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EFFECT OF VARIOUS POLYMERS ON FORMULATION OF CONTROLLED RELEASE (CR) IBUPROFEN TABLETS BY FLUID BED TECHNIQUE

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ABSTRACT

The need for controlled release (CR) formulations of ibuprofen tablet, is well recognized. Some such formulations have been marketed but in general only patented.

The purpose of this study was to develop an air suspension method, using a laboratory scale fluidized bed drier to coat the ibuprofen granules. Different polymers including, Eudragits L100, S100, RL100, RS100, L100+S100 (1:1), RL100+RS100 (1:1), ethyl cellulose (EC) and Eudragit RS100+EC (1:1) were utilized. The drug release medium consisted of buffer pH 1.2 for 1st 2h, buffer pH 4.5 for 2nd 2h and buffer pH 7.5 for remaining period of time in all experiments, but the release behaviour of the drug from some formulations was also studied using distilled water. Of the polymers investigated, Eudragit RS100, EC, Eudragit S100 and Eudragit RS100+EC (1:1) exhibited proper release characteristics when used as coating materials. The release patterns were analyzed from the standpoint of diffusion-controlled processes and as first-order kinetics.

INTRODUCTION

Ibuprofen, 2-(4-isobutylphenyl) propionic acid (1), is a widely used nonsteroidal anti-inflammatory drug (NSAID). It is weakly acidic in nature with a pKa of 5.2, and rapidly absorbed following oral administration. Its half-life is 1.8-2h, the short half-life and increased need of patient compliance, especially in the management of chronic rheumatic conditions, suggests the need for controlled release formulations of this drug (2). Various methods including, ion-exchange resin complexes, matrix tablet, osmotic pump, co-precipitation as well as microencapsulation process like coacervation-phase

separation and air suspension have been utilized to prepare the controlled release products (2-3). The air suspension technique appears to be a most attractive approach, from the process development and scale up points of view.

Formulation of ibuprofen-Eudragit co-precipitates as well as Eudragit matrix controlled release (CR) tablets of this drug were studied by other investigators (2,4).

Various polymers including, ethyl cellulose (EC) and Eudragits are used as retardant barriers. EC, is a cellulose ether made by the reaction of ethyl chloride and alkali cellulose. Each anhydroglucose unit has three replaceable OH groups, all or some of which may react with ethyl chloride (5). Poly (methacrylic acid, methylmethacrylate) resins with the designation L and S are weak acids that start to dissolve at values of pH above 5.5 or higher depending upon the composition of the copolymer. Poly (ethylacrylate, methylmethacrylate) trimethylammonioethylmethacrylate chloride (Eudragits RL and RS) are neutral polymers and are insoluble in entire physiological pH range. However, they possess a defined swelling capacity and permeability with respect to water and dissolved drugs, which are independent of pH (6).

The present investigation includes the preparation and evaluation of controlled release tablets of ibuprofen using various retardants by air suspension technique.

MATERIALS AND METHODS

Materials

Ibuprofen was obtained as a gift from Taito Koeki (Toyama, Japan). Similarly, the Eudragits and dibutyl phtalate (DBP) were gifts from Rohm (D-Weiterstadt, Germany). EC was obtained from Sigma (St. Louis, MD).

All chemicals were of analytical grade and were used as received.

Apparatus

A series of B.S. sieves and a mechanical sieve shaker were used for particle size selection. A (Korsh, Germany) tabletting machine was used for compression. Breaking strength was measured on a (Erweka, D-Heusentamm, Germany) hardness tester. A fluidized bed (Uni-Glatt) apparatus was used for particle coating. The USP dissolution apparatus I was used (Erweka, D-Heusentamm, Germany). A U.V. spectrophotometer (160 A, Shimadzu, Japan) was used for detection. A pH meter (corning, UK) was utilized for media pH adjustment.

Methods

A. Preparation of tablets : A wet granulation system was utilized to prepare the granules, using 10% W/V pregelatinzed starch as binder. Granules were coated by fluid bed technology (Wurster system) using various coating solutions. The coated granules were then lubricated. Tablets containing # 400 mg of drug were compressed to weigh 480 mg.

