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INVESTIGATION OF PROLONGED DRUG RELEASE FROM MATRIX FORMULATIONS OF CHITOSAN

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ABSTRACT

A hydrocolloidal matrix system containing complexes of chitosan was investigated for preparation of sustained release tablets and examined in-vitro.

Theophylline tablets using chitosan as a sustained release base were evaluated. It was found that when chitosan is used in a concentration of more than 50% of tablet weight, an insoluble non-erosion type matrix was formed. Tablets prepared with a chitosan concentration of less than 33% were fast releasing.

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Chitosan used in a concentration of about 10% acted as a disintegrant and the drug was dissolved within an hour.

Citric acid slowed down the release rates of chitosan based theophylline tablets. Theophylline tablets using carbomer-934P as a sustained release base were evaluated. Carbomer-934P in lower concentrations forms an erosion type matrix. In order to produce a twenty-four (24) hour sustained release tablet, more than 10% concentration of carbomer-934P is needed. Combination with chitosan and carbomer-934P produced slower releasing tablets.

A hydrocolloidal erosion type matrix was formulated using chitosan, carbomer-934Pand citric acid. Only 10% of chitosan was needed to prepare theophylline sustained release tablets in these mixtures.

The dose dumping potential of chitosan tablets due to rapid disintegration in alkaline media was eliminated by preparing hydrated erosion type matrix systems.

INTRODUCTION

The mechanism by which sustained release is achieved in matrix tablets is dependent on many variables. The operating principle is that a polymer

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binder partially hydrates on the outer layer of the tablet to form a pseudo-gel layer. Throughout the ingested life of the tablet, the rate of diffusion of drug out of the wet pseudo-gel and the rate of tablet erosion control the overall dissolution and drug availability (1). The dissolution rate for soluble drugs is controlled by both diffusion through the gel layer and by erosion. The dissolution mechanism with insoluble drugs is strictly dependent on tablet erosion.

Experimental evidence regarding the toxicity of chitosan has been presented by Arai et al. (2). Chitin is a cellulose like polymer which contains hydroxyl, amino and acetyl groups on a polysaccharide chain. Although there is no clear distinction between chitin and chitosan, it is generally accepted that chitin is extensively acetylated, while chitosan is virtually deacetylated (3).

The average molecular weight of chitins exceed 1 million. Since chitosan is prepared from chitin by alkaline deacetylation, it has a lower average molecular weight, usually ranging between 1×10^5 to 3×10^5. Chitosan displays a wide range of viscosities in diluted acid media which depend on the molecular weight. Chitosan dissolves in diluted acid

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solutions, and only chemically treated or acid hydrolyzed chitin forms viscous solutions (4). This insolubility of chitin is the main reason for considering chitosan for sustained release application. Citric acid not only forms a complex with chitosan but also results in a viscous gel.

Since chitosan is a cationic polyelectrolyte which forms a gel structure in acidic pH, it is different from commercial high molecular weight hydrocolloids which are generally neutral or polyanionic (5).

Water uptake of chitin and chitosan was found to be significantly higher than that of microcrystalline cellulose (6). This water uptake property of chitosan enables it to function in tablet formulations as a disintegrant.

Initially, chitosan was considered to be used as a pharmaceutical excipient, as a replacement for microcrystalline cellulose. Yachi Sawayanagi et al. used chitosan to compress tablets at a level of 30 - 60% (7).

Miyazaki et al. reported the usefulness of chitosan as a vehicle for sustained release preparations of indomethacin and papavarine hydrochloride (8). Yoichi Sawayanagi et al. examined chitosan as a vehicle for sustained release

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preparations of water soluble drugs such as propranolol hydrochloride (9). Both researchers showed that when dissolution was performed in acid medium these dosage forms show an excellent sustained release property. They also showed that the tablets disintegrated in water. When they used simulated intestinal fluid (pH 6.8) as a dissolution medium, the tablets disintegrated within ten (10) minutes.

Citric Acid and carbomer-934P were used as co-adjuvants in this study as acidifying agents which gel the chitosan and thus impart sustained release properties. Carbomer-934P forms a thick gel at alkaline pH. This gel forming tendency of carbomer-934P is very useful in conjunction with chitosan as it reduces the disintegration property of the chitosan containing tablets.

