Development of Extended-Release Solid Dispersions of Nonsteroidal Antiinflammatory Drugs with Aqueous Polymeric Dispersions: Optimization of Drug Release via a Curve-Fitting Technique

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Extended-release solid dispersions of nonsteroidal antiinflammatory drugs were prepared by using aqueous polymeric dispersions of Eudragit RS30D and Eudragit RL30D as the inert carriers. The effects of different polymer ratios of Eudragit RS30D and Eudragit RL30D, different particle sizes, and different combination of various formulations of solid dispersions on the *in vitro* release kinetics of drugs from the dosage forms were investigated. A computer curve-fitting process was developed to choose the optimum formulation of the solid dispersion with the desired drug release profile. This process might offer the advantages of efficiency and simplicity in the formulation development of extended-release solid dispersions.

KEY WORDS: optimization; curve fitting technique; solid dispersions; nonsteroidal antiinflammatory drugs (NSAIDs); extended release; aqueous polymeric dispersions.

INTRODUCTION

The unique approach of solid dispersions to reduce the particle size and increase the rate of dissolution and absorption of drug was first demonstrated by Sekiguchi and Obi (1). A solid dispersion is a multiparticulate delivery system and has been defined as a dispersion of one or more active ingredients in an inert carrier or matrix at a solid state prepared by melting (fusion), solvent, or melting-solvent methods (2). In addition to absorption enhancement, the solid dispersion technique can be used to formulate sustained-release dosage forms of soluble drugs by using poorly soluble or insoluble carriers and to delay absorption with good bioavailability, reproducibility, and predictability (3). Using polyacrylate polymers as a carrier and indomethacin as a model drug in a form of extended-release solid dispersion has been investigated (4). The solid dispersion technique has been applied to different types of enteric coating agents as inert carriers to control the release rate of water-insoluble and short-acting drugs (5). Prolonged-release solid dispersions of codeine prepared by the melting and solvent methods were also studied by El-Gindy *et al.* (6,7). Although recently there has been increased interest in using various types of polymers and organic solvents to prepare extended-release solid dispersions, there is little information about the utilization of aqueous polymeric dispersions as carriers in the preparation of solid dispersions.

The release kinetics of drugs from solid dispersions can be altered by modifying different polymer ratios of Eudragit RS30D and Eudragit RL30D, and by adjusting different particle sizes (8,9). However, optimization of the release kinetics of drug from the solid dispersion through the computer-fitting process has not yet been done. The purpose of this study is to prepare the extended-release solid dispersions of nonsteroidal antiinflammatory drugs (NSAIDs) using aqueous polymeric dispersions of Eudragit RS30D and Eudragit RL30D as the carriers and to optimize the release of drugs from the dosage forms via a computer curve-fitting process.

MATERIALS AND METHODS

Materials

The formulations of the extended-release solid dispersions in this study contained five major components: aqueous polymeric dispersions of Eudragit RS30D and RL30D (Rohm Pharma), tributyl citrate (Morflex), starch (City Chemical), avicel (pH102, FMC), and ketoprofen (Sigma) or flurbiprofen (Sigma).

Preparation of Solid Dispersions

Oral extended-release solid dispersions of selected NSAIDs, namely, ketoprofen and flurbiprofen, were prepared by using aqueous polymeric dispersions of Eudragit RS30D and Eudragit RL30D. The mixtures of Eudragit RS30D and RL30D containing about 9% (w/w) of drugs and 20% (w/w) of tributyl citrate as a plasticizer were cast on a Teflon sheet and then dried in an oven at 65°C for at least 6 hr. The dry residues were ground and mixed with avicel and starch as excipients to eliminate the stickiness of the solid dispersion. Each gram of solid dispersion mixture contained 50% (w/w) of solid dispersion, 35% (w/w) of starch, and 15% (w/w) of avicel. The particle sizes of solid dispersions were classified by a sieving method. The composition of polymers and the particle sizes of five formulations of solid dispersions for each drug are shown in Table I.

Determination of the Drug Content in the Solid Dispersion Mixture

For each formulation, 100 mg of solid dispersion mixture was dissolved in 100 ml of methanol containing 0.1 *M* acetic acid. The solution was then analyzed for the amount of drug by HPLC.

