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# Development and Preparation of Controlled Release (CR) Tablet Formulations of Procainamide Fluid-Bed Technique

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## Abstract

The need for controlled release (CR) formulation of procainamide, an antiarrhythmic drug is well known. The aim of this investigation was an attempt to establish controlled release procainamide tablet formulations by fluid bed technique. The procainamide granules were prepared, using PVP as binder. A laboratory size fluidized bed drier (Uni-Glatt) was used for coating the procainamide granules. As polymers, Eudragit RSPO, ethylcellulose and Eudragit S 100+ethylcellulose (1:1) have been utilized. Triethylcitrate (TEC)was used as plasticizer in this investigation. The ratio of TEC to polymers was 1:9 in most experiments. However, in some formulations this ratio was increased to (1:4).

The coated granules were compressed using an excentric tabletting machine. Drug release patterns of all formulations prepared were investigated. The dissolution media were consisted of hydrochloric acid buffer pH 1.5 for the first 2h and phosphate buffer pH 6.8 for remaining period of time in all experiments.For comparison, a commercially available brand of

procainamide controlled release tablet was included in this study. Cross section scanning electron micrographs of coated and uncoated granules were taken. Granules coated with Eudragit RSPO, ethylcellulose and the combination of Eudragit S 100 and ethylcellulose (1:1) exhibited proper release behaviour. The release profiles were analyzed to check whether the release was diffusion-controlled or followed first-order kinetics. The release from most of the formulations prepared seems to correspond to the first-order kinetics. It was also concluded that, air suspension technique is a suitable method for the fabrication of controlled release formulations of procainamide tablets.

**Key words:** Procainamide HCl,Fluid Bed,Controlled Release Tablets,Drug release

## Introduction

Procainamide, a widely used antiarrhythmic agent, is readily absorbed from the gastro-intestinal tract and has a very short half-life of 2.5 to 4h in healthy subject (1). This short half-life can lead to subtherapeutic plasma levels 4h after oral administration of conventional formulations. Therefore, many investigators attempt to prolong the apparent plasma half-life of procainamide, by utilization of sustained release preparations (2). The development of controlled release (CR) formulations of this drug is therefore of therapeutic relevance and has caught the attention of the pharmaceutical industry. Various methods including ion-exchange resin complexes, matrix tablets, osmotic pumps, co-precipitation as well as microencapsulation process such as coacervation-phase separation and air suspension have been utilized to prepare the controlled release products (3-8). The fluid-bed technique appears to be the most attractive approach especially from the process development and up scaling points of view as well as its reproducibility and cost

effectiveness (9-10). Different polymers including ethylcellulose (EC) and Eudragits are used as retardant polymers. Ethylcellulose (EC) is a cellulose ether made by the reaction of ethyl chloride and alkali cellulose (11).Poly(methacrylic acid, methylmethacrylate) resin with the designation S is weak acid that starts to dissolve at pH value above 7. The Eudragit RSPO is copolymer synthesized from acrylic and methacrylic acid esters with a low content of quaternary ammonium group (12-14).

The objective of present work includes the preparation and evaluation of controlled release tablets of procainamide using different retardants by air suspension technique.

## Methods

## Materials

Procainamide hydrochloride was a gift from Parke Davis (NJ,USA). Similarly, the Eudragits and triethylcitrate (TEC) were gifts from Rohm (Darmstadt, Germany). Ethylcellulose was obtained from Sigma (St.Louis, USA). PVP, talcum, sodium dihydrogen phosphate, acetone, ethanol, isopropanol and HCl were obtained from Merck & Co(Darmstadt, Germany). All chemicals were of analytical grade and were used as received.

## Equipment

A series of sieves and a mechanical sieve shaker were used for particle size selection. An eccentric (EKO, Korsch, Germany) tabletting machine was used for compression. Breaking strength was measured on an (Erweka, Germany) hardness tester. A fluidized bed (Uni-Glatt, Glatt, Germany)apparatus was used for particle coating. The USP dissolution apparatus II was used (Erweka, Germany) for drug release study. A UV spectrophotometer (160 A, Shimadzu,Japan) was used for detection. A pH meter (Corning, UK) was utilized for media pH adjustment.