Carbomer-934P is used in the preparation of tablets as a binder and a sustained release base. Long-acting methadone and quinine sulfate were prepared by Choulis et al. (10, 11). Other sustained release dosage forms were also studied such as that characterized by molecular entrapment etc. (12 - 15). The B.F. Goodrich Company has published several bulletins (16) detailing preparation of solutions of carbomer-934P and its physical properties etc. Chitin

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and chitosan are processed industrially from crustacean shell waste (17).

EXPERIMENTAL

Materials: Chitosan, powdered, (Protan Laboratories, Inc., Redwood, WA.), carbomer-934P 934P (B.F. Goodrich Company Inc., Cleveland, Ohio), theophylline anhydrous (Knoll Fine Chemicals, New York, NY) citric acid (Pfizer Chemical, New York, NY) stearic acid (Mutchler Chemical Inc., Westwood, NJ), magnesium stearate (Mutchler Chemical Inc., Westwood, NJ), silica gel (W.R. Grace & Co., Baltimore, Maryland).

Compression of tablets: Tablets were directly compressed using different combinations of chitosan, carbomer-934P and citric acid. Magnesium stearate, stearic acid and silica gel were used as lubricants prior to compression. Tablets were compressed using a Stokes B2 rotary tablet press. Tablet hardness was kept constant within the range of 8 - 12 kp using a Schleuniger tablet hardness tester.

In-vitro drug release studies: In-vitro release studies were performed on tablets using a six spindle dissolution apparatus (Distek Inc., New Jersey) at 50 RPM, paddle method, using 900 ml of deaerated, deionized water at 37^{o}C as a dissolution medium.

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On selected formulations, dissolution studies were conducted using simulated gastric fluid and simulated intestinal fluids. Dissolution samples were collected at various hourly time intervals and filtered samples were analyzed spectrophotometrically at 271 nm.

RESULTS AND DISCUSSION

The concentration of polymer in the matrix type formulation of chitosan based tablets was the determining factor in controlling dissolution rate of the drug.

Chitosan when used alone in a tablet formulation, did not impart sustained release properties at low concentrations such as 10%. When it was used in concentrations of 50% of the tablet weight, a non-erosion type matrix system was formed. Tablets containing 10% of chitosan, disintegrated rapidly within an hour (Figure 1). This data suggest that to make a non-erosion type matrix tablets of chitosan, it was necessary to use concentration of chitosan in excess of at least 50%. Swayanagi, et al (9) noted that at least 80% of chitosan was needed to achieve proper sustained release tablets.

An attempt was made to prepare a sustained release tablet with a reduced quantity of chitosan to achieve this.

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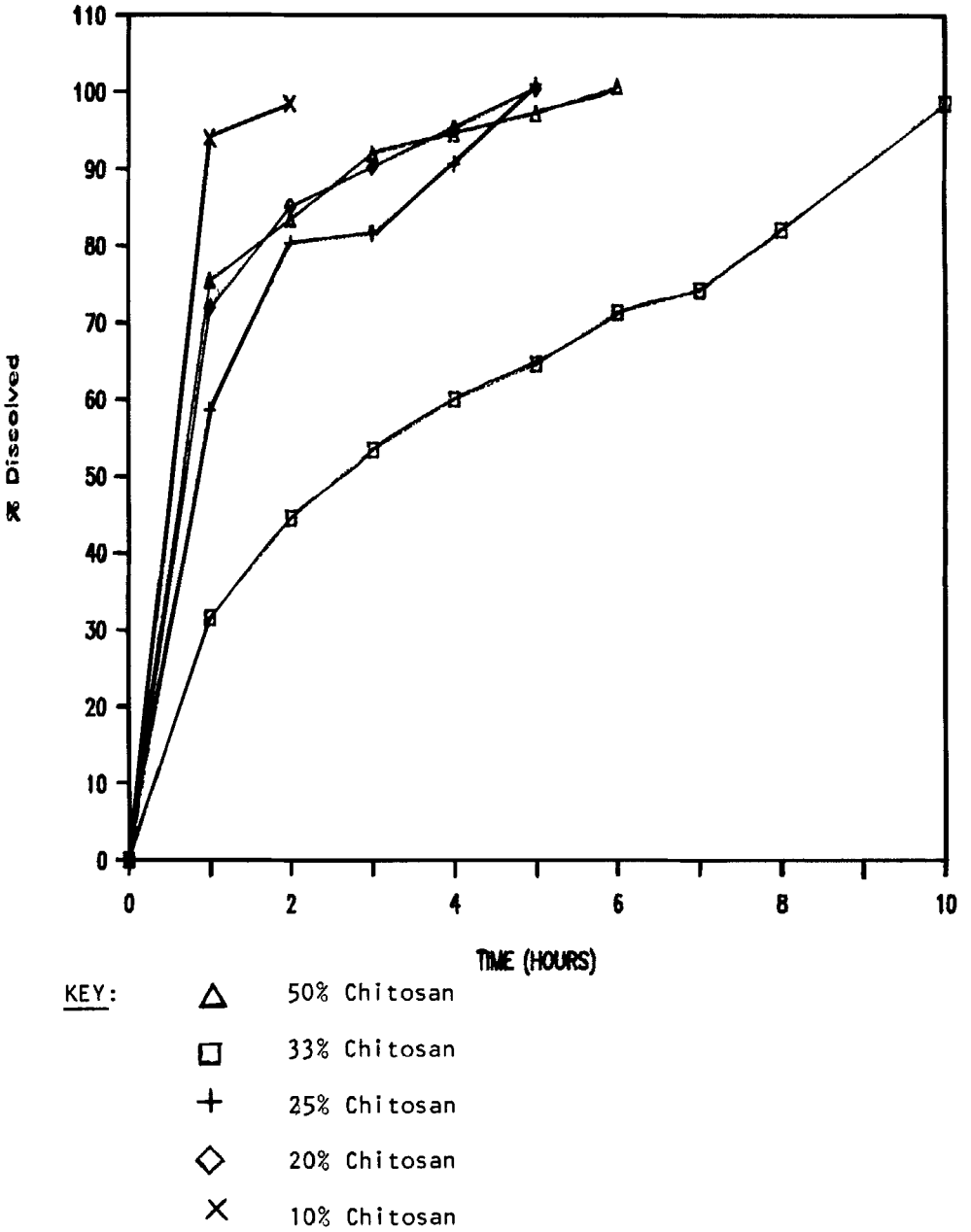

