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A SUSTAINED RELEASE DRUG DELIVERY SYSTEM USING CALCIUM ALGINATE BEADS

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ABSTRACT

Calcium alginate beads impregnated with sulphamethoxazole as model drug were prepared and characterized. Scanning electron microscope was used to examine their surface with and without the drug. The bead average diameter was 1.25mm and the sulphamethoxazole uptake by the beads was about half of the incorporated quantity. The release behaviour was followed using USP dissolution method. The effect on release of factors such as sodium alginate, calcium chloride concentration, pH, hydration and compression were studied. Sodium alginate concentrations had no pronounced effect on the release. The release was found to be a function of calcium chloride concentration. The higher the concentration the lower the release. The smaller the water content the lower the release from the beads. Compression of the beads yields a deformed beads with an increase in their release. Plain calcium alginate beads were not suitable for sulphamethoxazole loading . Sulphamethoxazole diffusion through calcium alginate film was determined. The dissolution patterns were discussed. The system may offer a simple and efficient sustain release preparation.

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INTRODUCTION

Alginic acid derivatives are widely used in the food and pharmaceutical industry as dispersing, thickening and disinte - grating agents. One of the promising future of alginates is their application in the biotechnological research in order to immobilize microbial cells and enzymes (1,2). Their ability to entrap the cells makes them as an attractive candidate for use in sustain release dosage form. The object of this work is to test such possibility.

MATERIALS

Sodium alginate: viscosity of 1.0%w/v solution 85c.p.using Haake falling ball viscometer.
Calcium chloride - and heptane, were from Riedel- De-Haen.
Sulphamethoxazole, was B.P. quality.
All reagents used were of analytical grade.

METHOD

Preparation Of The Beads

Sodium alginate solution 1.6%w/v in water was prepared by soaking the powder in distilled water for 3 hours. 8 grams of sulphamethoxazole were dispersed at room temperature in the sodium alginate viscous solution and filled into a glass cylinder having a diameter of 2.5 cm and the pore of the orfice 0.25 mm. in diameter. The end of the cylinder was connected to a source of compressed air. The alginate solution was forced through the capillary end into a beaker placed on a magnetic stirrer . The beaker contained 100ml of calcium chloride of 10% w/v solution and 200ml of heptane. The formed beads were

separated, washed with distilled water and dried on open trays at room temperature. The leached water was removed and the loss in the beads was recorded till constant weight. The beads were stored in a closed glass container. All batches were in triplicates.

The dried produced loaded beads were fractionated by a micro sieve set by shaking for 10 minutes. Beads with diameters 2.00 to 1.25 mm were used in this work.

Characterization Of The Calcium Alginate Beads:

Surface Characteristics:

Letiz scanning electron microscope was used to characterize the beads surface. One whole bead was placed on a metallic support with a thin adhesive material and the samples were coated with carbon-gold layers under vacuum. The surface was screened and photomicrographs were taken for the loaded and unloaded beads. A cross section was made from the loaded and unloaded beads and treated in a similar manner. Photoagraphs are presented in figure (1-a,b,c,d).

Sulphamethoxazole Content Determination:

The drug content was determined by powdering the obtained beads with a high speed chopper and extracting the drug with 0.1N sodium hydroxide. The absorbance was measured at 257 nm using Perkin Elmer spectrophotometer (model 550 S).

Release Measurements:

The release of sulphamethoxazole from calcium alginate beads was measured using USPXX dissolution apparatus. The basket was rotated at 100r.p.m. at 37° C. The dissolution medium used were 0.1N hydrochloric acid, 0.1N sodium hydroxide and a phosphate buffer (pH = 10.6). One gram of beads having an average dia-

meter of 1.25mm were placed loose in the basket. The release was followed up to 6 hours. Aliquots of 5ml were withdrawn and diluted to 100ml with0.1N sodium hydroxide. The absorbance was recorded at 257nm. The withdrawn samples from dissolution apparatus were replaced by the same quantity of the dissolution medium used. The results are presented in figures(2-6).