B. Preparation of coating solution : The solutions of Eudragits (L100, S100, L100+S100, RL100, RS100, RL100+RS100), ethyl cellulose (EC) and Eudragit RS100+EC in acetone were prepared. Dibutyl phtalate in ratio of 2:10 (plasticizer to polymer) was added to coating solution. The required amount of solutions sprayed on the granules.

Drug release studies

The dissolution tests were conducted using the USP basket method (Apparatus I) at 150 rev/min and 900 ml of dissolution fluid at 37± 0.5°C. Six tablets from each formulation were tested individually in simulated gastric fluid (SGF) pH 1.2 for first 2h, acetate buffer pH 4.5 for second 2h and simulated intestinal fluid (SGF) pH 7.5 for remaining period of time. At 1h intervals, 5ml samples were removed with replacement at appropriate time intervals and the total release was evaluated at 12h.

C. Scanning electron microscopy (SEM) : The coated granules were examined under a scanning electron microscope (SEM) (Model 5360 Cambridge instruments, GB-Cambridge) for morphology evaluation.

RESULTS AND DISCUSSION

Physical characteristics of ibuprofen tablet

Average size distribution of the granules coated with Eudragits (S, RS100), EC and Eudragit RS+EC varied from 641 to 663 micrometer. Bulk density of these granules differed from 0.36-0.43 g/cm^3. The breaking strength of these tablets differed from 83.8-115.4 N. However, the tablet friability of these formulations varied from 0.43 to 0.81%.

Drug release behaviors of ibuprofen (CR) tablet

Drug release profiles of ibuprofen from formulations containing various concentrations of different polymers in various media are depicted in Figure 1 and Figure 2. Each data point represents the mean of eighteen determinations. These profiles demonstrate that Eudragit RS resin with quarternary ammonium groups (3), has excellent retardant properties when used at 2% level. The Eudragit RL predictably showed less retardant effect at 2% level. However, with higher concentrations (2.5%), the release profile was similar to Eudragit RS. The Eudragit S100 as an anionic acrylic resin significantly retarded the drug release rate (7) at 2% level. Eudragit L100 polymer, in either a single resin formulation, or as a combination with Eudragit S100 polymer in 1:1 ratio, demonstrated little ability to retard drug dissolution (3). EC as insoluble, inert an acid sensitive polymer (8) exhibited at low concentration (1%) very reproducible and suitable controlled release properties. Combination of a cellulose ether derivative (EC) and methacrylate ester co-polymer (Eudragit RS100) in this investigation demonstrated predictable and suitable sustained release characteristics.

Figure 3 depicts, drug release behaviours of ibuprofen from CR formulations containing EC, Eudragit RS100, Eudragit S100 and EC+Eudragit RS100 in distilled water. These profiles demonstrate very slow release of the drug from different formulations due to its low solubility in aqueous media (9), in spite of the nature of the polymers used. Since ibuprofen is a weakly acidic substance, an increase in drug release in higher pH media (pH 7.5) is expected and, in fact exhibited in Figure 4. At this pH, almost linear release of ibuprofen from CR formulations containing Eudragit RS100, Eudragit S100, EC and Eudragit RS100+EC after 5h was demonstrated. Comparison of the data provided in Figures 1,2 and 4, exhibit that CR formulations containing Eudragit RS100 and S100 follow a pattern identical to that of brand sample. However, EC and the mixture of EC and Eudragit RS100 (1:1) exhibited better linearity in comparison with other formulations.

