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DUAL MICROCAPSULES : PREPARATIONS AND IN VITRO RELEASE RATE STUDIES

DUAL MİKROKAPSÜLLER : HAZIRLANMALARI VE İN VİTRO SALIM HIZI ÇALIŞMALARI

GÖKHAN ERTAN, ASLIGÜL KENDİRCİ, IŞIK SARIGÜLLÜ, TAMER GÜNERİ

Department of Pharmaceutical Technology, Faculty of Pharmacy, Ege University, Bornova 35100-İzmir, Turkey

Mikrocapsules are used especially to obtain sustained release dosage forms but also they are widely used to provide protection for the drug against atmospheric effects, to cover the unpleasent taste and to improve the stability etc (1). Dual-walled microcapsules are prepared to fulfil these aims in a greater extent. For example, to control the required drug release from microcapsules, to provide equal drug release according to time, to protect the drugs from the decomposition by sunlight or to give them a pearlized appereance (2-6). Generally some microcapsules, especially prepared with highly soluble drugs in water or acidic medium don't have satisfactory sustained release. Besides this, some microcapsules are not stable in intestinal medium (8-16). The aim of this study was to prepare dual microcapsules from the microcapsules mentioned above to provide appropriate sustained release action. Dual microencapsulation procedure could be used especially to obtain an appropriate sustained release action, to protect the sensitive microcapsules from decomposition by sunlight, to target the drugs according to the required medium and to cover the microcapsules for certain aims.

Mikrokapsuller, daha çok uzatılmış etki için, bunun yanında ilaçların dış etkilerden korunması, kötü tatların maskelenmesi, stabilitenin arttırılması v.s. amaçları için hazırlanmışlardır (1). İki katlı mikrokapsüller bu amaçların daha arzu edilen seviyelerde elde edilmesini sağlamaktadırlar. Örneğin, mikrokapsullerden ilaç salımının istenildiği gibi kontrol edilmesi, zamana göre eşit ilaç salımının sağlanması, ışıktan daha iyi koruma, sedefli görünüş sağlama gibi (2-6). Genellikle suda ve asit ortamda çok çözünen ilaçlarla hazırlanan mikrokapsüllerden arzu edilen uzatılmış etki elde edilmemektedir. Bunun yanında bazı mikrokapsüllerde barsak ortamında dayanıklı değildirler. (8-16). Bu çalışmanın amacı, bu çeşit mikrokapsüllerden dual mikrokapsül hazırlayarak istenilen uzatılmış etkinin sağlanmasıdır. Dual mikrokapsülasyon, güzel bir uzatılmış etki elde etmek için, ışığa hassas mikrokapsüllerin ışıktan korunması, istenilen ortama göre hedeflenmesi gibi, mikrokapsüllerin değişik amaçlarla kaplanması için kullanılabilir.

Introduction

One of the principal uses of microencapsulation for pharmaceuticals has been the preparation of the sustained release dosage forms which have been usually presented in the form of suspansions or gels. Also microencapsulation has been employed to provide protection of the core material against atmospheric effects, to cover the unplesant taste, improve the stability etc. (1).

There are some investigations about dual walled microcapsules in the literatures. For example, Sirine (2) in a patent assigned to NCR, described how the capsule walls could be covered incorparating carbon black to protect an en-capsulated oil from decomposition by sun light. Likewise Marinelli (3) described how to incorporate mica particules coated with titanium dioxide into the walls of gelatin-acacia microcapsules to give them pearlized appearence. Baxter (4), in a patent assigned to Moore Business Forms, described the preparation of dual walled capsules of a thin inner gelatin wall surrounded by a thicker gelatin-acacia gel. Borodkin et al. (5) and Donbrow and Samuelov (6) achieved zero order drug relase from double-layered film system where one of them serves as a drug resorvior while the other nondrug layer functions as a rate-controlling membrane prepared with a long and complex procedure. Harris (7) covered potassium chloride crystals with a wax or polymer layer and proceeding

this the particles were microencapsulated with acacia and gelatin coacervation system. The microencapsulated product offers better controlled release for this drug when compared to standart tablet and powder forms.