Effect of Hydration on the Release:

The fresh formed beads were kept on an open tray at room temperature. Their weight loss was recorded and their release was measured for each stage of water loss. The effect of water content is shown in figure (4).

Effect of Compression:

One gram of the free flowing beads was placed in a die of 1 cm diameter of a hydrolauic press and was compressed under 5 and 10 tons. The resulted deformed beads were tested for their release properties. The scanning electron microscope was used to characterize the effect of pressure on the granule surface as shown in Figure(1-d).

Loading of the Beads with the Drug:

A plain calcium alginate beads were produced as described in method of preparation. The beads were left to dry at room temperature then they were soaked in 0.5 %w/v of sulphamethoxazole for different periods of time. Beads were separated, washed with distilled water and the drug content was determined.

Effect Of Boiling:

Loaded and unloaded beads were boiled in water for 30 minutes. Shape and size of the boiled beads were visually examined.

Calcium Alginate Film Preparation And Charecterization

Sodium alginate solution 1%w/v was poured into a petridish and left to dry. 100ml of 10%w/v calcium chloride was added and left for 30 minutes. The formed film was washed and stored in a petridish under distilled water. The film was characterized under the scanning electron microscope. In order to study the permiability of the alginate film, the membrane was placed on the 250ml bottle mouth containing 0.100%w/v solution of sulphamethoxazole in 0.1N hydrochloric acid and the inverted bottle was placed in 2 liters beaker containing 500ml of 0.1N hydrochloric acid placed on a magnetic stirrer. Samples of 5ml were withdrawn and analysis was carried for their sulphamethoxazole content.The amount diffused through the membrane is shown figure (7).

RESULTS AND DISCUSSION

Preparation Variables:

The produced beads were fairly rounded spheres. Their size ranges between 2.00 - 0.325 mm with an average diameter of 1.25mm Calcium alginate beads size was found to depend on the rate of stirring in the recieving beaker. The higher the speed, the lower the average bead size. Sodium alginate viscosity plays the most important factor in determining the nature of the produced beads. The shape becomes more spherical with the increase of sodium alginate concentration. When 1%w/v solution of sodium alginate with a viscosity of 85 c.p. was used, irregular beads were yielded; having an average diameter of 0.80 mm. The particle size was 1.25mm in 1.6% and 2.0%w/v solutions, having viscosities of 239 c.p. and 716 c.p. respectively. Such change in the size may be attributed to the failure of the stirrer to disperse the viscous droplets of higher concentrations. However 2%w/v solution was difficult to manipulate. The 1.6%w/v solution yiel

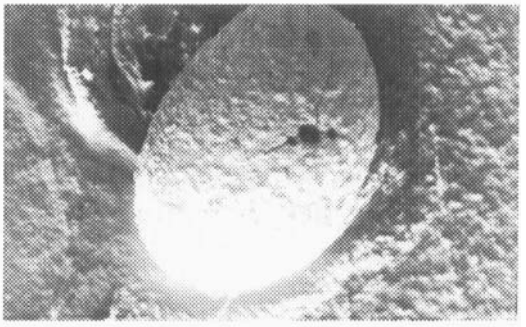
ded more reproducible spheres therefore such concentration was selected as the working concentration in the present work.
The spherical shape resulted was dependent on the hydrophobicity of the organic phase in the receiving vessel. Butyl acetate, cyclohexane and chloroform were not suitable to produce uniform spherical beads. Heptane offers the best alternative as in addition to its hydrophobicity it doesnot dissolve sulphamethaxozole or calcium alginate. However, beads can be formed without the organic phase but heptane presence faciliated the production of more spherical beads due to the reduction in the interfacial tension of the falling drop. Different sulphamethoxazole particle size was used and found not to have any effect on the beads size or shape. The average sulphamethoxazole particle size used in this study was 0.100mm. The variation in calcium chloride concentration was found not to effect the shape and size of beads

