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PREPARATION AND EVALUATION OF SUSTAINED RELEASE ETHYLCELLULOSE ENCAPSULATED ASPIRIN

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ABSTRACT

Aspirin microcapsules were prepared by the solvent evaporation method. Ethylcellulose was used as the coating material at 18:2, 17:3 and 16:4 core : coat ratios. The prepared microcapsules were separated into sieve fractions. Each Fraction was evaluated for drug content and dissolution characteristics. Scaling-up was developed to evaluate the adopted microencapsulation method for large scale production.

The adopted method was simple, efficient and reproducible. A prolonged release pattern of the drug was obtained by increasing the coat/core ratio. Larger microcapsules released aspirin at a slower rate than did smaller microcapsules. Scaling-up did not significantly affect the release characteristics of drug from the prepared microcapsules. Histological studies on the Guinea pig gastric mucosa after the oral administration of encapsulated aspirin revealed a lower incidence of this product compared to unencapsulated drug.

INTRODUCTION

Aspirin is the drug of choice for the treatment of the arthritis, particularly rheumatic arthritis[1-4]. Sustained release dosage forms of aspirin are frequently used in chronic administration to reduce its side effects[5]. In the last years, considerable attention has been given to modify the dosage forms in which aspirin is administered in an attempt to increase its efficacy or to reduce its side effects. Buffering, enteric coating, solution forms and formulations with various other analgesic or anti-inflammatory agents as well as amino acids have been studied[6-12].

Among the more significant factors in aspirin-induced gastric haemorrhage are area and duration of contact of the solid drug particles with mucosal cells[13]. Significant less gastric bleeding occurred with prolonged action aspirin formulations compared to conventional preparations.

A sustained release product of aspirin would be advantageous to maintain therapeutic concentrations, particularly throughout the night, thus alleviating morning stiffness. The results of several studies indicated that sustained release aspirin, in the proper dosage, provided and maintained blood levels at therapeutic concentration over 8-10 hours, a duration that was about twice as long as that provided by non sustained release products[14-19].

Ethylcellulose was used as coat material for preparation of microcapsules containing aspirin[20-27]. The solvent evaporation method was described in many of these prepartions[23-27]. Of the available data about aspirin release from the prepared microcapsules is that the time required for 50% of the drug to be released ranged from less than one hour to two hours[20,24,25].

The aim of this study is to develop a sustained release product of aspirin. The work describes the encapsulation of aspirin with ethylcellulose employing the solvent evaporation technique. The effect of drug/polymer ratio and scaling-up on the properties of the prepared microcapsules was studied.

EXPERIMENTAL

Materials :

Aspirin (El-Nasr Pharm. Chem. Co., Abu Zaabal, Egypt). Ethylcellulose N 100 (Hercules. Inc. Wilmington). Ethyl acetate A.R. (Wilkinson-Vickere Ltd., Yorkshire, England). All other chemicals were of analytical reagent grade. Simulated gastric fluid (USP XXI, pH 1.3) without enzyme but containing 0.02% w/v polysorbate 80 was prepared.

Procedure :

Microcapsule preparation :

The solvent evaporation method described by Kitajima et al[25] was adopted. An illustrative example of the method was as follows : Ethylcellulose was dissolved in ethyl acetate (3 g /35 ml). The calculated amount of aspirin (< 100 um) was dispersed in the volume of polymer solution containing the required amount of ethylcellulose. The dispersion was then added while stirring to water saturated with aspirin (1:3).

The pH of the system was adjusted at 2.5 (pH of maximum stability of aspirin)[28] by adding hydrochloric acid. Stirring was effected mechanically at a rate that no turbulent movement can be arised in the system. Stirring was continued at room temperature to allow complete evaporation of the polymer solvent. The formed microcapsules were collected and washed with cold acidified water. The microcapsules were then dried, in an oven, at 50°C for about 24 hours. The

dried microcapsules were fractionated by sieving employing a set of standard sieves. Different ratios of aspirin and ethylcellulose namely, 18:2, 17:3 and 16:4, were tested. Scaling-up was tried at tenfold ratio.

Assay Procedure for Drug Content :

Accurately weighed amounts of 100 mg of microcapsules of the test samples were crushed in a mortar. Simulated gastric fluid was then added to the mortar content and quantitatively transferred through filter paper to a volumetric flask. The drug concentration was measured spectrophotometrically at 278 nm using simulated gastric fluid as a blank. The test was done on three samples of each fraction size and the results given are the average of the three experiments. The test was done on the three fraction sizes representing the majority of the prepared microcapsules.

Dissolution Studies :

Accurately weighed amounts of 320 mg of microcapsules of the test samples were used. The USP paddle method was employed at 100 rpm. Simulated gastric fluid without enzyme but containing 0.02% w/v polysorbate 80, at 37°C, (one liter) was used as the dissolution medium. Polysorbate 80 was added to overcome the poor wettability of microcapsules and make the medium more closely resemble the surface tension of the gastrointestinal fluid. At specified time intervals samples (5 ml) of the dissolution medium were withdrawn and spectrophotometrically assayed at 278 nm, using simulated gastric fluid as a blank. The 5 ml aliquots were replaced with the same volume of fresh dissolution medium. The test was done on the three fraction sizes representing the majority of the prepared microcapsules. It is worthy to note that the addition of polysorbate 80 to the dissolution medium did not interfere with the assay method.

Effect on Gastric Mucosa :

In this study, 21 mature Guinea pigs were used. The animals were kept under control for two weeks before study. They were divided into seven groups each of three pigs. One of these groups served as a control (Received no medication). Another group received the unencapsulated aspirin (Intact drug). A third group received a commercially marketed microencapsulated aspirin (Colfarit, Bayer). Four prepared microencapsulated aspirin products were tested. Each of these products was tested using one of the other four animal groups.