## Tablet preparation

A mixture of PVP and ethylcellulose (EC) (10.5+10.5% W/V) in ethanol was added to procainamide HCl powder (for the granules which were coated with EC and Eudragit S 100) in a kneader (Erweka, Germany) and blended for 15 min. The wet mass then passed through a 12 mesh screen sieve in an oscillating granulator and dried. However, the binder of granules coated with Eudragit RSPO was a mixture of PVP and Eudragit RSPO (10.5+15% W/V) in the mixture of ethanol and acetone (1:1). All the dried granules were sieved and the fraction finer than 20 mesh was discarded and coarser granules were used for coating. Granules were coated by fluid - bed technology (Wurster system) using various polymers in different concentrations in acetone and isopropanol as the coating solutions. The coated granules were then lubricated with talcum and Mg stearate. Tablets containing 750 mg of drug were compressed.

## Preparation of coating solution

The solutions of ethylcellulose (EC) in isopropanol, EC+Eudragit S 100 and Eudragit RSPO in the mixture of isopropanol and acetone (40:60) were prepared. Triethylcitrate (TEC) in ratio of 1:9 and 1:4 (plasticizer to Polymer) was added to the coating solutions. The required amount of the solutions sprayed on the granules. The conditions for optimum coating are given in Table 1.

Table 1 The process conditions for optimum particle coating.

| | |
|---|---|
| Bed weight | 100 g |
| Coating solution | Different polymers in acetone and isopropanol |
| Solution delivery rate | 5 ml/min |
| Atomizing air pressure | 1.2 Bar |
| Air temperature inlet | 35 - 40 °C |
| Air temperature outlet | 23 - 25 °C |

## Drug release studies

The dissolution tests were conducted using the USP paddle method (Apparatus II) at 100 rev. min-1 and 900 ml of dissolution fluid at 37±0.5°C. Six tablets from each formulation were tested individually in hydrochloric acid buffer pH 1.5 for the first 2h and phosphate buffer pH 6.8 for remaining period

of time. At 1h intervals, 5 ml samples were removed with replacement at appropriate time intervals and the total release was evaluated at 12h. Samples were filtered, diluted, and analyzed. The amount of drug released was estimated spectrophotometrically at 271 nm for buffer pH 1.5 and at 279 nm for buffer pH 6.8, respectively.

## Scanning electron microscopy (SEM)

The coated granules were examined under a scanning electron microscope (SEM) (Model S360 Cambridge Instruments, UK) for morphology evaluation.

## Results and Discussion

## Physical characteristics of procainamide HCl tablet

Average size distribution of granules coated with ethylcellulose, ethylcellulose + Eudragit S 100 and Eudragit RSPO varied from 727 to 781 $\mu$m (Table 2). Bulk density of these granules differed from 0.41 to 0.44 g/cm3 (Table 3). The breaking strength of these tablets differed from 115-130 N. However, the tablet friability of these formulations varied from 0.58 to 0.89%.

Table 2 Comparison of average size (as $\mu m$) distribution of procainamide coated granules prepared with different polymers as measured by U.S. standard sieves

| Sample | Weight size distribution ($\mu m$) |
|---|---|
| Uncoated granules | 680.66 |
| Eudragit RSPo | 767.84 |
| Uncoated granules | 692.06 |
| EC | 774.37 |
| Uncoated granules | 692.06 |
| EC + Eudragit S100 | 781.03 |

Table 3 Tapped bulk density of different procainamide granules as measured by cylindrical methods

| Sample | Bulk Density ($g/cm^3$) |
|---|---|
| Ethylcellulose | 0.41 |
| Eudragit RSPo | 0.44 |
| Ethylcellulose + Eudragit S100 | 0.44 |

## Dissolution behaviours of the tablets

Figure 1 shows the drug release profiles of procainamide HCl from brand sample and fabricated formulations containing different polymers in various media.