Surface Characterization:

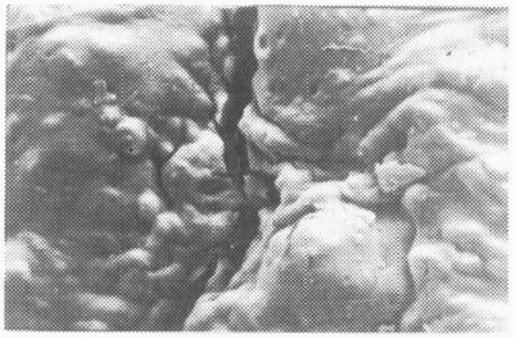
Electron microscope scanning studies, showed that the beads had uneven rough surface. When the unloaded beads were examined, their surface did not show any clear pores as shown in figure (1-a). When the beads were loaded with the drug the surface was covered with adsorped sulphamethoxazole particles, cracks and fissures as appear, in figure (1-b,c). When sulphamethoxazole was kept at a very low concentration the cracks on the surface did not disappear.
A cross section in a loaded bead showed that the sulphamethoxazole particles are embodied in the calcium alginate matrix.
To further the understanding of the beads surface, loaded and unloaded alginate films were examined, their surface were similar to that of the beads . When loaded beads were subjcted to 5 and 10 tons of pressure, the bead cracked from one end forcing its content out of the core as appears in figure (1-d) .

FIGURE (1):
Scanning electron microscope photographs.

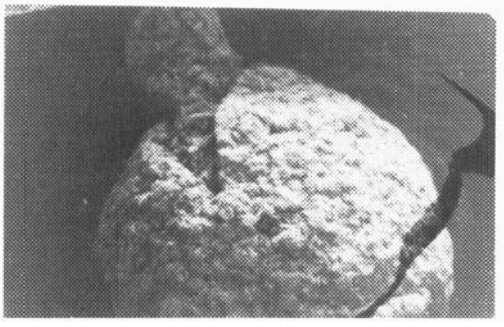
a- The surface of calcium alginate bead without the drug.



b- The whole loaded calcium alginate bead with the drug.



c- Cracked surface of the loaded calcium alginate bead.



d- Loaded compressed bead.

Drug Content Determination :

Five batches each of 10 grams of dried calcium alginate beads were prepared. Their mean content of sulphamethoxazole was 510.5mg/G (S.D = $\pm$ 0.80) Generally the drug comprising 50% of the total dried beads weight. Concentrations of sodium alginate or calcium chloride had no effect on the entrapped amount of sulphamethoxazole. The reproducibility of the sulphamethoxazole content in the system may be attributed to the insolubility of the sulphamethoxazole in the calcium chloride solution or the organic solvent. However when the beads were exhausted by soaking for 16 hours in 0.1N hydrochloric acid the released sulphamethoxazole was found to be 85% of the embodied quantity indicating that the remained amount is strongly trapped in the beads' body.

Release Studies:

Chemistry Of Alginates.

It is accepted that alginic acid is a long chain of polysaccharides consisting of three main 1,4 - linked structural blocks, poly -D- mannuronic acid, poly-L- guluronic acid and blocks in which the two uronic acids occur together through 1-4 glycoside linkage (3) Alginic acid salts of alkaline metals are soluble and they absorb up to 10 times of their weight water. On the other hand, the divalent salts of alginic acid are insoluble in water. The insolubility occurs due to the cross linking of the divalent ion of two chains of alginic acid yielding a cross linked insoluble gel. Consequently, the cross linking increase with the increase of the divalent ion availability. The result of the conversion of sodium to calcium alginate is the accompanied by a loss of water from the gel.