The properties of these four microcapsule products were as follows:

Product	1	2	3	4
Core/coat Ratio	18:2	16:4	17:3	16:4
Fraction size(um)	(400-630)	(400-630)	(400-630)	(630-1000)

The calculated amount of each product[29] was filled into hard gelatin capsules. Each animal received one capsule daily on an empty stomach for 15 consecutive days. After the end of the test period, the animals were sacrified, the stomach was dissected, cut, opened and washed with saline solution. The fundic part was then cut into thin slices (10 um in thickness), fixed in formaline and processed to obtain paraffin sections. The sections were stained with haematoxylin and eosin

for general histological studies and with periodic acid schieff for polysaccharides. The stained sections were examined microscopically and photographed.

RESULTS AND DISCUSSION

A solvent evaporation technique was adopted to encapsulate aspirin. Ethylcellulose was used as the coating material at different core/coat ratios. In this study, ethyl acetate was used as the solvent for ethylcellulose. This selection was based on a previous work[30], where in, ethylcellulose films cast from ethyl acetate showed a slow rate of water vapour transmission, exhibited an excellent mechanical properties and give a controlled permeation profile of aspirin. Therefore, it could be predicted that on the use of ethyl acetate as the polymer solvent in the preparation of ethylcellulose coated microcapsules, the prepared microcapsules will enhance the aspirin stability against moisture, will withstand high compression pressures and will give a controlled release pattern of the drug.

The adopted method of microencapsulation seemed to be simple, efficient and reproducible (Table 1 and 3). The prepared microcapsules were spherical in shape and did not exhibit any aggregation behaviour (Figure 1).

Table 1 : Effect of Core : Coat Ratio and Scaling-up on The Percentage Yields of Ethylcellulose Encapsulated Aspirin.

Core : Coat	Yield (%)	
	A	B
18:2	93.96	97.30
17:3	92.75	96.85
16:4	93.17	98.07

A : 30 g. Batch. B : 300 g. Batch.

Table 2 : Effect of Core : Coat Ratio and Scaling-up on The Particle Size Distribution of Ethylcellulose Encapsulated Aspirin.

Size Range (um)	Mean size (um)	% Fraction for the Given Core:Coat Ratios					
		18:2		17:3		16:4	
		A	B	A	B	A	B
630-1000	815	33.50	86.00	31.56	84.12	30.42	64.24
400-630	515	47.80	12.60	48.18	14.00	41.75	32.47
315-400	358	14.97	1.16	13.30	1.62	15.19	2.60
200-315	258	3.36	0.20	6.15	0.21	9.73	0.52
100-200	150	0.37	0.00	0.81	0.05	1.42	0.17
< 100	-	0.00	0.00	0.00	0.00	0.49	0.00

A : 30 g. Batch B : 300 g. Batch.

Table 3 : Effect of Core : Coat Ratio, Fraction Size and Scaling-up on The Drug Content of The Prepared Microcapsules.

Core/Coat Ratio	Fraction size um	Mean size um	Drug Content %	
			A	B
18:2	630-1000	815	91.3	89.8
	400-630	515	90.5	89.4
	315-400	358	90.7	88.8
17:3	630-1000	815	86.2	84.9
	400-630	515	85.9	84.3
	315-400	358	85.5	84.4
16.4	630-1000	815	80.1	80.8
	400-630	515	80.1	79.1
	315-400	358	79.6	79.2

A : 30 g. Batch B : 300 g. Batch

Table 2 shows that : At the low scale level, the majority of the prepared microcapsules were in size range of 315-1000 um. Scaling-up lead to a slight increase in the size range of the prepared microcapsules where the majority of these microcapsules were in the size range of 400-1000 um. Increasing the coat ratio from 10 to 20% was found to be accompanied by decrease in the microcapsule size. An effect which can be attributed to a finer dispersion of aspirin due to the use of large volume of polymer solution with increaseing the coat ratio. The slight increase in the microcapsule size due to scaling-up may be due to a decrease in the stirring efficiency in the large volume of encapsulating vehicle.

Table 1 shows the effect of core/coat ratio and scaling-up on the yield of microcapsules. It is clearly evident that the change in core/coat ratio did not significantly affect the yield of microcapsules at either of the tested scale levels. Scaling-up was found to improve the yield of microcapsules. A result which can be attributed to a decrease in the ratio of loss upon increasing the total working ingredients.

Table 4 : Approximate Time for 50% ($t_{0.5}$) for Aspirin to be Dissolved, in Minutes, As A Function of Core/Coat Ratio and Microcapsule Fraction Size.

Microcapsule Fraction size (um)	Mean size (um)	Calculated $t_{0.5}$ for The Given Core/Coat Ratios		
		18.2	17.3	16.4
315-400	358	42	70	68
400-630	515	56	82	120
630-1000	815	59	96	137

In-Vitro Release Study :

The *in-vitro* release pattern of the prepared microcapsules was studied using simulated gastric fluid as the dissolution medium. Simulated gastric fluid was used as the test medium was selected on the basis that the drug is mainly absorbed from the stomach and its undesirable effect is on the gastric mucosa. From the results of this study (Figures 2-7 and Table 4) the following can be deduced.

1-Increasing the coat ratio was found to decrease the release rate of aspirin from its microcapsules. An effect which can be attributed to the increase in coat thickness upon increasing the coat ratio hence, the distance through which the diffusion of either envading aqueous medium or leaching drug molecules is increased.