In Vitro Release Kinetics of Solid Dispersion

The *in vitro* release studies were conducted in order to obtain the release profile of each formulation. One gram of solid dispersion mixture, containing 45 mg of the drug, was used for each release study. The *in vitro* release studies were conducted by using USP dissolution apparatus 2. The stirring rate was 100 rpm and the experiments were carried out at 37°C. The dissolution medium was 500 ml of 1/15 *M* phos-

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Table I. The Composition of Polymers and the Particle Sizes of Extended-Release Solid Dispersions

Formulation	Ratio of Eudragit RS30D/RL30D (%)	Particle size (mm)
1	50/50	0.25–0.42
2	85/15	0.25–0.42
3	100/0	0.25–0.42
4	100/0	0.42–0.85
5	100/0	0.85–1.18

phate buffer solution (pH 7.4) containing 0.02% of Tween 80. One milliliter of the solution was withdrawn through a filter needle (5 micron) at a particular time interval and analyzed by HPLC. At least three replications of release studies were made for each formulation.

Analytical Method

The HPLC system consisted of a Waters (M-6000A) pump, a Waters (440) detector, and a Hitachi (AS-2000) autosampler. A Waters Novapak C_{18} column (3.9 × 150 mm) was used. The mobile phases of methanol–0.1 *M* acetic acid at ratios of 55:45 and 60:40 were used to determine the ketoprofen and flurbiprofen, respectively, at a flow rate of 1 ml/min and UV detection at 254 nm.

Optimization Procedures

A computer curve-fitting process was developed to examine the possibility of combining different formulations of solid dispersions to achieve the desired drug release profiles. The schematic diagram of the process is illustrated in Fig. 1 and the steps of estimating the required amount of each formulation in the development of the optimum formulation are explained as follows.

1. First, the input data, $Q(t)_i$, are experimental cumulative amounts of the drug released from each formulation as a function of time, where $i = 1, 2, 3, \ldots, n$ stands for different formulations.
2. By applying the curvilinear regression, the release profile of the drug from each formulation can be expressed by the best-fit equation in the form of

$$E(t)_i = C_1 * t^B + C_2$$

or

$$E(t)_i = C_1/[C_2 * (1/t) + C_3]$$

where B, C_1, C_2, and C_3 are constants to be estimated.

3. Input the desired release profile of the optimum formulation, $Q(t)_o$.
4. Estimate the coefficient value of A_i until the constraint for $Q(t)_o = E(t)_o = \Sigma_{i=1}^{n} A_i * E(t)_i$ is satisfied.
5. The value of A_i represents the relative amount of each formulation required for the preparation of the optimum formulation.

The computer-fitting process was performed by the RS/1 program (10) run on the VAX computer (Digital Equipment Corporation).

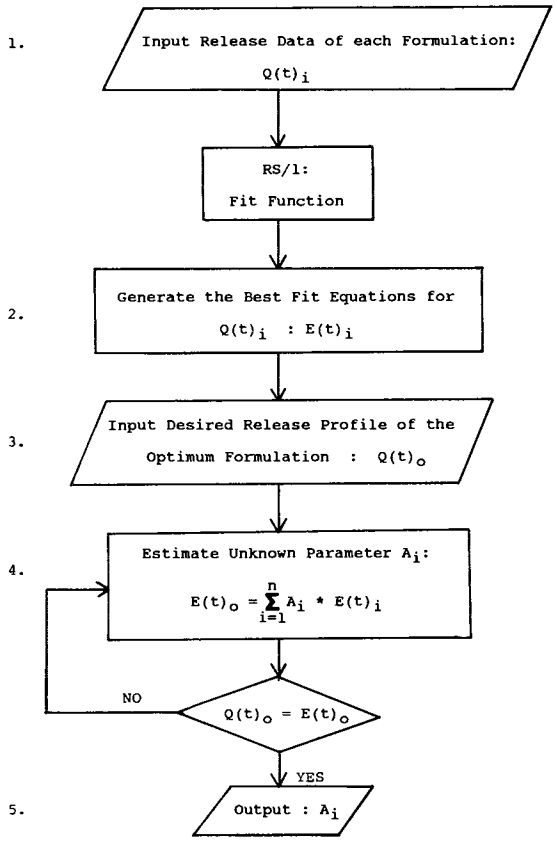

Fig. 1. Steps of the computer curve-fitting process for the optimization of the drug released from extended-release solid dispersions.

