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COMMUNICATIONS

Preparation and Evaluation of Theophylline Sustained-Release Tablets

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ABSTRACT

Formulations were prepared containing 50% theophylline; 0%, 5%, 10%, 20%, 30%, or 49.5% of a new sustained-release agent (Carbopol® 974P); 0.5% lubricant, with the remainder of the formula consisting of spray-dried lactose. Similarly, a formulation containing 30% Carbopol 934P was prepared for comparative study. The tablets produced showed good mechanical properties. The disintegration time of the tablets was dependent on the type and percentage of the sustained-release agent as well as the pH of the medium. The drug release profiles were consistent with the disintegration time; increasing the percent of Carbopol 974P in the tablet and holding its weight constant resulted in a decrease in drug release rate. Approximately 10% Carbopol 974P provided the same sustained-release mechanism as 30% Carbopol 934P without tablet sticking during compression. Carbopol 974P matrices exhibited release profiles which were best described by mixed zero-order and Higuchi linear square root of time relationships. This means that mixed barrier and matrix diffusion-controlled mechanisms were operative.

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INTRODUCTION

Swellable matrix systems such as Carbopol® 934P, Klucel®, HXF, and others are being widely investigated by several workers since they are currently recognized as desirable systems for the delivery of drugs in a controlled-release manner (1–9).

A new carbomer, Carbopol 974P, is a synthetic high molecular weight cross-linked polymer of acrylic acid. It is a white to off-white powder, with a slight characteristic odor (slightly acetic) (10). It could be used as a dissolution rate-controlling excipient. So, it was of interest to investigate the kinetics and mechanism(s) of theophylline release from tablets containing this agent. In addition, the replacement of Carbopol 934P by Carbopol 974P could solve the problem of tablet sticking produced by the use of the first polymer (9).

EXPERIMENTAL

Material

- Carbopol 974P and Carbopol 934P (both from B. F. Goodrich, Cleveland, OH, USA)
- Theophylline (Knoll, USA)
- Spray-dried lactose (Sheffield Products, Norwich, NY, USA)

Tableting

Tablet formulations proposed in this study are listed in Table 1. The powders for each formulation were each passed through a No. 20 mesh screen, efficiently well mixed in a glass wide-mouth jar, and compressed into tablets using a single-stroke Erweka tablet press fitted with round, flat-faced punches of 7/16 in. The target weight of the tablet was 400 mg and the hardness was held constant (8–10 Kp) for comparative dissolution studies.

Physical Tests

The weight uniformity, thickness, hardness, and friability were determined for each batch of the prepared tablets. Disintegration testing was performed according to the USP XXII. The USP/NF XXII dissolution method I was used with a rotational speed at 50 rpm and a dissolution medium of 900 ml of distilled water at 37° ± 0.5°C. Dissolution media simulating the fluid in the gastrointestinal tract were also used (0.1 N HCl and pH 7.2 phosphate buffer). The dissolution samples were filtered, suitably diluted, and analyzed spectrophotometrically at 272 nm. The means of three determinations were determined.

RESULTS AND DISCUSSION

Physical Characteristics

All the formulas presented in Table 1 satisfied the USP XXII requirements for weight uniformity (% *RSD* < 0.52). The friability test (less than 1%) as well as the hardness test (% *RSD* < 5.7) were also satisfactory. Tablets containing Carbopol 974P showed swelling and gel formation with erosion while tablets with pure lactose (F-6) completely passed through the mesh in less than 1 hr. As the percent of Carbopol 974P in the formulations increased, the disintegration time increased, reaching 2.5 hr with F-5. This was probably due to the high gel formed with the high percentage of Carbopol

Table 1

Formulations of Theophylline Tablets

Formula	Theophylline	Carbopol 974P	Carbopol 934P	Lactose	Magnesium Stearate
F-1	50	5	—	44.5	0.5
F-2	50	10	—	39.5	0.5
F-3	50	20	—	29.5	0.5
F-4	50	30	—	19.5	0.5
F-5	50	49.5	—	—	0.5
F-6	50	—	—	49.5	0.5
F-7	50	—	30	19.5	0.5

974P, which resisted rapid erosion of the tablets. In addition, at equal polymer percentages (F-4 and F-7), Carbopol 974P provided longer disintegration time than Carbopol 934P (85 and 45 min, respectively).

Dissolution Studies

The drug release profiles in distilled water were consistent with the time taken for complete disintegration of the tablet. Increasing the percentage of Carbopol 974P in the tablet and holding its weight constant resulted in a decrease in drug release rate (Fig. 1). Similar results were obtained in 0.1 N HCl or pH 7.2 phosphate buffer. The figure also shows that tablets containing 10% of Carbopol 974P are equivalent in drug release to those containing 30% of the 934P formulation.