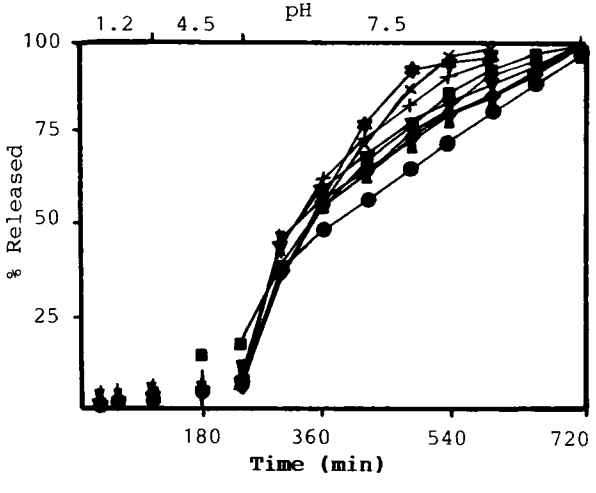

FIGURE 1

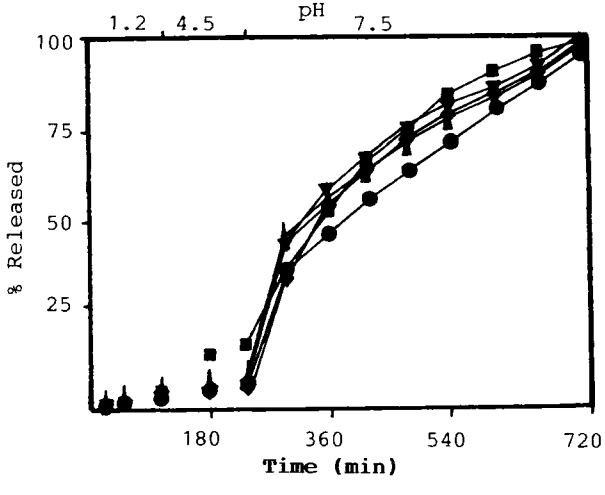

FIGURE 2

Drug release profiles of controlled release (CR) ibuprofen tablets preparing with different polymers as compared with brand sample in SGF (pH 1.2), acetate buffer (pH 4.5) and SIF (pH 7.5) as measured by basket system (Apparatus I) at 37°C.
Symbols: (■) brand sample;(▼) RS100 (2% W/W); (▲) Ethyl cellulose (1.5% W/W); (●) RS+EC (1%+0.75% W/W); (+) RL100 (2% W/W); (▼) RS+RL (1%+1% W/W); (◆) S100 (2% W/W); (✱) L100 (2% W/W); (×) S+L (1%+1% W/W).

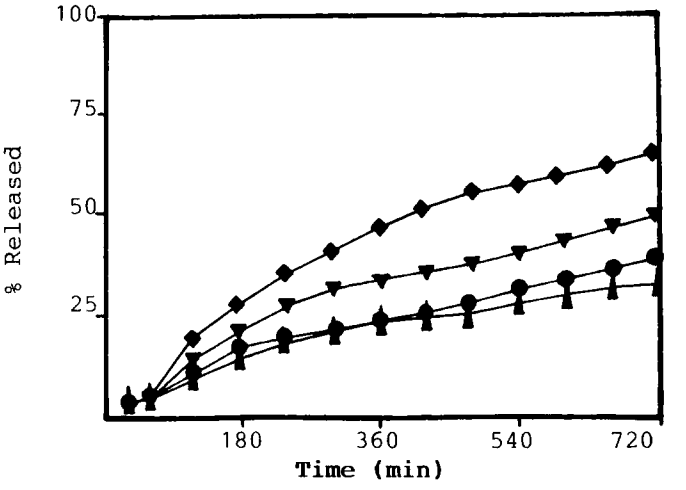

FIGURE 3

Drug release profiles of controlled release (CR) ibuprofen tablets containing different polymers in distilled water as measured by basket system (Apparatus I) at 37°C. **Symbols:** (▼) RS100 (2% W/W); (▲) Ethyl cellulose (1.5% W/W); (●) RS+EC (1%+0.75% W/W); (◆) S100 (2% W/W).