2-The increase in microcapsule size was found to decrease the release rate of drug. A result which can be attributed to the decrease in surface to volume ratio ($4 \pi r^2/4/3\pi r^3$) by increasing the microcapsule size. Thus, the increase in size lead to a decrease in the surface/unit volume. i.e. A decrease in the available area of diffusion.

Plotting the data according to both first order kinetics (log amount retained vss. time) and the diffusion-controlled mechanism[31] (Amount released vss, square root of time) revealed that the release (up to 60%) pattern is in accordance with the diffusion-controlled mechanism (figures 5-7). Scaling-up did not significantly alter either the release rate or the release mechanism.

The time required for 50% of drug to be released was calculated (Table 4). It has been suggested as the most reasonable parameter to explain the coating effect on the dissolution behaviour of coated solid dosage forms[32].

Histological Study :

Different aspirin products were tested for their possible effect on the gastric mucosa of Guinea pigs. The results are given by the photomicrographs 1-9 (Figure 8). The photomicrographs show :

1-Untreated animals (control): The gastric mucosa looks healthy with intact mucous secreting cells, the fundic glands are regulary arranged with well defined oxyntic and peptic cells, lamina propria is scanty among the glands.

2&3-Unencapsulated aspirin; There are drastic changes involve all elements of gastric mucosa, significant degenerative changes in the mucous lining cells as well as the fundic glands which look atrophied and widely separated.

4&5-Microcapsules (core/coat 18:2): There are degenerative changes but less than that observed in 2 and 3 (unencapsulated aspirin).

6-Microcapsules (core/coat 17:3); The cells lining the glands look healthy with very slight destruction on the mucous secreting cells.

7-Microcapsules (core/coat 16:4); The picture is more or less similar to control, the fundic mucosa is intact with healthy mucous lining cells.

8-Colfarit microcapsules: There is a slight change include oedema in connective tissues, Focal destruction of surface lining-epithelium.

9-Microcapsules (core/coat 16:4 & fraction size 630-1000 um); The picture is more or less similar to control. The fundic mucosa looks healthy with intact glands.

Histochemical changes(Figure 9).

1-Untreated animals (control): There is abundant polysaccharide in the apical parts of surface lining epithelium.

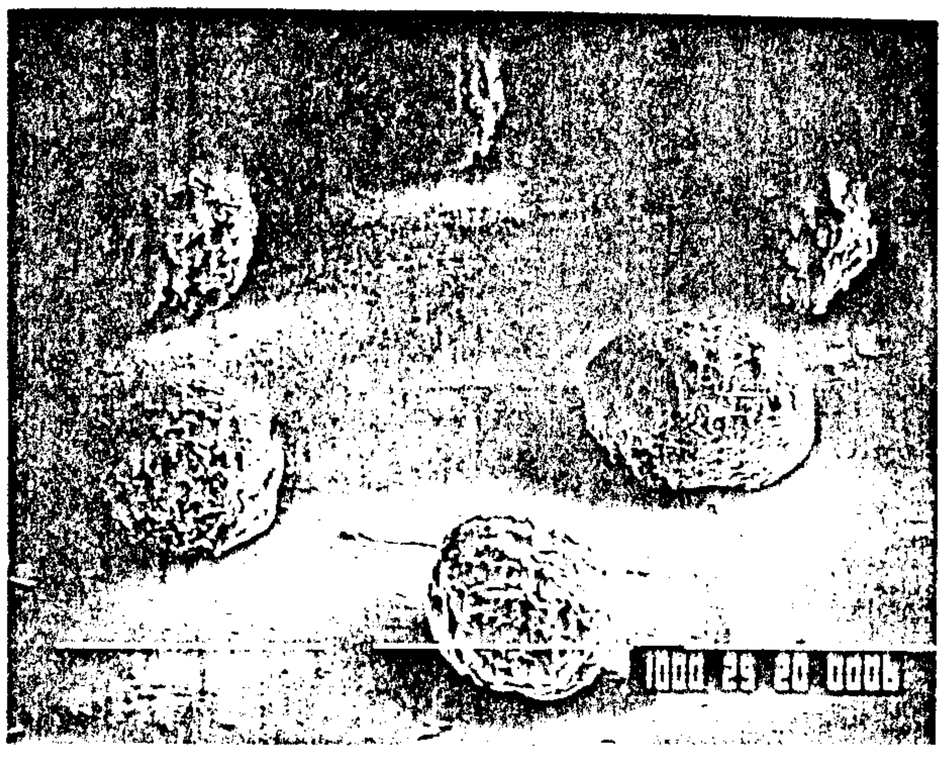
2-Microcapsules (core/coat 16:4): An increase in the amount of polysaccharide was observed in the apical part of the lining epithelium as well as in the cells lining the glands. This may be due to a slow absorption of the drug.

3-Colfarit microcapsules: The polysaccharide content is more or less similar to control.

4-Unencapsulated aspirin: High reaction for polysaccharide was observed in the surface epithelium and the apical parts of cells lining the glands. The presence of polysaccharide is regarded as a protective agent against the unencapsulated aspirin.

The exhaustion of polysaccharide in the cells is related to the state of activity in these cells as well as the rate of transport across them. Thus, any increase in the amount of polysaccharide may point to the low transport of the drug substances across the cells.

In conclusion, the prepared aspirin microcapsules seemed to be suitable for formulating sustained release products. These microcapsules exhibited a dissolution pattern similarly related to that reported in the USP patients. In addition, they offered a reasonable protective action to the gastric mucosa.