FIGURE 1

EFFECT OF CONCENTRATION OF CHITOSAN ON DISSOLUTION RATE OF THEOPHYLLINE TABLETS

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An erosion-type hydrocolloidal matrix of chitosan was formulated. Matrix hydration and the solubility of the matrix is a very important factor for a successful erosion-type matrix. It is known that organic acids such as citric acid form water soluble complexes with chitosan.

The viscosity of Chitosan was determined using various concentrations of citric acid. Figure 2 shows that as the concentration of citric acid was increased the viscosity also increased. Maximum hydration and solubilization occurred at 10% citric acid concentration. This property of the gelling of chitosan in the presence of citric acid was used in preparation of the erosion type matrix formulation.

Theophylline tablets were prepared using 10% chitosan as a sustained release binder with citric acid as a gelling agent. Tablets containing chitosan disintegrated and dissolved in one (1) hour. Tablets containing both citric acid and chitosan formed a hydrated erosion-type matrix system. Tablets with 5 - 8% citric acid dissolved for an extended period of time, about 14 to 16 hours. (Figure 3). This demonstrates that the concentration of citric acid was very important for the formation of a hydrated matrix.

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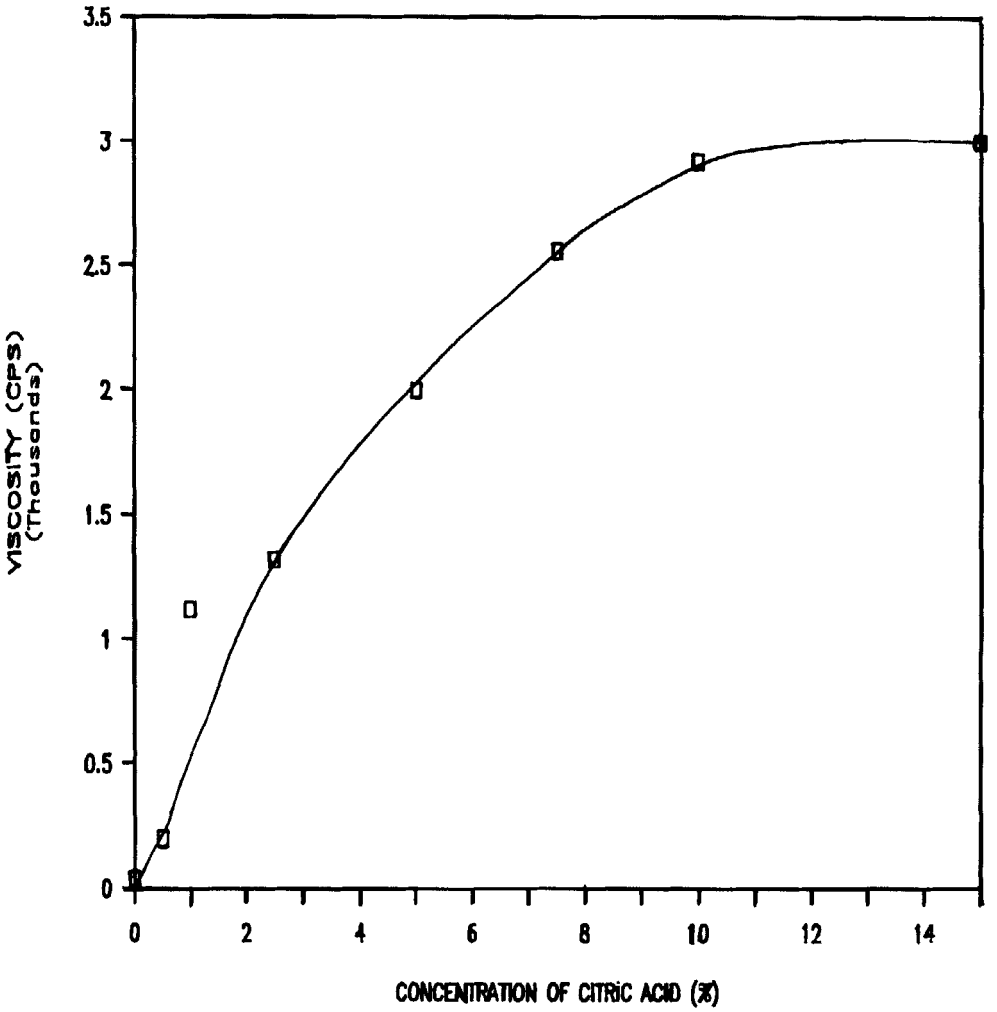

FIGURE 2

EFFECT OF CITRIC ACID ON VISCOSITY OF CHITOSAN GEL

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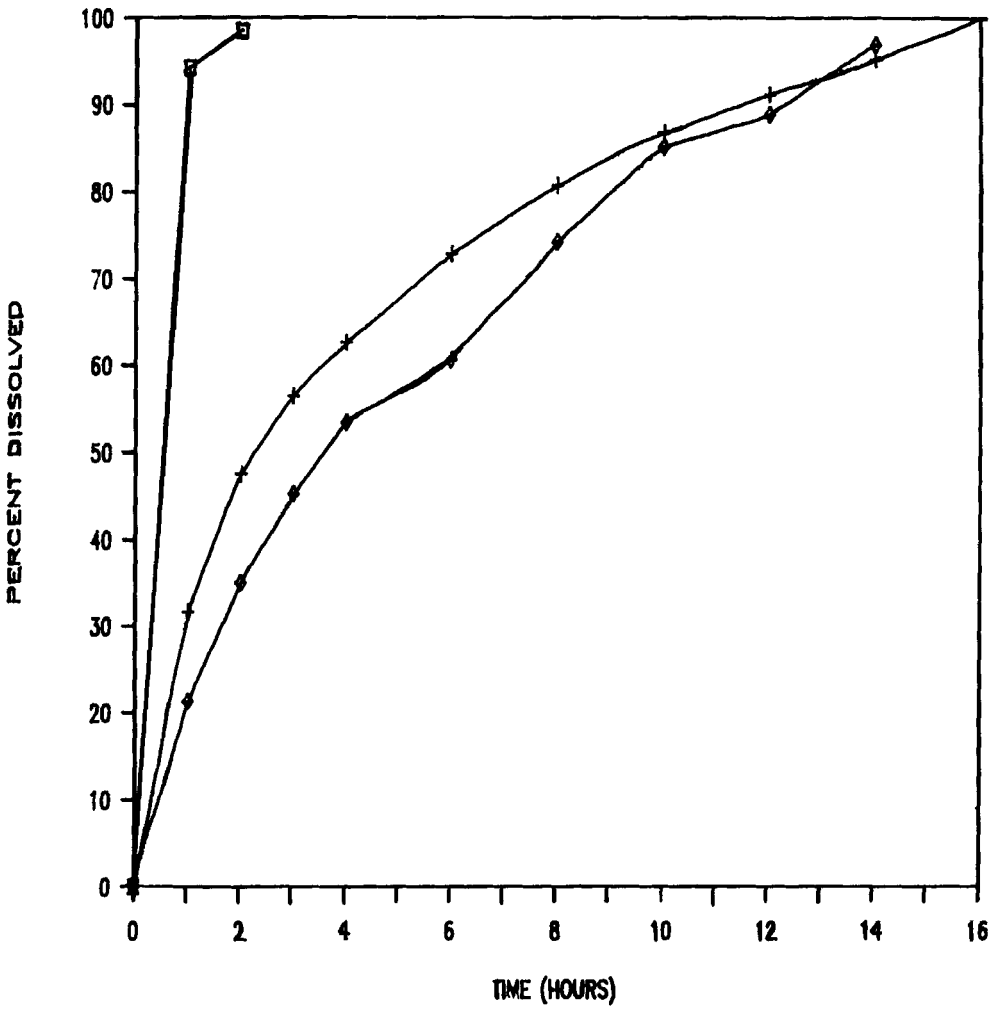