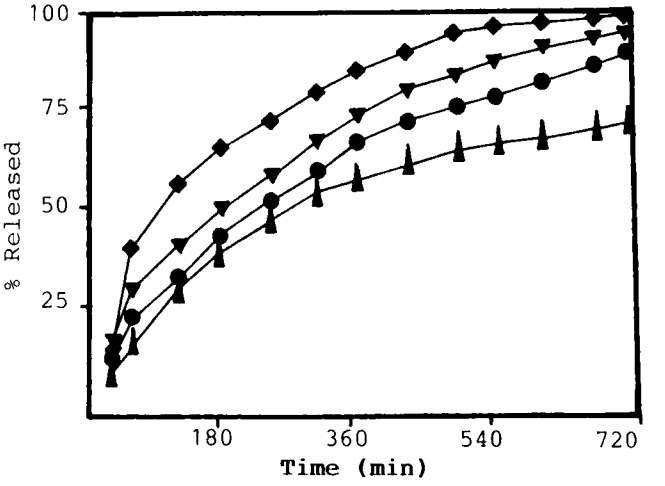

FIGURE 4

Drug release profiles of controlled release (CR) ibuprofen tablets containing different polymers in SIF (pH 7.5) as measured by basket system (Apparatus I) at 37°C. **Symbols:** (▼) RS100 (2% W/W); (▲) Ethyl cellulose (1.5% W/W); (●) RS+EC (1%+0.75% W/W); (◆) S100 (2% W/W).

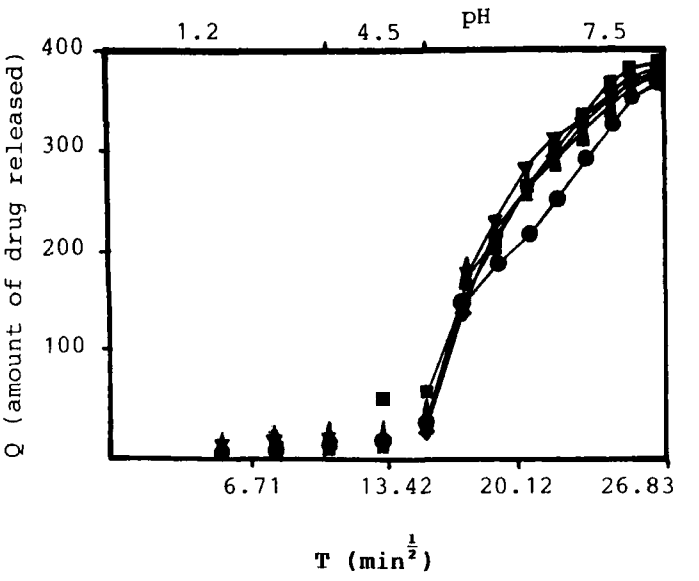

FIGURE 5

Ibuprofen release from tablets as a function of the square root of time (according to Higuchi equation) in SGF (pH 1.2), acetate buffer (pH 4.5) and SIF (pH 7.5). **Symbols:** (■) brand sample ; (▼) RS100 (2% W/W); (▲) Ethyl cellulose (1.5% W/W); (●) RS+EC (1%+0.75% W/W); (◆) S100 (2% W/W).

Methacrylic acid co-polymers (Eudragit L100 and Eudragit S100)are insoluble in acids and pure water, because of their content of carboxylate groups (6). It is evident from Figure 1 that Eudragit L100 and mixture of Eudragits L100 and S100 (1:1) were considered not to be suitable candidates for controlled release formulation of ibuprofen due to faster in-vitro release as well as, variability of stomach pH in fasted (pH 1.5-2.0) and fed (pH 2-6) states (10,11).

Kinetics of ibuprofen release from CR formulations

The release of ibuprofen from controlled release tablet may either be a first-order or a diffusion controlled process (12). Drug release data from formulations prepared with Eudragit RS100, EC, Eudragit S100 and EC+Eudragit RS100 were plotted according to the Higuchi equation (Figure 5) and first-order kinetics (Figure 6).