The pH of the dissolution medium was found to affect the drug release profiles from Carbopol 974P containing tablets, as shown in Fig. 2. The drug release from water and phosphate buffer exhibited insignificant difference. However, significant difference in the drug release was obtained from 0.1 N HCl as compared to that from phosphate buffer as indicated by Student's *t* test at the 0.05 significance level. This was probably due to the fact that Carbopol formed a strong gel at pH 7.2 which was responsible for the sustained drug release (5).

Since at equal polymer percentages in the tablets (30%, F-4 and F-7), Carbopol 974P resulted in longer disintegration time (85 min) than Carbopol 934P (45 min), much slower drug release was experienced with the first as compared with the second in the three dissolution media (Fig. 2).

Discussion of the Drug Release Mechanism(s)

Different methods were used to explore the drug release kinetics and mechanism(s) from Carbopol 974P containing tablets (9):

1. Tablet appearance: All Carbopol 974P tablets showed swelling and a gel-like layer was formed on the tablet surfaces in different pH media. However, the degree of gel formation was pH dependent. This gel layer obviously played a critical role in the sustained-release action.
2. The dissolution data were analyzed using the Surefit nonlinear computer program with different drug release kinetic models (11). It was found that a mixed zero-order and Higuchi linear square root of time relationship with lag

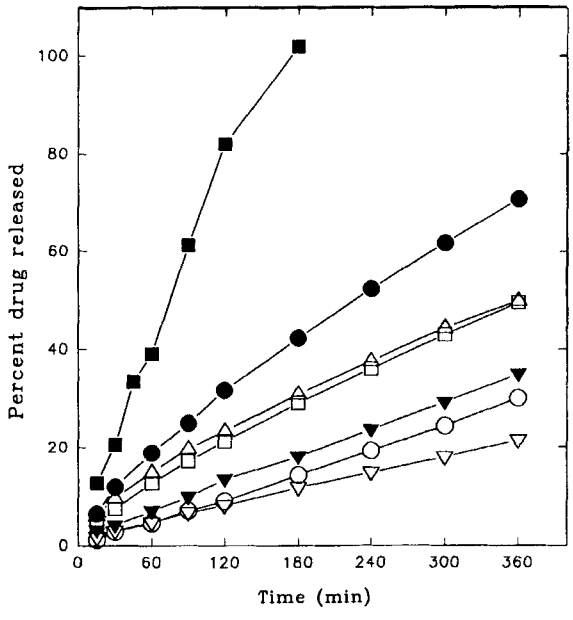

Figure 1. Tablet dissolution profiles in distilled water from 50% theophylline/ *x*% Carbopol 974P in lactose. Carbopol content—Carbopol 974P: ●, 5% (F-1); □, 10% (F-2); ▼, 20% (F-3); ○, 30% (F-4); ▽, 49.5% (F-5); ■, 0.00% (F-6). Δ, 30% Carbopol 934P (F-7).

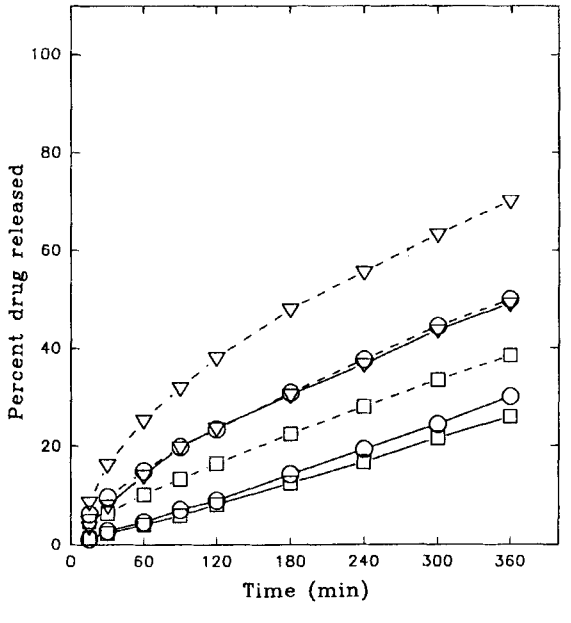

Figure 2. Tablet dissolution profiles in different pH media from 50% theophylline/30% Carbopol in lactose. ___Carbopol 974P; ------Carbopol 934P. ○, distilled water; ▽, acid; □, phosphate buffer (pH 7.2).

time [Model 6, Eq. (1)] was the best model to describe the drug release kinetics from Carbopol 974P containing tablets in terms of the low weighted sum of square residual (0.1–1.8), the high goodness of fit (0.973–0.999), and the low Akaike information criteria (0.0–11.2).

$$Y = K_1 t + K_2 t^{1/2} \quad (1)$$

CONCLUSION

The mechanism of drug release from both Carbopol formulations was dependent on the degree of gel formation. The gel formation was dependent on the type of the polymer, its percentage in the tablet, and the pH of the medium. Approximately 10% Carbopol 974P provided the same sustained-release mechanism as 30% Carbopol 934P.

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