RESULTS AND DISCUSSION

Effects of Polymer Ratio and Particle Size on the Release of Ketoprofen and Flurbiprofen

Figures 2 and 3 show the release profiles of ketoprofen and flurbiprofen from different formulations of solid dispersions, respectively. As shown in the figures, the release profiles can be expressed by the best-fit lines and equations via the curvilinear regression. It was noted that the release of the drug from each formulation of solid dispersion was highly reproducible (<3% error).

The release of ketoprofen or flurbiprofen from each formulation can be fitted to the Higuchi model (11), $1 + 2F - 3F^{2/3} = Kt$, where F is the fraction of the drug remaining in the solid dispersion at the time t and K is a combined rate constant. The results are presented in Table II and Figs. 4 and 5. It was shown that the release rates of drugs decreased by increasing the amount of Eudragit RS30D in the formulation as well as by increasing the particle size of the solid dispersion.

Optimization of Release Rates of Drug from the Solid Dispersions

Although the release of drugs from the solid dispersions can be controlled by modifying the polymer ratio and particle size, this approach provides only a provisionally accept-

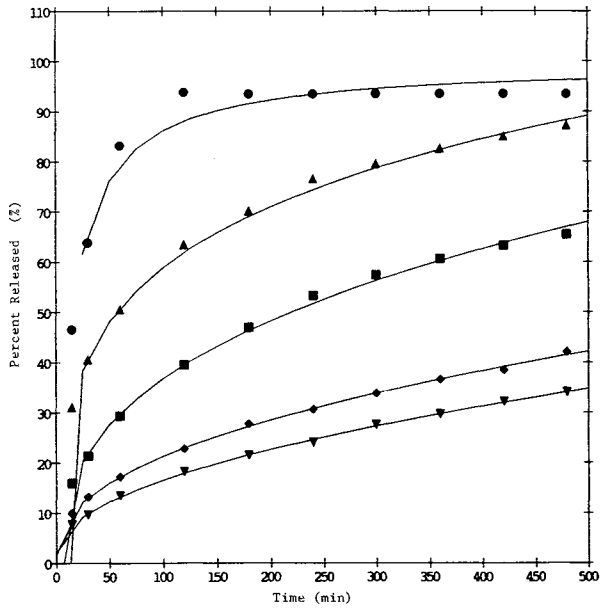

Fig. 2. The cumulative percentage of ketoprofen released from the solid dispersion versus time. The symbols represent the observed release profiles of ketoprofen from different formulations: 1 (●); 2 (▲); 3 (■); 4 (♦); 5 (▼). The solid lines represent the best-fit lines obtained by the curve-fitting procedure.

able solution rather than an optimum solution. In an attempt to obtain an optimum formulation without preparing and testing a large number of formulations, a computer curve-fitting process as described in the previous section has been developed. The validation of the computer fitting process for

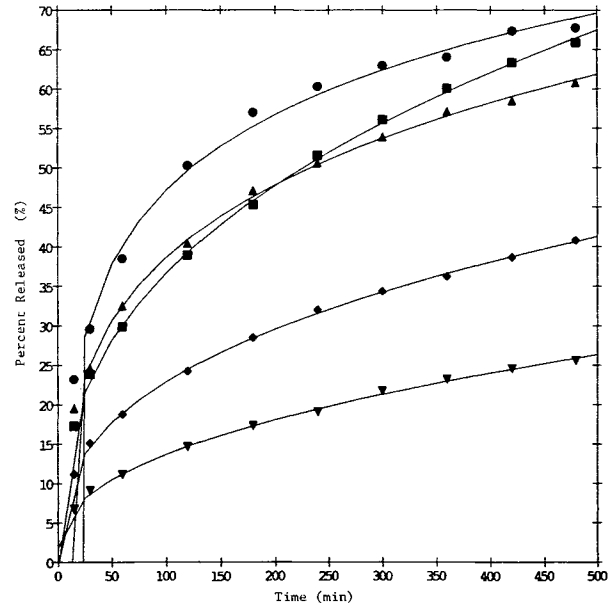

Fig. 3. The cumulative percentage of flurbiprofen released from the solid dispersion versus time. The symbols represent the observed release profiles of flurbiprofen from different formulations: 1 (●); 2 (▲); 3 (■); 4 (♦); 5 (▼). The solid lines represent the best-fit lines obtained by the curve-fitting procedure.