Each data point represents the mean of 18 determinations. Apparently, the dissolution from the tablets was dependent on the amount and the type of polymers used. Since procainamide HCl has an extremely high aqueous solubility (15), the quantity and the type of the retardant polymers for coating of procainamide HCl granules is very essential.Furthermore, as plasticizers

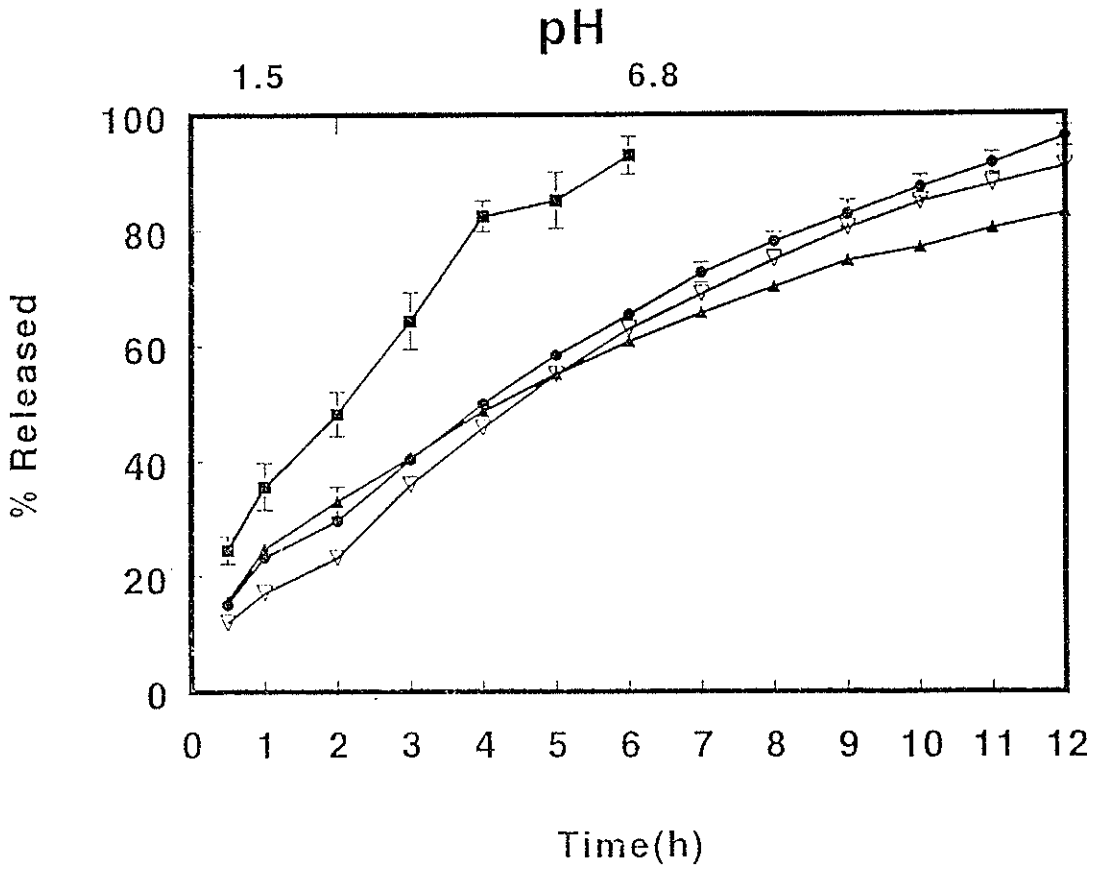


Figure 1:

Drug release profiles of controlled release (CR) procainamide HCl tablets preparing with different polymers as compared with brand sample in hydrochloric acid buffer pH 1.5 and phosphate buffer pH 6.8 as measured by paddle system (Apparatus II) at 37 °C. Symbols:

(▩) Brand sample; (▲) ethylcellulose; (●) Eudragit RSPo; (▽) ethylcellulose + Eudragit S100.

improve the flexibility and reduce the brittleness of the polymeric films, the selection of the proper plasticizer and its ratio to the polymer used is crucial. Eudragit RSPO is neutral polymer which is insoluble in entire physiological pH range. However, it possesses a defined swelling capacity and permeability with respect to water and dissolved drugs, which is independent of pH (12).Its film coating behaviours around the procainamide HCl granules has been

improved by using the triethylcitrate (TEC) as plasticizer in the ratio of 1:4 (plasticizer to polymer). This polymer exhibited a proper sustained release profile when was applied on the procainamide HCl granules at 28% ( W/W polymer to drug) concentration. Ethylcellulose (EC) is an insoluble, inert acid sensitive polymer (11).The film coating properties of this polymer was improved when triethylcitrate (TEC) in the ratio of 1:9 was used as plasticizer. Ethylcellulose (EC) demonstrated reproducible and suitable controlled retardant behaviour when used at 14% ( W/W polymer to drug) level. Double coating procedure (which was used for the first time in this study), using a cellulose ether derivative (EC) for the first coating and an anionic polymer (Eudragit S 100) for the second coating (in the presence of TEC as plasticizer in the ratio of 1:9) demonstrated predictable and profound controlled release behaviours when used at 8% (W/W for each individual polymer) level. Although, Eudragit S 100 as a methacrylic acid co-polymer is soluble in the pH above 7.0 (16). However, there was no significant difference in release characteristics of the granules coated with this polymer in two different media (buffer pH 1.5 and buffer pH 6.8). These results exhibit that ethylcellulose and methacrylate ester co-polymers are among the most reliable retardants which could be utilized in the preparation of the sustained release (SR) formulations of procainamide HCl and have been in agreement with previous data obtained by Rafiee-Tehrani et al. (5,9,10).Unexpectedly, brand sample has not shown a proper release behaviour as a controlled release oral preparation .As an average slightly more than 92% of the drug was released after 6h from this formulation.

## Kinetics of procainamide HCl release from CR formulations

The release of procainamide from a controlled release tablet formulation may either be a first-order or a diffusion-controlled process (17). Drug release data from formulations prepared with all polymers as well as brand sample were plotted according to the Higuchi equation (Fig. 2) and first order-kinetics (Fig.3).

