. 1)}$$

where x is the weight of coat in percentage. The coefficients of determination for this line is 0.884, which is fairly good when considering all data of these three lots being plotted together on the same coordinate. In practice the weight of coat may be accurately controlled by monitoring the coating conditions and time. Therefore, this above relationship will provide a valuable tool as a guideline in formulating and developing sustained release products.

FOOT NOTES

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a. Aeromatic AG, Switzerland.

b. Hanson Research, U.S.A.

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