Generally some Microcapsules, especially prepared with highly soluble drugs in water or acidic medium don't have satisfactory sustained release and some others show a rapid release in alkaline medium. These kinds of microcapsules could be covered with a second polymer layer by microencapsulation with formalized gelatin, carboxymethylcellulose (CMC) and ethylcellulose (EC) for protection of microcapsules from these disadvantages.

From this point of wiev, in this work the oxolamine citrate: EC microcapsules were covered with formalized gelatin, nitrofurantoin: gelatin microcapsules were encapsulated with CMC, oxolamine citrate: EC microcapsules were again encapsulated with EC and amoxycillin: gelatin-CMC microcapsules were encapulated with EC. Oxolamine citrate, nitrofuratoin and amoxycillin were used as model drugs.

Oxolamine citrate is one of the synthetic derivatives of 3, 5 - disubstituted -1, 2, 4-oxodiazole, used particularly for its antitussive activity. Its usual dose is 200 mg four times a day (8).

Nitrofuration is an urinary tract antiseptic. Its use is limited by side effects such as nausea and vomiting, probably due to the rapid absorption or gastric irritation (9). Also it has a short biological half-life<1h. Its usual dose is 50-100 mg four times daily (10, 11).

Amoxycillin is a semisynthetic penicillin which is acid resistant and can therefore be given orally (12). Its biological half-life is about 1-2 hours (13).

This study was proposed to provide a more appropriate sustained release action from previously prepared microcapsules in our laboratory (14-16). This suggestion is simple and could be used for all covered particules to achieve various aims such as good sustained release in both acidic and alkaline medium, increased coating and drug trageting.

Materials

CMC, with a viscosity (1% solution at 27°C) of 7.1 cps, was purchased from Sigma, USA. EC type N-100 was obtained from Hercules. Gelatin (pH of 1% Solution: 3.8-7.6), formaldehyde (37% w/w) and isopropanol were obtained from Merck, Germany. Aluminium sulphate was purchased from Riedel de Haen AG, Germany. Other chemicals and solvents were of analytical grade.

Methods

Preparation of dual microcapsules

Oxolamine citrate: EC (1:1)(14), nitrofurantion: gelatin (1:2) (15) and amoxycillin: gelatin-CMC (1:1) (16) microcapsules, prepared in our laboratuary previously were used in this study.

Priorly, oxolamine citrate: EC microcapsules were dual encapsulated with gelatin at 1:1 ratio. For this purpose 2.5 g gelatin was soaked in 25 g of distilled water for 30 min. Then it was inserted into a water bath of 40°C while stirring with a mixer at a speed of 200 rpm. 2.5 g oxolamine citrate: EC microcapsules were added and when the mixture became homogenous 50 ml. of 20% sodium sulphate solution was added dropwise. The microcapsules were recognized microscopically and another 5 ml. of 20% sodium sulphate solution was added. The mixture was taken out from the water bath, 125 ml. cold 7% sodium sulphate solution was added and the system was inserted into a cold water bath where its temperature was adjusted to lower than 10°C in order to complete the gelling process. The microcapsules formed were filtered and 100 ml of chilled isopropanol was added to achieve dehydration of the product. The microcapsules were hardened with 3.7% w/v formaldehyde solution for 2 hours and filtered and washed with cold water in order to remove the hardening agent on the surface. Then they were allowed to dry at room temperature.

Secondly, nitrofurantoin: gelatin microcapsules hardened with 14.85% w/v formaldehyde for two hours were encapsulated with CMC at 1:1 core:wall ratio. For this 1 g CMC was dissolved in 20 g boiling water. The mixture was cooled to room temperature and 1 g of nitrofurantoin: gelatin microcapsules were suspended in this viscous polymer solution by continous stirring at 1000 rpm and 4% aluminium sulphate solution was added dropwise. The mixture was filtered and the microcapsules so obtained were washed with water and dried at 80°C for 2-5 hours.