Table II. Effects of Polymer Ratio and Particle Size on the Higuchi Rate Constant Values

	Ketoprofen		Flurbiprofen	
Formulation	K^a	r^b	K^a	r^b
1	0.005287	0.9856	0.000869	0.9999
2	0.001497	0.9955	0.000488	0.9980
3	0.000519	0.9999	0.000456	0.9987
4	0.000155	0.9993	0.000159	0.9986
5	0.000092	0.9990	0.000055	0.9989

[a] Higuchi rate constant.
[b] Correlation coefficient of the linear regression of $(1 + 2F - 3F^{2/3})$ on time t.

the optimization of formulation development was tested by preparing and evaluating the predicted optimum formulation.

A desired release profile of ketoprofen, as represented by the double line in Fig. 6, was proposed in the formulation of extended-release solid dispersion. Based on the computer fitting process, a best-fit equation for the desired release profile of ketoprofen from the optimum formulation was derived as follows:

$$E(t)_o = 0.30 * E(t)_2 + 0.78 * E(t)_3$$

where $E(t)_2$ and $E(t)_3$ represent the best-fit equations for the release profiles of ketoprofen from formulations 2 and 3, respectively, and the coefficients of 0.30 and 0.78 are the estimated amounts of formulations 2 and 3 required for the predicted optimum formulation. Therefore, a 1.08-g solid dispersion of ketoprofen was prepared by mixing 0.30 g of formulation 2 and 0.78 g of formulation 3, and the *in vitro*

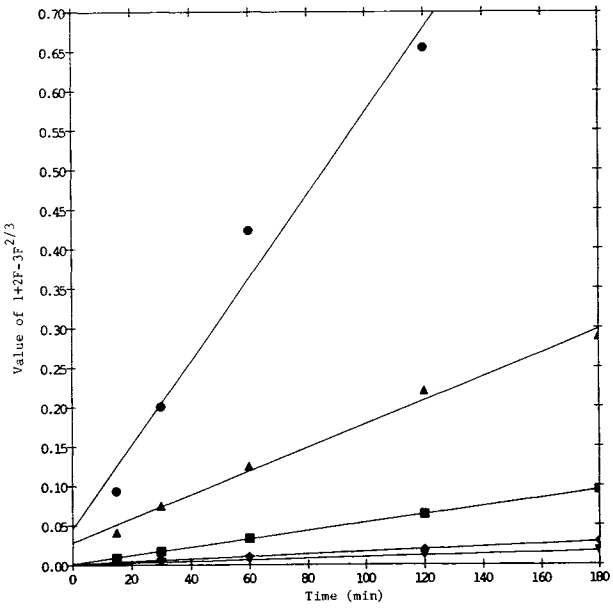

Fig. 4. Relationship between calculated value of $(1 + 2F - 3F^{2/3})$ and time for ketoprofen released from different formulations of solid dispersions. Formulation 1 (●); 2 (▲); 3 (■); 4 (♦); 5 (▼).