Treatment Of Release Data:

Many expressions have been forwarded to describe the release from different sustained-release products. In general, models used for derivation were based on release from salp with a unit cross section and with known porosity and containing a unit quantity . Higuchi (4,5) was the first to derive an equation describing the drug release from porous matrix when the amount of drug present is greater than its solubility by a factor of three or four. Such treatment (6) was extended to describe the release from planes when the drug is present in low content. Diffusion from plane sheets and cylinders were considered (8,9), Recently solution for equations describing release from spheres and the effect of interfacial transport on the kinetics process was provided. When no phase boundries take place, the equation was derived and simpilified as follows:

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(-n^2 \pi^2 \tau \right) \quad \ldots\ldots(1)$$

Where:

Mt : The amount of drug which diffuses out of sphere at time "t"

M_∞ : The amount of drug that would be released after infinite time.

$$\tau = \frac{Dt}{r_o^2} \quad \ldots\ldots \text{" as normalized parameter"} \qquad (2)$$

Where:

D : The integral diffusion coefficient of the substrate

r_o : Radius of the sphere used.

Accordingly =

$$t = \frac{\tau r_o^2}{D} \quad \ldots\ldots(3)$$

At very short time $\tau << 1$, $\tau^{1/2} > \tau$

$$M_t = 6 M_\infty \tau^{1/2} \pi^{-1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

Assuming that r_o and D are constants, Equation(4) can be re-written as

$$M_t = K\sqrt{t} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (5)$$

Equation (5) yields a straight line when M_t plotted against square root of time . This expression is similar to the expression previously derived for plane surface (4,5). Dissolution tests were carried out to examine the suitability of the alginate to act as a matrix for prolong release systems. Dissolution pattern is represented by plotting the cumulative quantity released against the square root of time. Different formulation factors such as sodium alginate and calcium chloride concentrations, compression pH and hydration were studied and their effect on the release of sulphamethoxazole is recorded as seen in figure (2,3,4,5,6) Sulphamethoxazole release in 0.1N HCL is taken as control. Figure (2) shows the pronounce delay in the dissolution time of sulphamethoxazole by incorporting in alginate matrix

The amount released appears not to vary with the sodium alginate concentration.

However, the release of 50% of the sulphamethoxazole content is taking place after 120,160 and 200 minutes for 1,1.6 and 2% w/v of sodium alginate solution respectively. The total release of sulphamethoxazole when 1%w/v solution of sodium alginate was used found to be in the proximity of 75% of the total drug content, in comparison to 60 and 65% of total drug content for 1.6 and 2% sodium alginate solutions. As the concentration of calcium chloride was similar in the three formulations used one would expect that the calcium ion will replace the sodium ion. Since a cross linking takes place between the long chain polysaccharide polymers, the system becomes less flexible when higher sodium