Thirdly, oxolamine citrate: EC and amoxycillin: gelatin-CMC microcapsules were encapsulated with EC at 1:1 core:wall ratio. For the preparation of amoxycillin: gelatin-CMC microcapsules, CMC and gelatin solutions (3:7) were prepared by dispersing

each colloid (4%) in distilled water and allowed to hydrate for 12 hours. The solutions were then adjusted to pH 3.5 with 0.1 N hydrochloric acid or 0.1 M sodium hydroxide solution. Coacervates were prepared at 37°C by adding the CMC solution to the gelatin solution, while stirring at 700 rpm. The coacervate mixture was allowed to stand for 5 minutes before being subjected to further procedure. Amoxycillin was suspended in this viscous polymer solution by continious stirring at 700 rpm. After ten minutes, 50 ml cooled hydrochloric acide solution was added. The coacervation mixture was cooled to 4°C for 10 minutes. Then 100 ml (2x50) of formaldehyde/ isopropyl alcohol (10/90) solution was added as hardening agent and left for two hours. The coacervation mixture was filtered and washed with isopropyl alcohol and dried at room temperature. For dual microencapsulation with EC, into a 500 ml three-necked flask, fitted with a stirrer, thermometer and a reflux, 200 ml cyclohexane was added; 4 g of EC was added at 50°C by continuous stirring at 560 rpm. The temperature was first raised to 70°C slowly over 20 min. The temperature was raised from 70°C to 80°C over a period of 75 min. 1 g of amoxycillin: gelatin-CMC microcapsules were then dispersed as the core material in the polymer solution with continious stirring at 560 rpm for 10 min. The mixture was then cooled to room temperature with constant stirring to solidify the coating. The microcapsules were separated by filtration and dried at room temperature. All microcapsules obtained in this study were used for in vitro dissolution studies without sieving procedure.

In vitro dissolution studies

Prepared microcapsules equivalent to 200 mg oxolamine citrate, 50 mg nitrofurantoin and 500 mg amoxycillin were tested individually for their dissolution rates by using the USP XXII basket method of a stirring rate of 100 rpm in the simulated gastric medium (SGM) prepared according to the USP XXII (17). In the experiments a certain amount of sample was withdrawn from the dissolution medium at selected times with the aid of an injector fitted with a milipor HA 0.45 μ filter paper. An equal volume of medium was added to the system after each withdrawal for replacement and the sample was then assayed, according to our previous studies (14-16).

Kinetic evaluations

The results thus obtained from dissolution studies were evaluated kinetically by $(Bt)^a$, First-order, Zero-order, Hixon-Crowell, RRSBW, Q t, Higuchi, Hopfenberg Spherical, Hopfenberg Cylindrical and Hopfenberg Slab equations. The release rate constants (k), correlation coefficients (r) and determination coefficients (r^2) were calculated by the aid of a computer program (18).

Optical microscopic studies

The oxolamine citrate crystals and the prepared oxolamine citrate-EC/gelatin dual microcapsules were examined under an optical microscope (Carl Zeiss Jena).

Results and Discussion

Four kinds of dual microcapsules were prepared by simple coacervation method for the first time in our laboratory. There is no literature dealing with the dual microcapsules but some studies were purposed for more than one covering of the drug particles. For example, Harris (7) coated potassium chloride particles with polymer (cellulose acetate phthalate, hydroxy propyl methylcellulose, cellulose acetate butyrate and EC), wax (stearic acid), polymer and wax mixture by spray-coating method. Then these coated particles were microencapsulated with accacia and gelatin (1:1) mixture by coacervating at pH 3.9. In another study, laminated double-layered films comprising a drug-containing and drug-free layer were prepared using tripellenamine, barbiton, salicylic acid and caffeine dispersed in hydroxypropylcellulose attached to EC films containing various proportions of polyethylene glycol or HPC to enhance permeability (6).

The drug contents of the prepared microcapsules are given at Table 1. Normally, drug contents of the dual microcapsules decreased when compared to the monolayered microcapsules.