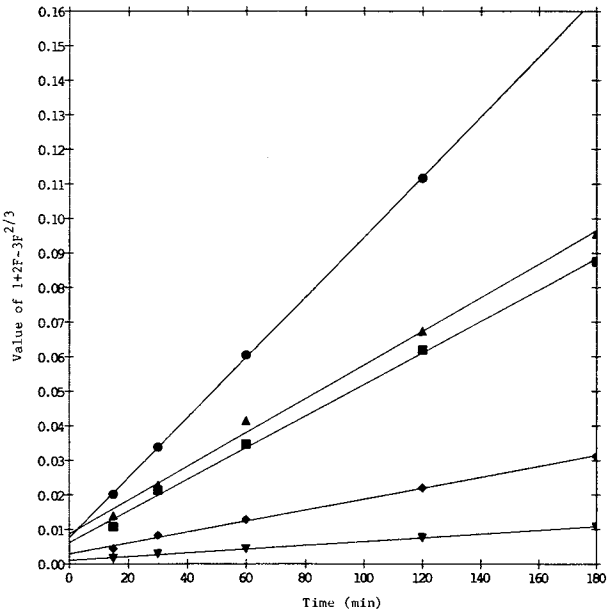

Fig. 5. Relationship between calculated value of $(1 + 2F - 3F^{2/3})$ and time for flurbiprofen released from different formulations of solid dispersions. Formulation 1 (●); 2 (▲); 3 (■); 4 (♦); 5 (▼).

release study was conducted. As shown in Fig. 6, the experimental release data are not significantly different from that of the predicted optimum formulation ($P = 0.05$, chi-square test).

The above optimum formulation was prepared by mixing formulations 2 and 3, which have the same particle size but different polymer ratios. Another optimum formulation was proposed by combining the formulation 1 and 5, which have both different particle sizes and polymer ratios. A similar result was observed, as shown in Fig. 7, that the experimental release data were comparable with the predicted release profile of the optimum formulation ($P = 0.05$, chi-square test).

The validation of the computer fitting process was further confirmed by a test in optimizing the release of flurbiprofen from extended-release solid dispersions. An optimum formulation of flurbiprofen was prepared by combining 0.047 g of formulation 3 and 1.177 g of formulation 4. As shown in Fig. 8, the release data of flurbiprofen from such formulation are not significantly different from the predicted release profile ($P = 0.05$, chi-square test).

The results of the study indicated that aqueous polymeric dispersions of Eudragit RS30D and RL30D can be used to prepare extended-release solid dispersions with ketoprofen and flurbiprofen. It was also observed that the concentration of Eudragit RL30D in the solid dispersions

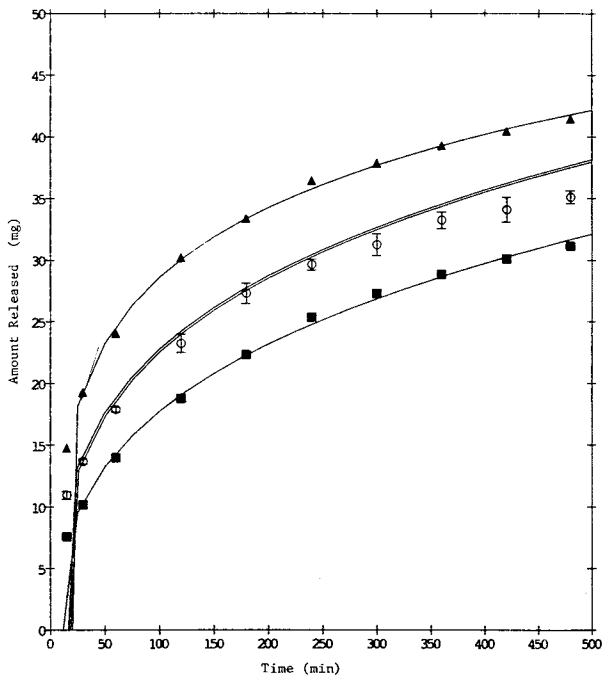

Fig. 6. The cumulative amount of ketoprofen released from the solid dispersion versus time. The symbols represent the observed release profiles of ketoprofen from formulations 2 (▲) and 3 (■) and the optimum formulation (○). The solid lines represent the best-fit lines for the released profiles of formulations 2 and 3 and can be expressed by the equations $E(t)_2 = 79.23 * (t^{0.07}) - 81.78$ and $E(t)_3 = 7.40 * (t^{0.27}) - 8.29$, respectively. The double line represents the desired release profile of the optimum formulation and can be expressed by the best-fit equation $E(t)_o = 0.30 * E(t)_2 + 0.78 * E(t)_3$.