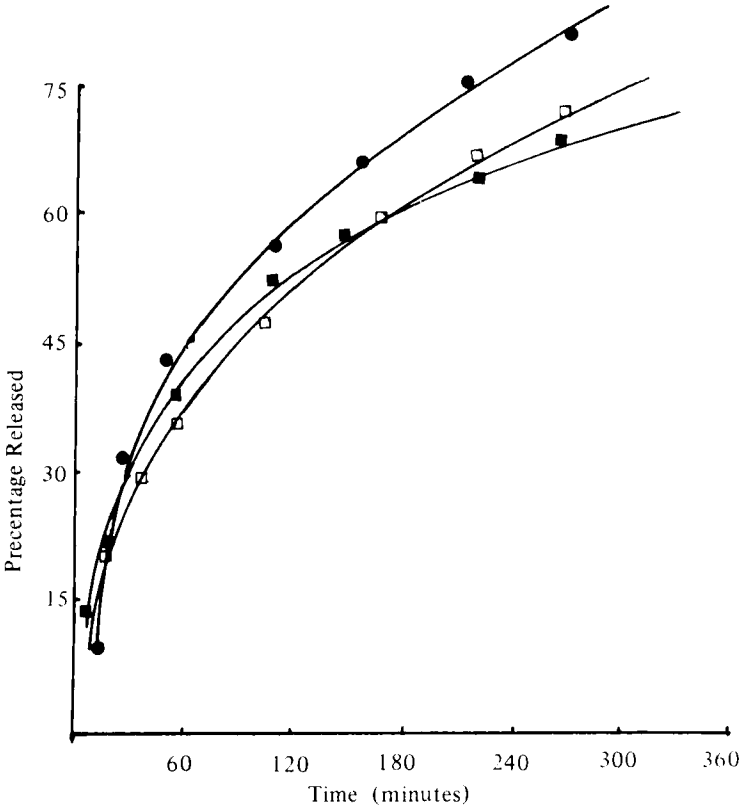


FIGURE (2)
Percentage released of sulphamethoxazole in 0.1N HCl with different concentrations of sodium alginate used.
● -1.0% w/v sodium alginate - 10% w/v calcium chloride
□ -1.6% w/v sodium alginate - 10% w/v calcium chloride
■ -2.0% w/v sodium alginate - 10% w/v calcium chloride

alginate concentration is used. When different calcium chloride concentrations were used (5-15%) with 1.6%w/v of sodium alginate solution a pronounced difference in the release was observed as shown in figure (3). The slopes of M_t Vs $t^{\frac{1}{2}}$ plots give the appearent release constant. Slopes were plotted against calcium chloride concentration ,a linear relationship was obtained, Such linearity indicates the importance of calcium ion in forming cross linked polymers, consequently increasing the compactness of the formed insoluble matrix.

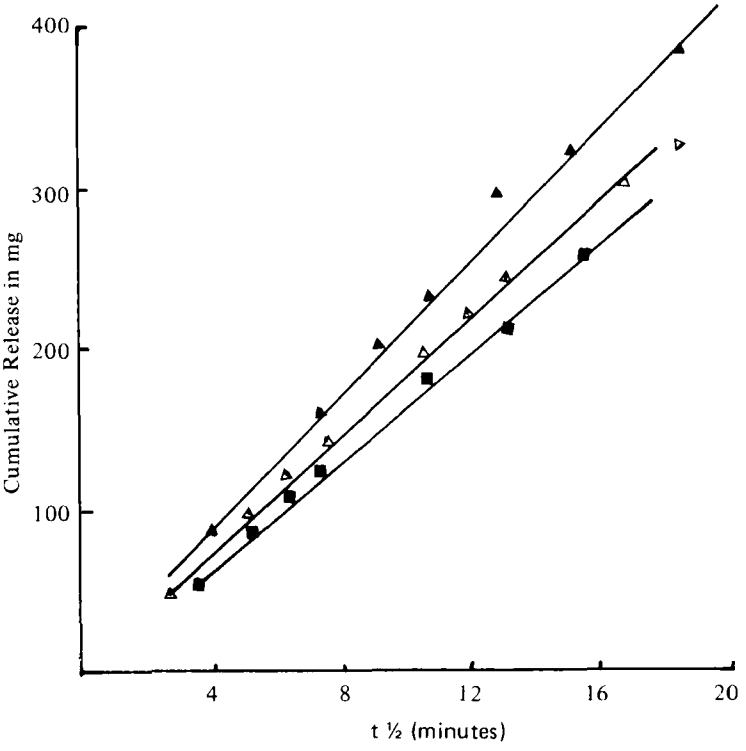
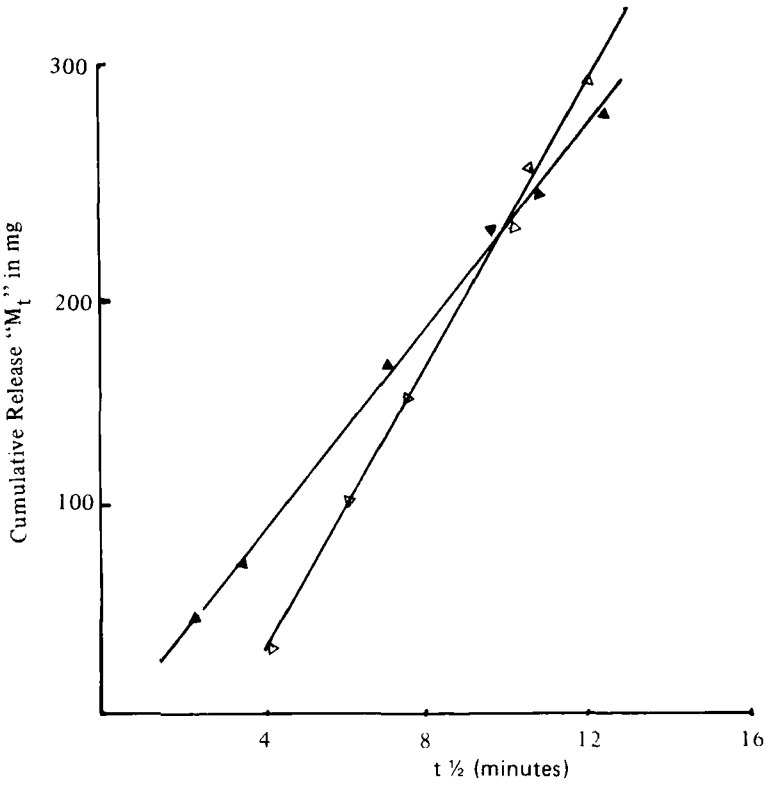