Table 1. Drug contents of the mono and dual microcapsules.

Mono microcapsules I	Dual microcapsules prepared from mono microcapsules II	% Drug Contents I	%Drug Contents II
Oxolamine citrate:ethylcellulose	Oxolamine citrate:ethylcellulose/ gelatin	50.8	35.8
Nitrofurantoin:gelatin	Nitrofurantoin:gelatin+CMC	45.2	35.2
Amoxycillin: gelatin+CMC	Amoxycillin: gelatin+CMC/EC	60	35.3
Oxolamine citrate:ethylcellulose	Oxolamine citrate:ethylcellulose/ EC	50.8	44

Table 2 and Fig.1 show the dissolution rate results of oxolamine citrate: EC and dual gelatin microcapsules prepared from ECmicrocapsules. In vitro drug released was sustained from 30 minutes to 10 hours and sustained action could be adjusted with formalization degree of gelatin. A good-sustained action was obtained with these dual microcapsules. In a previous study, zero-order drug release was demonstrated in two laminated films using 18-45% pentobarbital, methapyrilene, or salicylic acid contained in HPC as the reservoir layer and mixtures of hydroxypropyl cellulose and polyvinyl acetates as the membrane layer (5). Donbrow (6) also obtained zero-order drug release from laminated double-layered films containing tripellenamine, barbiton, salicylic acid and caffeine.

Table 2. Dissolution results of oxolamine citrate:EC and dual microcapsules prepared with gelatin.

Time (min)	% Drug Released	
	Mono Microcapsule	Dual Microcapsule
5	45.8	
10	77.4	
15	89.6	16
20	90	
25	91.6	
30	96	23.2
45		26
60		33
120		41.2
180		48.8
240		56
300		62.12
360		65.3
420		70.4
480		80.8
540		84.4
600		86.2

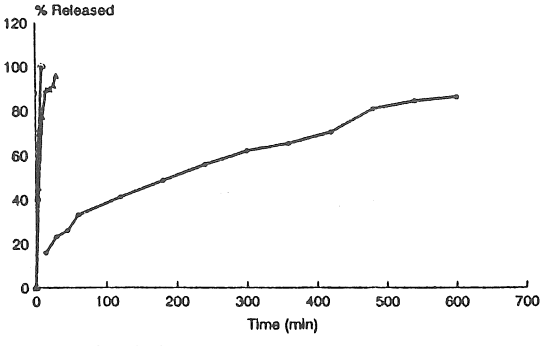

Fig. 1. Dissolution profiles of oxolamine citrate mono and dual microcapsules in SGM. —○—, oxolamine citrate, —▲—, EC, —●— , EC/gelatin

Table 3 and Fig. 2 show the dissolution rate results of nitrofurantoin:gelatin and dual CMC microcapsules prepared with gelatin-microcapsules. Nitrofurantoin release from dual microcapsules was more slow when compared to mono-layered microcapsules yet an improvement was obtained for the sustained action.

Table 3. Dissolution results of nitrofurantion:gelatin and dual microcapsules prepared with carboxy-methylcellulose

Time (min)	% Drug Released	
	Mono Microcapsule	Dual Microcapsule
15	24.26	12.07
30	43.2	22.35
60	65.14	36.43
120	86.25	51.87
180	91.13	59.18
240	94.37	63.79
300	96.53	68.11
360		68.38
420		70.02

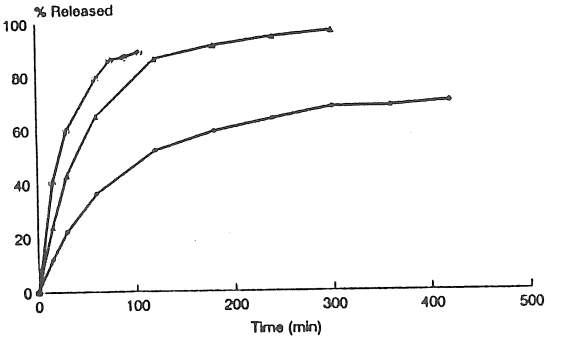

Fig. 2. Dissolution profiles of nitrofurantion mono and dual microcapsules in SGM. —○—, nitrofurantoin, —△— , gelatin, —●—, gelatin: CMC