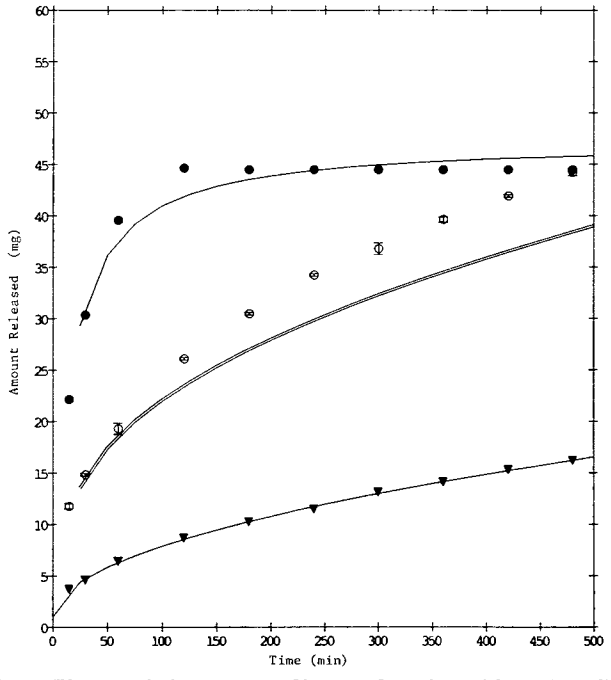

Fig. 7. The cumulative amount of ketoprofen released from the solid dispersion versus time. The symbols represent the observed release profiles of ketoprofen from formulations 1 (●) and 5 (▼) and the optimum formulation (○). The solid lines represent the best-fit lines for the released profiles of formulations 1 and 5 and can be expressed by the equations $E(t)_1 = 35.69/[11.55 * (1/t) + 0.76]$ and $E(t)_5 = 0.67 * (t^{0.51}) + 0.99$, respectively. The double line represents the desired release profile of the optimum formulation and can be expressed by the best-fit equation $E(t)_o = 0.18 * E(t)_1 + 1.85 * E(t)_5$.

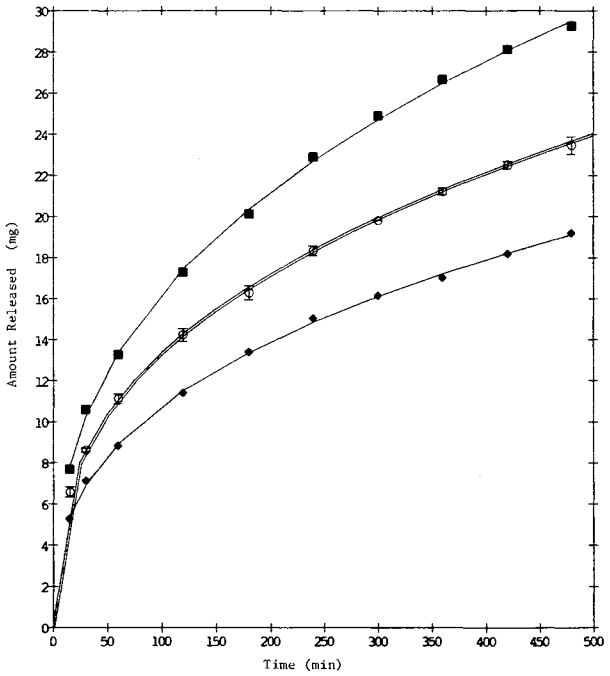

Fig. 8. The cumulative amount of flurbiprofen released from the solid dispersion versus time. The symbols represent the observed release profiles of flurbiprofen from formulations 3 (■) and 4 (◆) and the optimum formulation (○). The solid lines represent the best-fit lines for the released profiles of formulations 3 and 4 and can be expressed by the equations $E(t)_3 = 3.00 * (t^{0.37}) - 0.41$ and $E(t)_4 = 2.05 * (t^{0.36}) - 0.12$, respectively. The double line represents the desired release profile of the optimum formulation and can be expressed by the best-fit equation $E(t)_o = 0.047 * E(t)_3 + 1.177 * E(t)_4$.

can affect the release rate of drugs. Increasing the amount of Eudragit RL30D in the solid dispersions would increase the release rate of drugs. The release of drugs from the solid dispersions decreases as the particle size of the solid dispersions increases. The curve-fitting technique can be applied to the formulation development of extended-release solid dispersions and offers the advantages of simplicity and efficiency. By utilizing this technique, a relatively small number of experiments is required to find the optimum formulation with the desired release profile.

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