FIGURE 3

EFFECT OF CITRIC ACID ON DISSOLUTION

RATE OF CHITOSAN BASED THEOPHYLLINE TABLETS

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Tablets prepared with 8% citric acid showed slower dissolution of theophylline than the one prepared with 5% citric acid.

It is possible to produce either an erosion type or a non-erosion type of matrix formulations of chitosan. Figure 4 shows that to produce a non-erosion type formulation, it was necessary to use at least 50% of chitosan in a tablet. On the other hand, a similar dissolution profile was obtained by using only 10% chitosan and 5% citric acid in an erosion type matrix formulation.

The effect of carbomer-934P on the dissolution rate of chitosan based theophylline tablets was studied. Theophylline tablets with 10% of chitosan containing concentrations of 1% and 2.5% of carbomer-934P were prepared. The dissolution profiles (Figure 5) showed that as the concentration of carbomer-934P was increased, the dissolution rate decreased. Theophylline in tablets containing 2.5% carbomer-934P dissolved in approximately eight (8) hours whereas the tablets containing 2.5% carbomer-934P and 10% chitosan lasted for eighteen (18) hours. This data shows that carbomer-934P forms a complex with chitosan and produces a hydrated erosion type of matrix.

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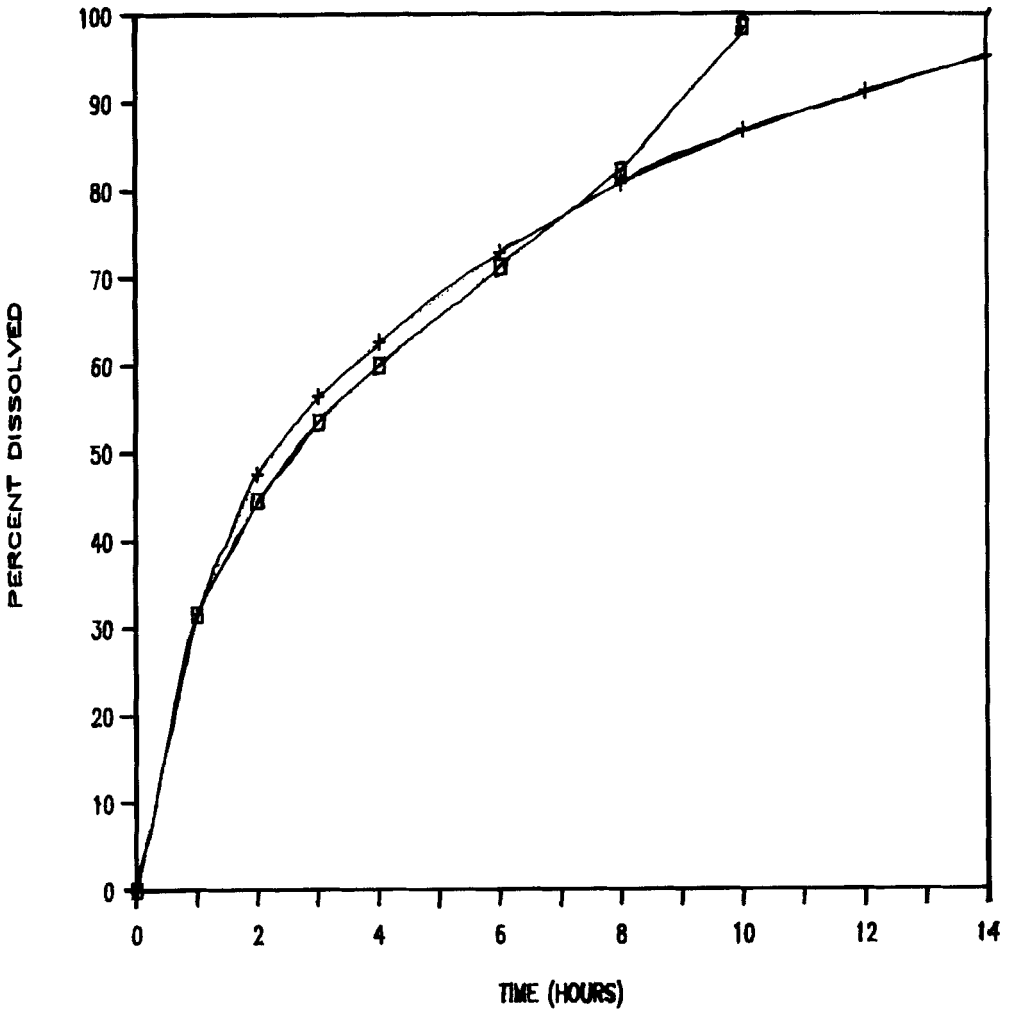