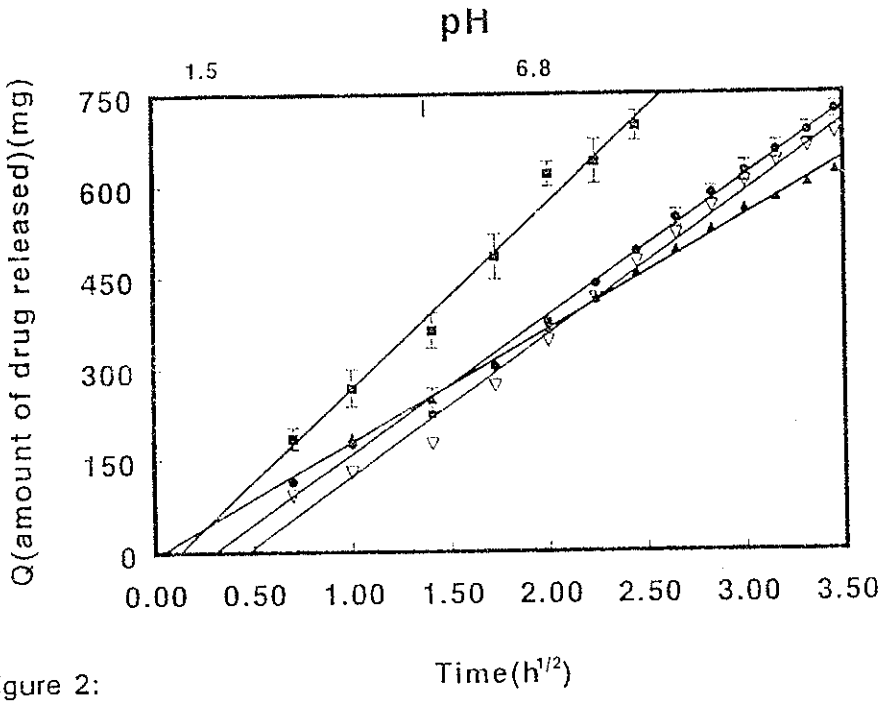


Figure 2:

Procainamide HCl release from (CR) tablets as a function of the square root of time (according to Higuchi equation) in hydrochloric acid buffer pH 1.5 and phosphate buffer pH 6.8.

Symbols:

(▩) Brand sample; (▲) ethylcellulose; (●) Eudragit RSPo; (▽) Ethylcellulose + Eudragit S100.

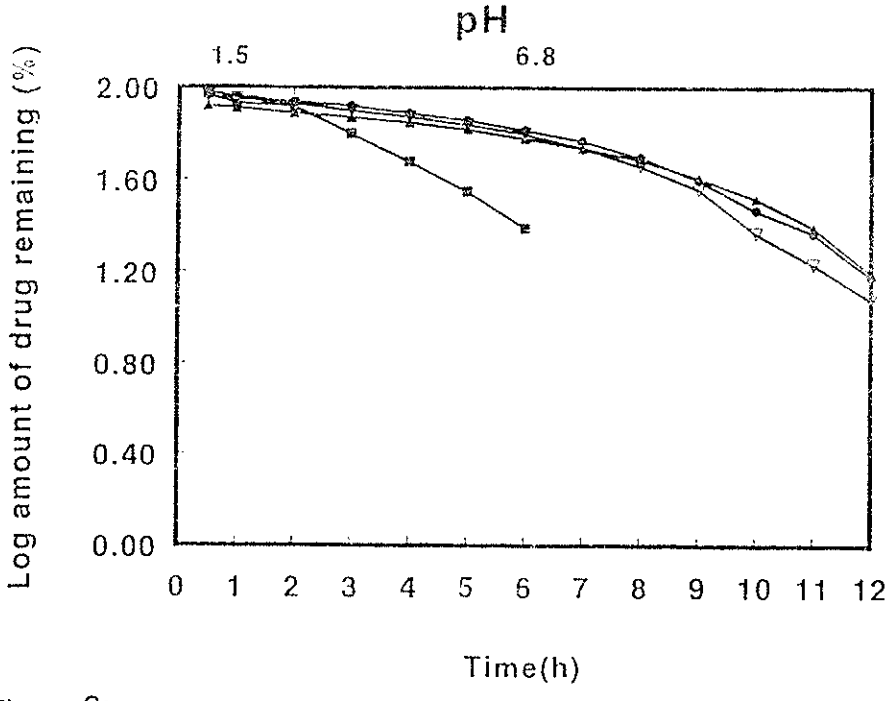


Figure 3:

Release profiles of procainamide HCl from (CR) tablets when plotted according to first-order kinetics in hydrochloric acid buffer pH 1.5 and phosphate buffer pH 6.8.

Symbols:

(▩) Brand sample; (▲) Ethylcellulose; (●) Eudragit RSPo; (▽) Ethylcellulose + Eudragit S100.

The relationship expressed by Higuchi equation (diffusion-controlled process) in its modified form can be written (18):

$$Q = Kt^{1/2}$$

were Q is the amount of drug released after time t per unit exposed area and K is the Higuchi rate constant. Release rate constants value, according to different mechanisms for the various formulations undr study were calculated and are shown in Table 4.

Drug release from formulation coated with ethylcellulose seems to fit the best to first-order kinetics. However, the release patterns of other formulations appear to fit the best to the Higuchi equation and correspond to a diffusion mechanism.