X 35

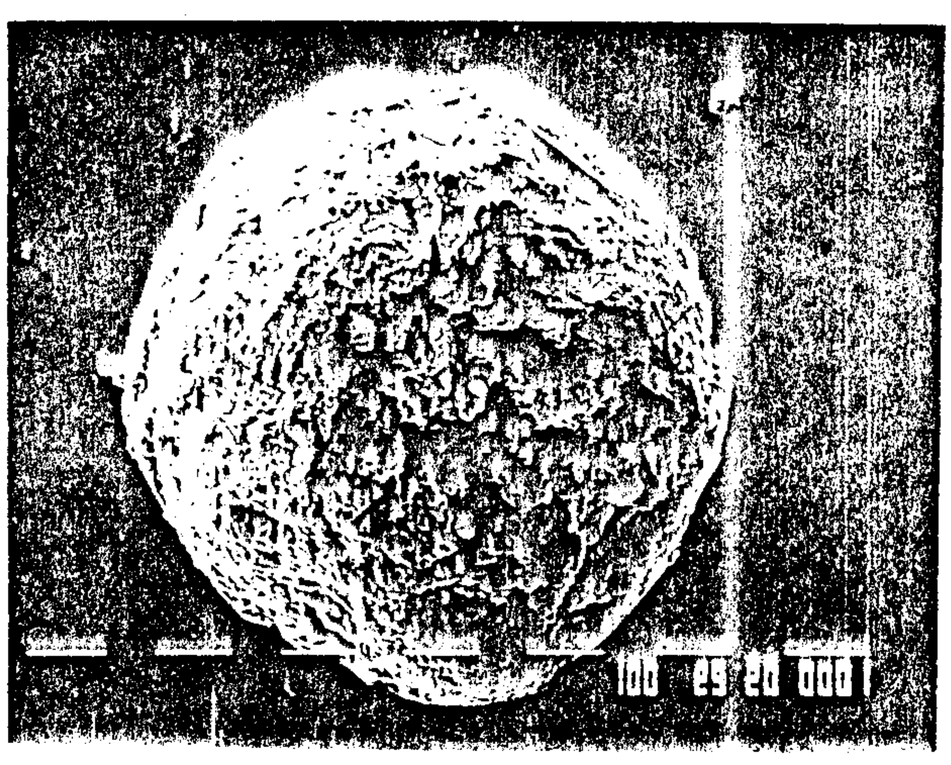


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Figure 1: Electron micrographs of aspirin microcapsules prepared by using ethylcellulose as the coating material (core/coat : 17:3).

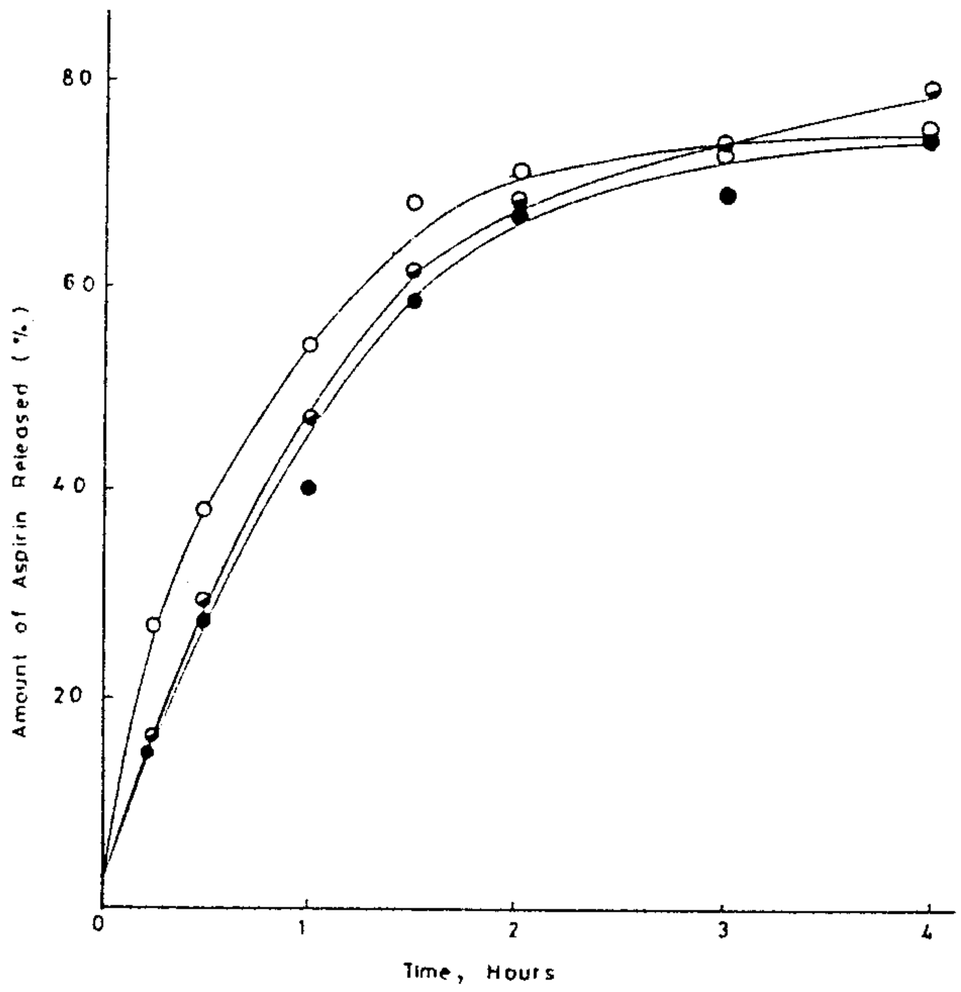

Fig. 2 In-Vitro Release Profile of Aspirin from its Microcapsules. Core: Coat Ratio 18:2
Key: Microcapsule fraction size; (O) 315-400 um. (Θ) 400-630 um, (●) 630-1000 um.