KEY:

□ 50% Chitosan-Non-Erosion Type

\+ 10% Chitosan + 5% Citric Acid - Erosion Type

FIGURE 4

COMPARISON BETWEEN EROSION TYPE AND NON-EROSION TYPE MATRIX FORMULATIONS OF THEOPHYLLINE TABLETS

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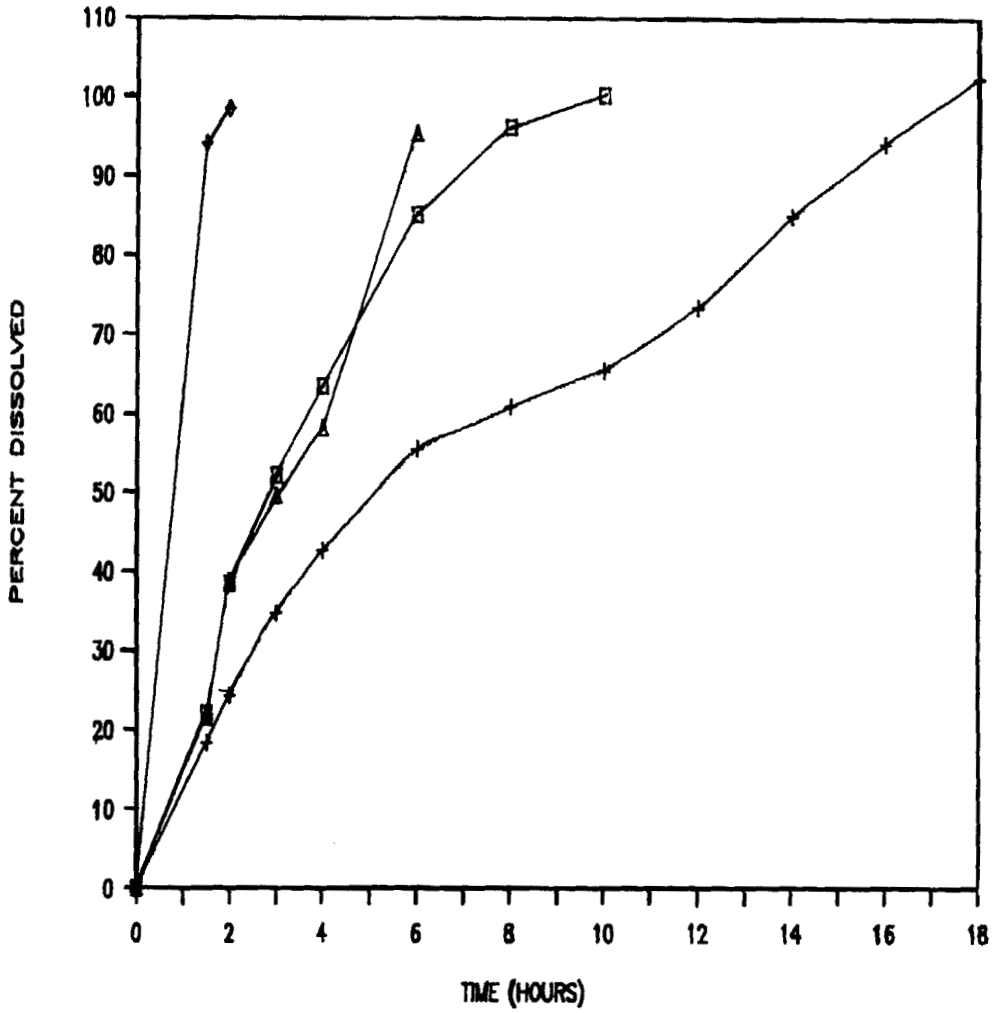