FIGURE (3)
Release of sulphamethoxazole when 1.6% w/v sodium alginate was used with different calcium chloride percentage.
▲ - 5% $CaCl_2$ △ - 10% $CaCl_2$ ■ - 15% $CaCl_2$

Different pH media were used as dissolution medium. In 0.1N sodium hydroxide solution 92% of sulphamethoxazole content was released in 90 minutes. This is due to the free solubility sulphamethoxazole in alkaline medium. When phosphate buffer (pH 10.6) was used as dissolution medium, it became turbid and the beads loose their compactness as the cross linking former escape to the dissolution medium forming calcium phosphate. In an acidic medium 0.1N hydroclric acid 65% of the sulphamehoxazole was released in 360 minutes.

Release was tested for freshly prepared beads during their equilibrium with atmosphere. Figure (5) shows that the higher



FIGURE(4)
Effect of pH on the release of sulphamethoxazole from calcium alginate beads
▲ - pH 10.6
△ - pH 1.0

the water content, the higher the release, this may be attributed to the swelling effect of cracks due to hydration consequently facilitating the sulphamethoxazole release.

Beads prepared from 1.6% w/v of sodium alginate and 5% of calcium chloride were compressed under 5 and 10 tons respectively. Compressibility increased with the increase of pressure. The compressed tablet resulted lost its compactness following the immersion in the dissolution medium. When the release properties were followed, the beads exposed to higher pressure released their content faster indicating the increase in cracks on the surface,