The dissolution rate results of amoxycillin: gelatin+CMC and dual EC microcapsules prepared from these microcapsules are shown in Fig. 3 and Table 4. A good sustained action was also obtained with these dual microcapsules. Although, drug release decreased with the dual EC microcapsules prepared from oxolamine citrate:EC microcapsules, only 40% of the drug content difused out of the microcapsules because of the microcapsule

particles binding to each other (Table 5, Fig.4).

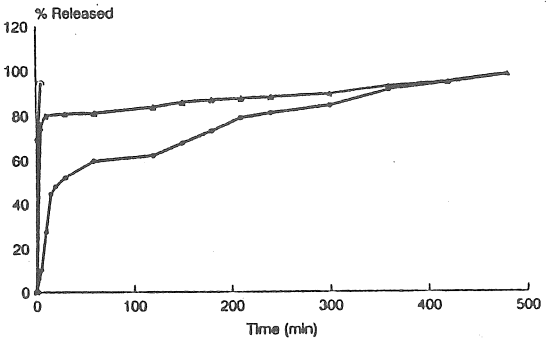

Fig. 3. Dissolution profiles of amoxycillin mono and dual microcapsules in SGM. —o—,amoxycillin, —▲— , gelatin: CMC, —●— , gelatin:CMC/EC

Table 4. Dissolution results of amoxycillin:gelatin-CMC and dual microcapsules prepared with EC.

Time (min)	% Drug Released	
	Mono Microcapsule	Dual Microcapsule
5	74.9	10.16
10	80.0	27.44
15		44.38
20		47.84
30	80.9	51.92
60	81.2	59.58
120	83.7	62.04
150	85.8	67.70
180	86.8	73.06
210	87.4	78.93
240	88.0	81.01
300	89.3	84.20
360	92.7	91.08
420	94.6	94.14
480	98.0	97.60

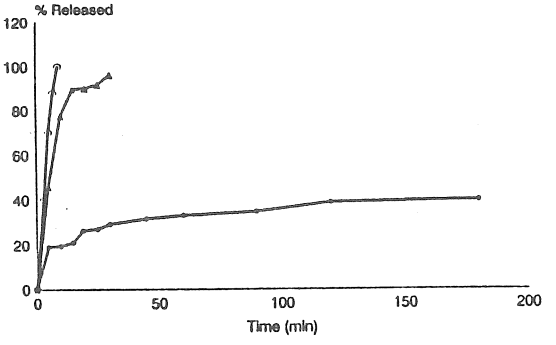

Fig. 4. Dissolution profiles of oxolamine citrate mono and dual EC microcapsules in SGM. —o— , oxolamine citrate, —▲— , EC, —●— ,EC

Table 5. Dissolution resutls of oxolamine citrate:EC and dual microcapsules prepared with EC.

Time (min)	% Drug Released	
	Mono Microcapsule	Dual Microcapsule
5	45.8	19.08
10	77.4	19.44
15	89.6	21.06
20	90.0	26.28
25	91.6	27.00
30	96.0	29.16
45		31.50
60		32.94
90		34.50
120		38.52
180		39.60

The kinetic data for mono and dual microcapsules are given in Table 6 and Figures 5-10. It was observed that dual microencapsulation changed the kinetic models of oxolamine citrate:EC and amoxycillin:gelatin+CMC microcapsules. Normally, $t_{63.2}$ values of the RRSBW distributions decreased for the dual microcapsules as a result of the slower drug release.

Table 6. Kinetic models of the mono and dual microcapsules.