The relationship expressed by Higuchi equation (diffusion controlled process) in its modified form can be written (13):

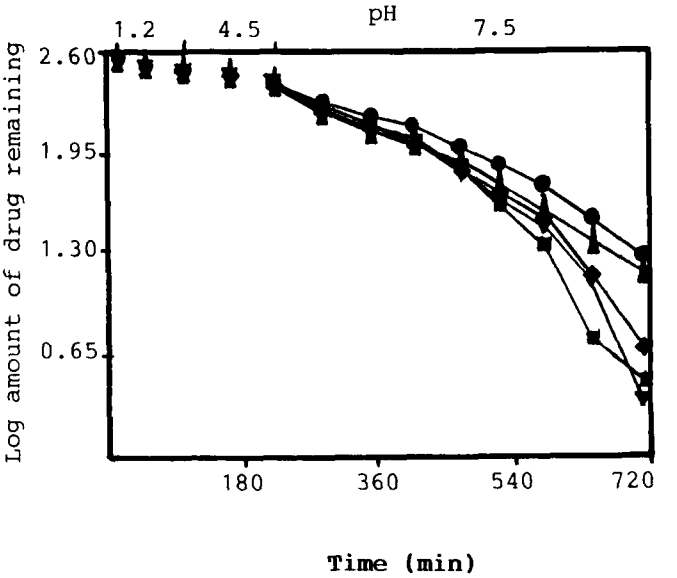

FIGURE 6

Release profiles of ibuprofen from tablets when plotted according to first-order kinetics in SGF (pH 1.2), acetate buffer (pH 4.5) and SIF (pH 7.5). **Symbols:** (■) brand sample ; (▼) RS100 (2% W/W); (▌) Ethyl cellulose (1.5% W/W); (●) RS+EC (1%+0.75% W/W); (◆) S100 (2% W/W).

$$Q = K\, t^{\frac{1}{2}}$$

Where Q is the amount of drug released after time t per unit exposed area and K is Higuchi rate constant. Release rate constants value, according to either mechanisms for the various formulations under study were calculated and exhibited in Table 1. Drug release from all these formulations in simulated intestinal fluid (pH 7.5)seems to fit the Higuchi equation and to correspond to a diffusion mechanism. However, the release characteristics of these formulations in acid media appears to fit first-order of kinetics.

An average of 45.14%, 46.99%, 39.19% and 37.81% of ibuprofen was released after 5h from formulations containing Eudragit RS100, EC, Eudragit RS100+EC and Eudragit S100, respectively. However, the release of drug reached 94.78%-99.44% of total content within 12h.

TABLE 1

Release rate constants calculated according to the first-order or Higuchi equation in simulated gastric fluid (pH 1.2, 1st 2h), acetate buffer (pH 4.5, 2nd 2h) and simulated intestinal fluid (pH 7.5, 4-12h).

	*B.S.	RS100	EC	RS-EC	S100
First 4h at pH 1.2 and pH 4.5					
$K_1(min^{-1})x10^{-3}$	-0.39	-0.15	-0.19	-0.16	-0.13
r_1	-0.971	-0.985	-0.984	-0.983	-0.977
$K_2(mg\ cm^{-2}min^{-\frac{1}{2}})$	6.82	2.64	3.38	2.28	2.79
r_2	0.956	0.958	0.956	0.953	0.944
Remaining period of time (4-12) at pH 7.5					
$K_1(min^{-1})x10^{-3}$	-4.46	-4.01	-2.46	-3.65	-2.42
r_1	-0.967	-0.918	-0.986	-0.966	-0.969
$K_2(mg\ cm^{-2}min^{-\frac{1}{2}})$	25.75	22.09	20.31	24.45	23.95
r_2	0.982	0.988	0.994	0.977	0.999

r_1 and r_2 are correlation coefficients

K_1 and K_2 are the release rate constants according to the first-order or Higuchi equation, respectively.

* Brand Sample

Scanning electron microscopy (SEM)

A cross-sectional view of the coated ibuprofen granules shows a clear interface between the core and the coating. The coating thickness is about 1 micrometer (Figure 7).

CONCLUSIONS

It is concluded that the ibuprofen tablets formulated with Eudragit RS100, EC, Eudragit S100 and Eudragit RS+EC (1:1) showed suitable controlled release characteristics and drug release from all

FIGURE 7

Cross section scanning electron micrograph (1000 x magnification) of ibuprofen CR granules (coated with Eudragit RS100).

these formulations appears to correspond to a diffusion mechanism (Higuchi equation). It was also demonstrated that fluidized bed technique is a reliable method for producing a controlled release formulation of ibuprofen tablet.

ACKNOWLEDGEMENTS

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