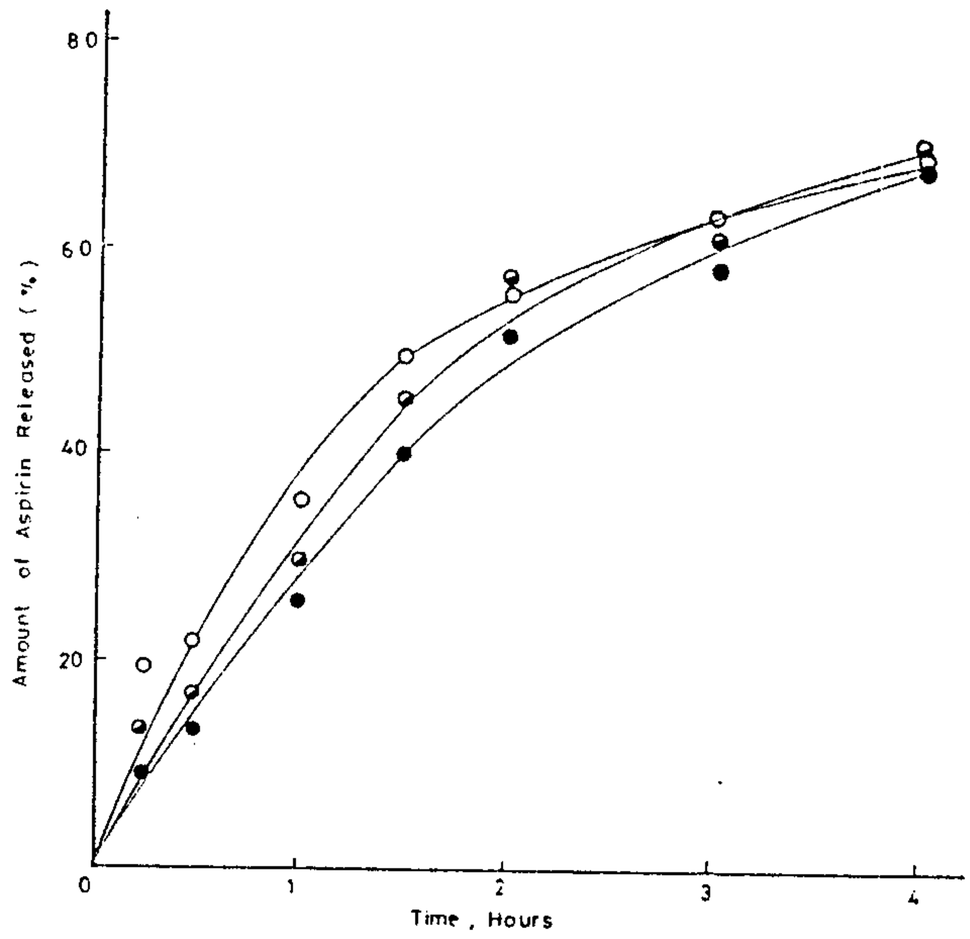

Fig. 3 : In-Vitro Release Profile of Aspirin from its Microcapsules, Core: Coat Ratio 17:3.
Key: Microcapsule fraction size;(O) 315-400 um, (Θ) 400-630 um, (●) 630-1000 um.