FIGURE 5

EFFECT OF CARBOMER-934P ON DISSOLUTION RATE OF CHITOSAN BASED THEOPHYLLINE TABLETS

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Theophylline tablets were prepared using citric acid and carbomer-934P with 10% of chitosan. The combination containing both citric acid and carbomer-934P produced tablets (Figure 6) in which theophylline dissolved in about twenty-four (24) hours. Theophylline in tablets containing chitosan and citric acid dissolved in sixteen (16) hours as compared to tablets containing chitosan and carbomer-934P in which theophylline dissolved in nine (9) hours.

It was also shown that first hour theophylline dissolution using carbomer-934P was slower than that in tablets containing citric acid. This was probably due to the gel forming property of carbomer-934P which itself forms a hydrogel.

In order to define the mechanism of drug release through the matrix formulations of chitosan, various kinetic equations were used. Higuchi's squareroot equation (18) for fused matrix systems was used to elucidate the release characterestics. A plot (figure # 7) of squareroot of time versus percent dissolved shows a linear relationship, which indicates diffusion controlled mechanism for both erosion type and non-erosion type formulations.

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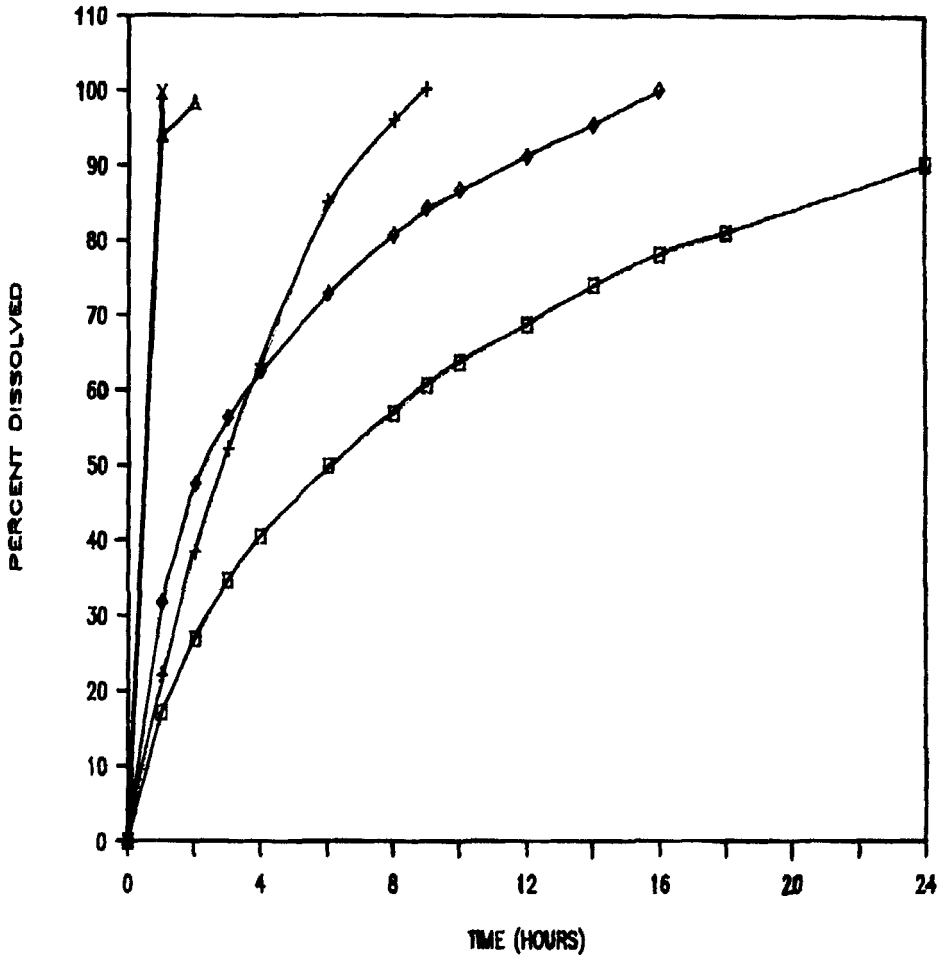