An average of 33.17%, 29.83% and 23.35% of procainamide HCl was released after 2h from formulations containing EC, Eudragit RSPO and EC+Eudragit S100, respectively. After 12h, the release of drug reached 83.03-96.12% of total content.

### Scanning electron microscopy (SEM)

A cross-sectional view of the coated procainamide granules shows a clear interface between the core and the coating (Fig.4).

## Conclusions

It has been demonstrated that controlled release procainamide HCl tablets prepared with ethylcellulose and methacrylate ester co-polymers (Eudragits RSPO and S100) revealed suitable drug release characteristics. Drug release from most of these formulations appears to correspond to a diffusion mechanism. It was shown that the dissolution rate of brand sample was much faster than expected. It is also exhibited that the fluidized bed technique is a

reliable method for producing a controlled release procainamide HCl formulaitons consisting of coated granules compressed to a tablet.

Table 4 Release rate constants calculated according to the first-order and Higuchi equation in hydrochloric acid buffer pH 1.5 (1st 2h) and phosphate buffer pH 6.8 (remaining period of time), as measured by Paddle system (Apparatus II) at 37 °C.

| | Ethylcellulose | Eudragit RSPo | Eudragit S100+EC | Brand Sample |
|---|---|---|---|---|
| $K_1(min^{-1}) \times 10^3$ | - 1.382 | - 2.372 | - 1.957 | - 3.638 |
| $r_1$ | 1.000 | 0.935 | 0.985 | 0.973 |
| $K_2$ (mgcm$^{-2}$min$^{-½}$) | 24.666 | 29.092 | 28.930 | 34.48 |
| $r_2$ | 0.998 | 0.991 | 0.981 | 0.993 |

$r_1$ 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.

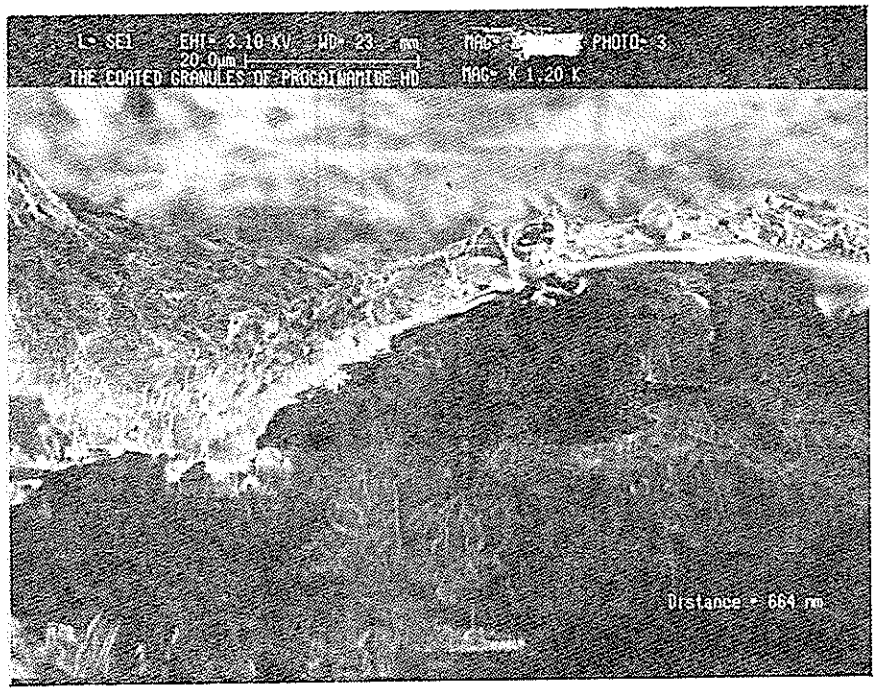


Figure 4:
Cross section scanning electron micrograph (1200 x magnification) of procainamide HCl CR granules (coated with Eudragit RSPo).

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