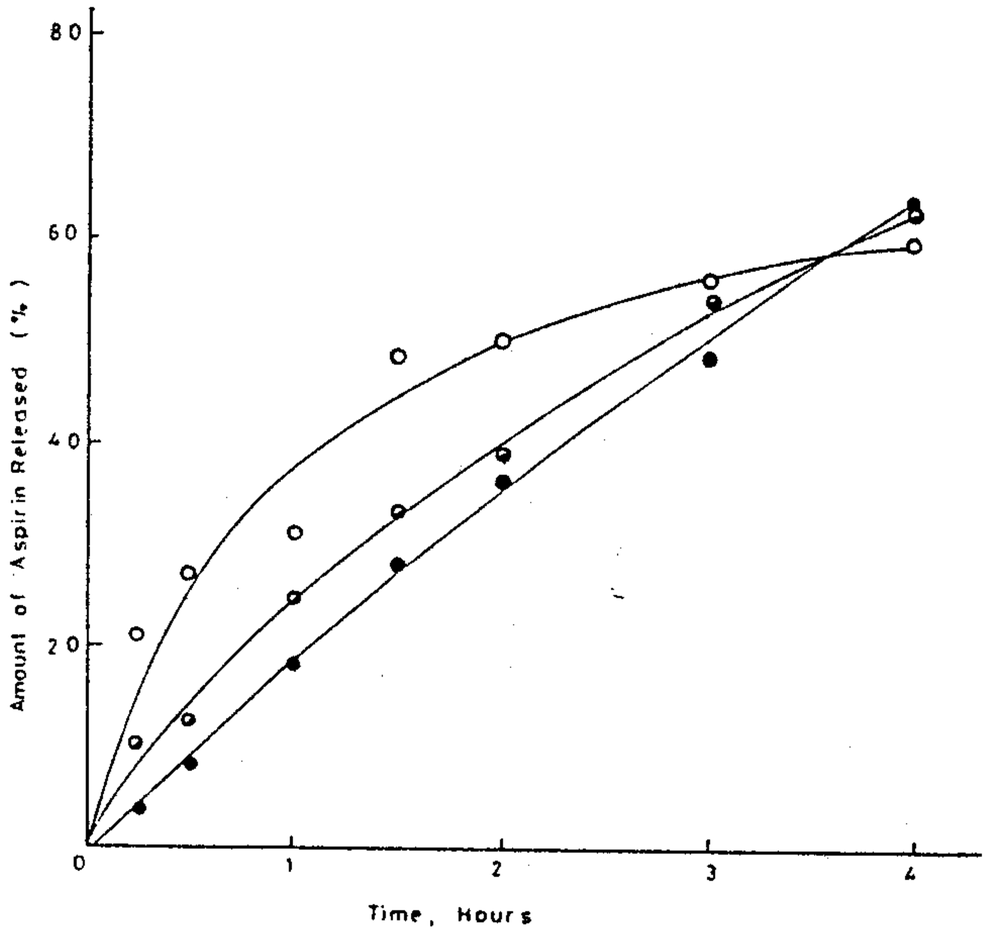

Fig. 4: In-Vitro Release Profile of Aspirin from its Microcapsules. Core : Coat Ratio 16:4.
Key: Microcapsule fraction size;(O) 315-400 um.
(●) 400-630 um, (●) 630-1000 um.

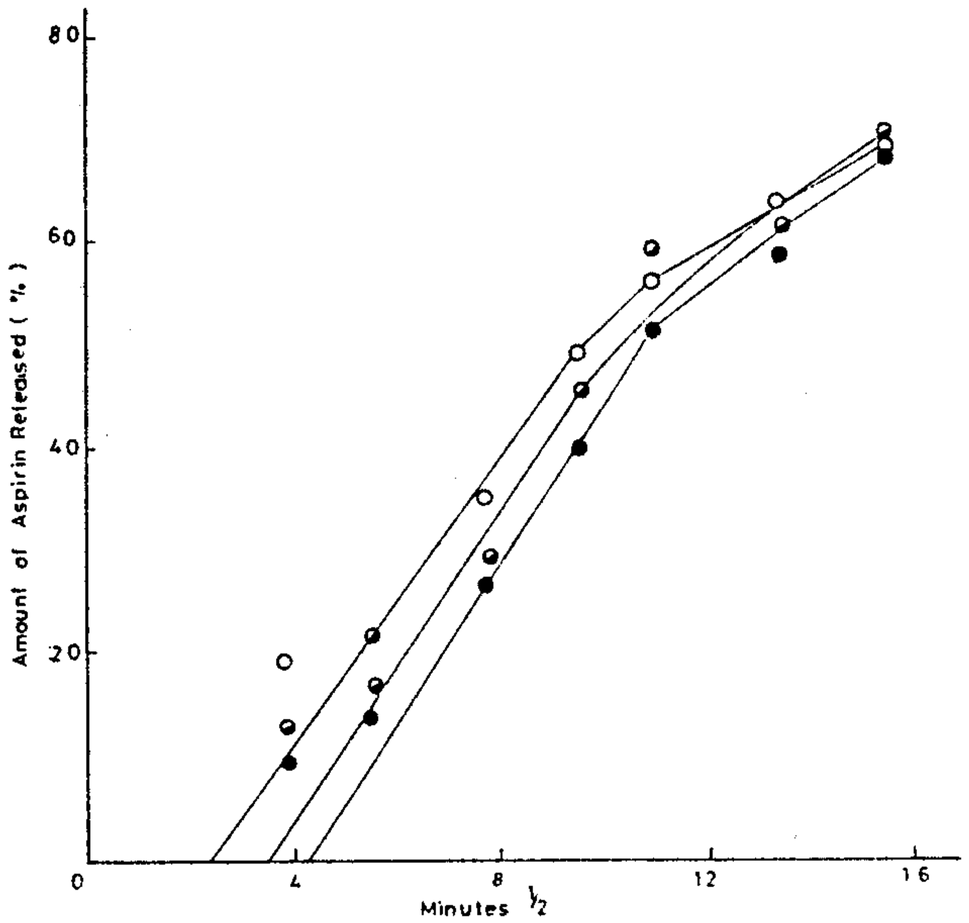

Fig. 6: Apparent Diffusion-Controlled Release Profile of Aspirin from its Microcapsules. Core: Coat Ratio 17:3
Key: Microcapsule fraction size; (O) 315-400 um,
(●) 400-630 um, (●) 630-1000 um.