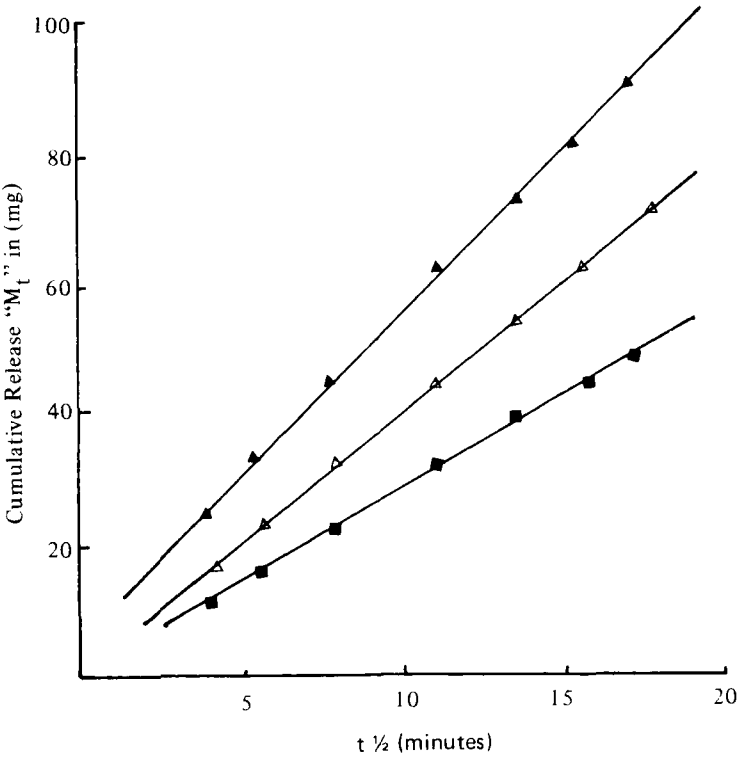


FIGURE (5)
Effect of hydration on the release of sulphamethoxazole from calcium alginate beads.
▲ - 78% water
△ - 54% water
■ - 22% water

Consequently, the contact with the dissolution medium and the release increased too. When the same amount of sodium alginate and 15% of calcium chloride were used in preparing beads and exposed to 5 tons, the release was slower and the total amount released was smaller as shown in figure (6) . The rigidity of the beads made them easier to be ruptured hence their release was higher than the release from beads containing 5% calcium chloride in the intial stage. On the other hand, the release after 360 minutes was lower than the other formulation due the high percentage of cross linking taking place under such high

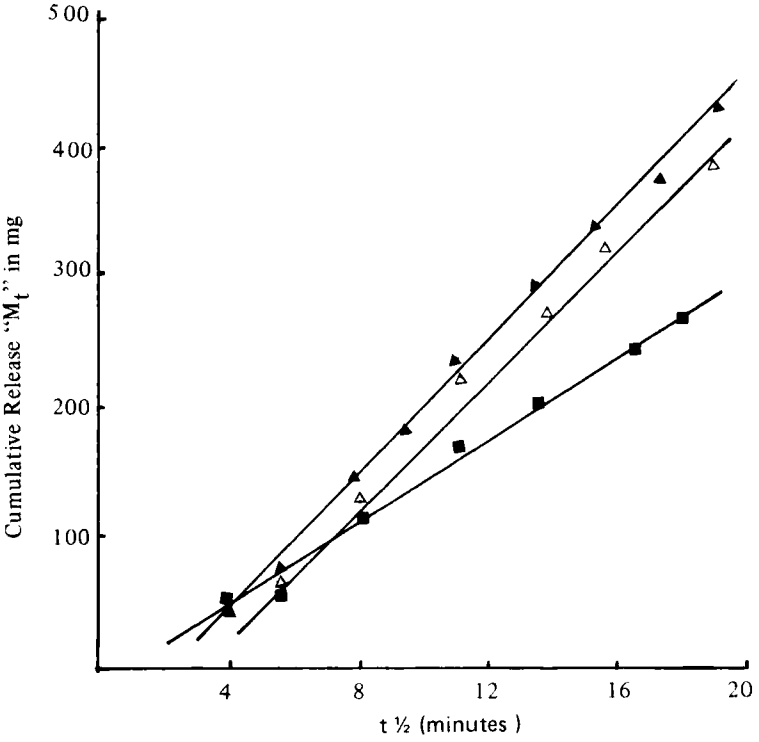


FIGURE (6)
Release of sulphamethoxazole in 0.1N HCl from calcium alginate beads with different concentrations of calcium chloride and under 5 and 10 tons of pressure.
▲-5% calcium chloride-1.6% w/v sodium alginate - 5 tons
△-5% calcium chloride-1.6% w/v sodium alginate - 10 tons
■-15% calcium chloride-1.6% w/v sodium alginate - 5 tons

concentration of calcium chloride. In general, compaction force deformed the beads but did not fragment it, this is due to its elasticity nature. In addition, compression enlarges the cracks as shown in figure (1-d). However , when the release from the compressed beads was compared to the release from ordinary beads, it was found that the compression increases the release.