KEY:

□ 10% Chitosan + 1% Carbomer + 5% Citric Acid

\+ 10% Chitosan + 1% Carbomer

◇ 10% Chitosan + 5% Citric Acid

△ 10% Chitosan

× 10% Avicel pH 101

FIGURE 6

EFFECT OF CITRIC ACID AND CARBOMER ON DISSOLUTION RATE OF THEOPHYLLINE TABLETS CONTAINING 10% CHITOSAN AND USING D.I. WATER AS DISSOLUTION MEDIUM

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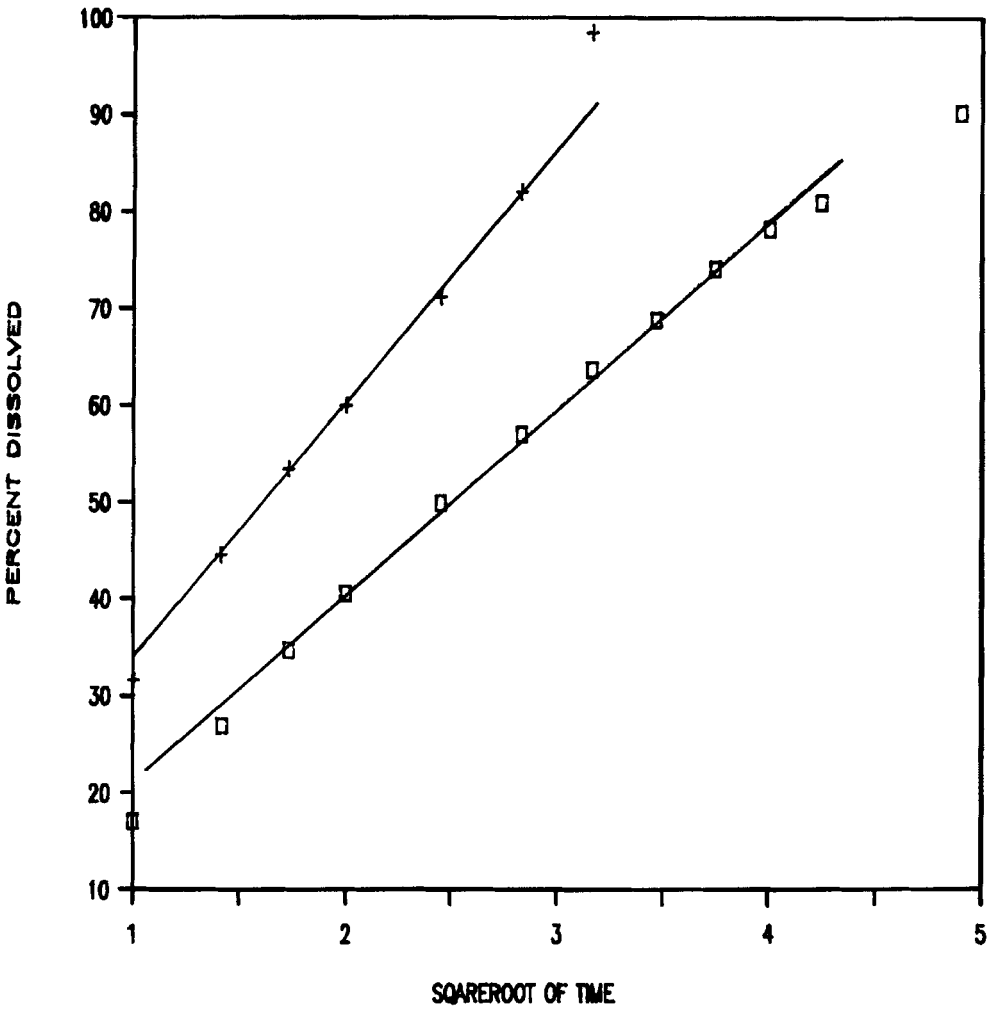

FIGURE 7

PLOT OF SQUARE ROOT OF TIME VERSUS PERCENT DISSOLVED

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CONCLUSION

From these experiments, one can conclude that an erosion-type matrix formulation of chitosan is superior to a non-erosion type matrix formulation. Both citric acid and carbomer-934P can be used as gel forming agents with chitosan. The hydration and gel formation of chitosan is very much dependent on the concentration of citric acid and carbomer-934P and sustained release properties can be varied by adjusting the concentrations of these adjuvants.

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