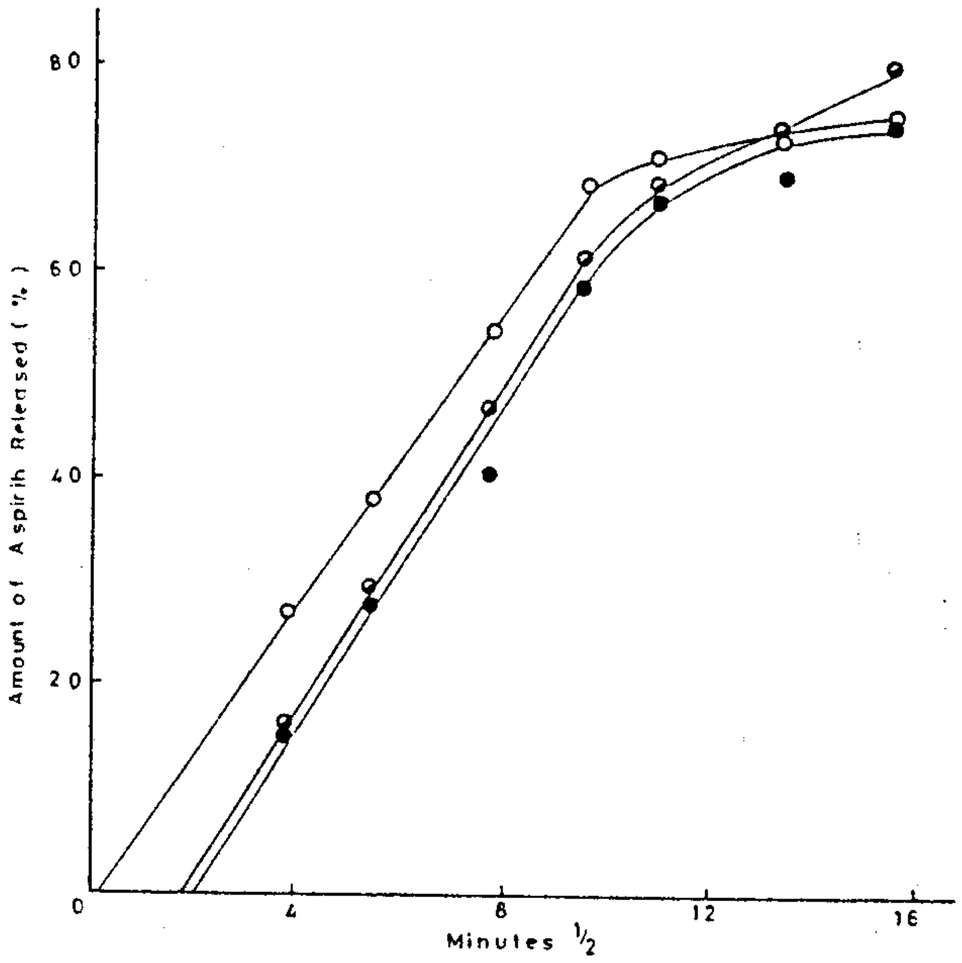

Fig. 5: Apparent Diffusion- Controlled Release Profile of Aspirin from its Microcapsules. Core: Coat Ratio 18:2
Key: Microcapsule fraction size;(O) 315-400 um,
(●) 400-630 um, (●) 630-1000 um.

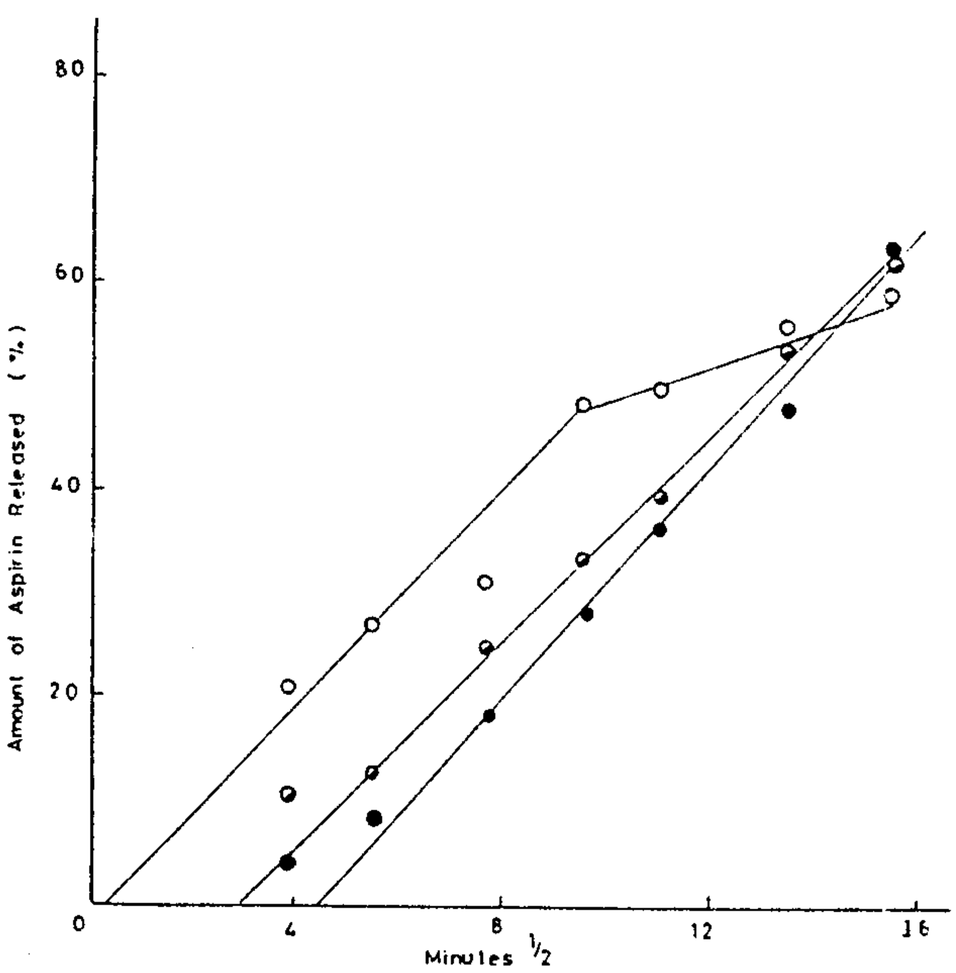

Fig. 7: Apparent Diffusion-Controlled Release Profile of Aspirin from its Microcapsules; Core: Coat Ratio 16:4
Key: Microcapsule fraction size:(O) 315-400 um,
(●) 400-630 um, (●) 630-1000 um.

Preparation and Evluation of Sustained Release Ethylcellulose Encapsulated Aspirin.