Unfortunately, the attempt to load the calcium alginate beads from a solution of sulphamethoxazole was not successful. The total sulphamethoxazole content after soaking was less than

1% of the sulphamethoxazole in solution. It is more likely that such amount was adsorped on the beads surface.

When loaded and unloaded beads were boiled to test their resistance for boiling, the beads retain their shape. 18% of the total content of sulphamethoxazole was released which may be due to the increase in solubility of sulphamethoxazole in boilin water.

The electron microscope photographs indicate the presence of cracks and fissures on the surface of the loaded beads. Obviously the release from the beads would take place through such channels. To elucidate the understanding of such mechanism, the diffusion through calcium alginate film from the same ingredients used to prepare the beads was investigated. When the concentration of diffused sulphamethoxazole was plotted against time a straight line passing through the origin was obtained. This is in accordance with an equation derived from ficks law.

$$C_t = K. \frac{A}{V} . C . t \quad \text{.....(6)}$$

Where:

C_t : Concentration of the drug at time "t"

A : Effective area of membrane

C_o : Concentration at 0 time

K : Diffusion rate constant

By substituting the practical values obtained for A,V and C equation (6) may be expressed as

$$C_t = K' t$$

Where K' is the slope in figure (7)

Accordingly, the diffusion rate constant for sulphamethoxazole

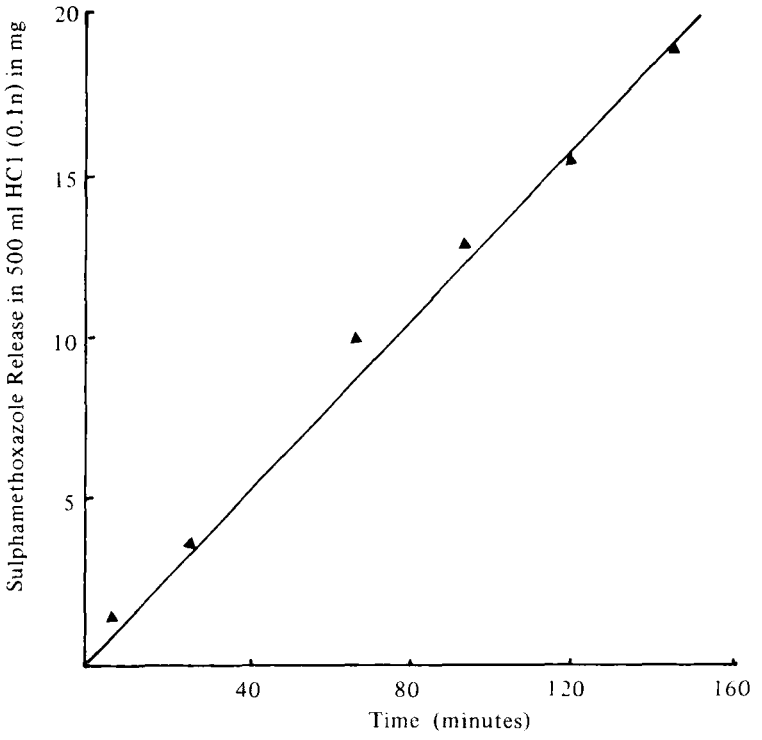


FIGURE (7)
Diffusion of sulphamethoxazole through calcium alginate fil .

was 1.2×10^{-3} cm^2/min indicating that the sulpa diffuses through the formed membrane.

In the conclusion, sulphamethoxazole releases from alginate matrix is through the crack and fissures in the surface and a very negligable quantity diffuses through the matrix body.

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