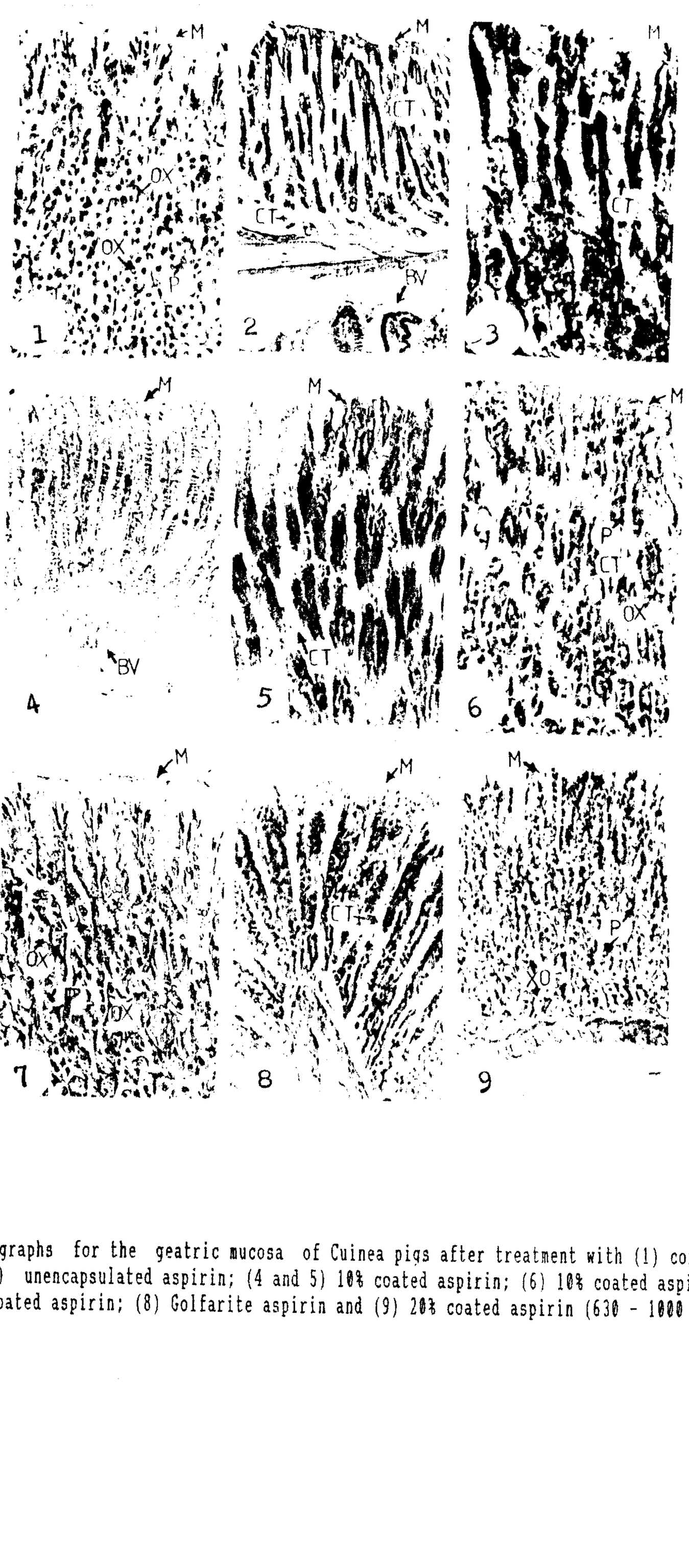

Fig. 8: Photomicrographs for the geatric mucosa of Cuinea pigs after treatment with (1) control; (2 and 3) unencapsulated aspirin; (4 and 5) 10% coated aspirin; (6) 10% coated aspirin; (7) 20% coated aspirin; (8) Golfarite aspirin and (9) 20% coated aspirin (630 - 1000 um).

Fig. 9: Photomicrographs for histchemical studies of Guinea pigs gastric mucosa after treatment; (1) control; (2) 20% coated aspirin; (3) Colfarite aspirin; and (4) unencapsulated aspirin.

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تحضير وتقييم اسبرين طويل المدى محوصل باثيل السليلـــــــــوز

السيد على ابراهيم ـ حسين عبد المنعم سيد ـ احسان حافظ ابراهيم

احمد مصطفـى السيد ـ سـعاد شاكر علـى*

قسم الصيدلانيات ـ كلية الصيدلـــــــه ـ وقسم الهستولوجيا*

كلية الطب ـ جامعـــــة اسـيوط

تم حوصلة الاسبرين باستخدام طريقة تبخير الوسط المنتشر (المذيـــــــب للبوليمر) للمستحلب . واستخدم اثيل السليلوز كمادة مغلفة بنسب مختلفه منـه مقارنة بالعقار . وقد تم تقييم الحويصلات المحضرة بتعيين المحتوى الدوائـــى وخصائص الاذابة وكذلك تأثيرها على الغشاء المخاطى للمعدة فى الخنازيـــــر الغينيـــه .

وقد أثبتت الطريقة المستخدمه فعاليتها فيما يتعلق بكمية المنتـــج من الحويصلات أو المحتوى الدوائى لهذه الحويصلات وكذلك معدلات الاذابـــــــة . وقد وجد أن معدلات الاذابة للحويصلات المحضرة تتأثر بكل من حجم الحويصـــلات ونسبة المادة المغلفة الى العقار كما أنها لاتتأثر بالتحضير عند مستويـــات عالية فى اختبارات التدرج . كما أثبتت الدراسات الهستولوجية على الغشـــاء المخاطى لمعدة الخنازير الغينيه ان العقار المحوصل أكثر أمنا فى استخدامـــه عن طريق الفم مقارنة بالعقار نفسه .

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