Mono microcapsules	Dual microcapsules	Kinetic Models	
I	II	I	II
Oxolamine citrate:EC	Oxolamine citrate:EC/gelatin	RRSBW β=0.863 r^2=0.938 t(63.2%)=7.41 min	Q=kt k=2.33 r^2=0.994
Nitrofurantoin:gelatin	Nitrofurantoin:gelatin/CMC	RRSBW β=0.826 r^2=0.99 t(63.2%)=62.1 min	RRSBW β=0.663 r^2=0.972 t(63.2%)=246.5 min
Amoxycillin:gelatin+CMC	Amoxycillin:gelatin+CMC/EC	Hopfenberg cylindrical k=6.1x10^{-4} r^2=0.952	Higuchi r^2=0.983
Oxolamine citrate:EC	Oxolamine citrate:EC/EC	RRSBW β=0.863 r^2=0.938 t(63.2%)=7.41 min	RRSBW β=0.274 r^2=0.953 t(63.2%)=1842.5 min

Photographic observations showed that, when compared to uncoated oxolamine crystals (Fig. 11 a) there are thin EC and thick gelatin layers on the microcapsulated particles which can be seen on the photograph (Fig. 11 b-c).

In conclusion, it is obvious that dual microcapsules can be used for improvement of the release profiles of the microcapsules and for obtaining a good sustained action.

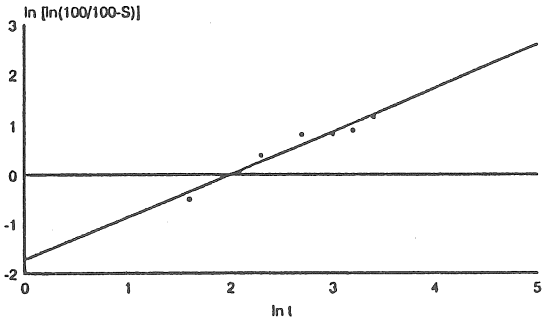

Fig 5. RRSBW distribution of oxolamine citrate:EC microcapsules

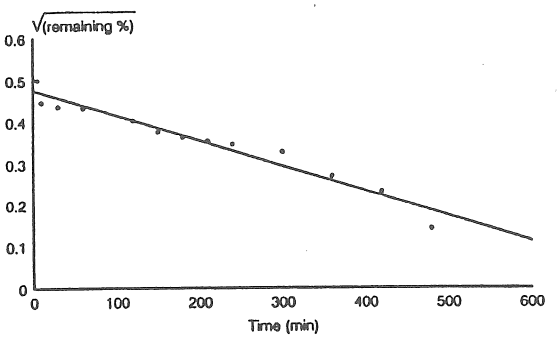

Fig. 8. Hopfenberg cylindrical distribution of amoxycillin:gelatin+CMC microcapsules

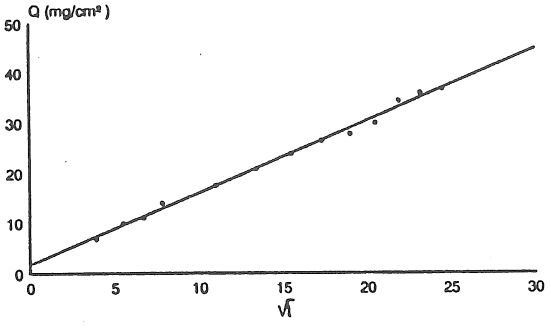

Fig. 6. $Q\sqrt{t}$ distribution of oxolamine citrate:EC/gelatin dual microcapsules

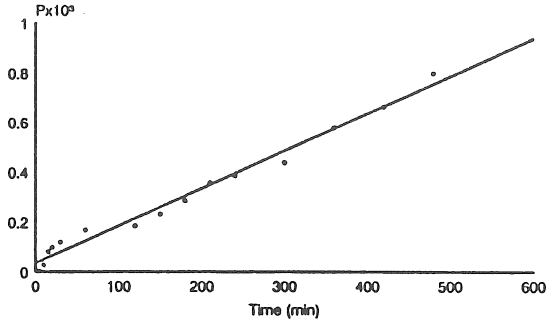

Fig. 9. Higuchi distribution of amoxycillin:gelatin+CMC/EC dual microcapsules

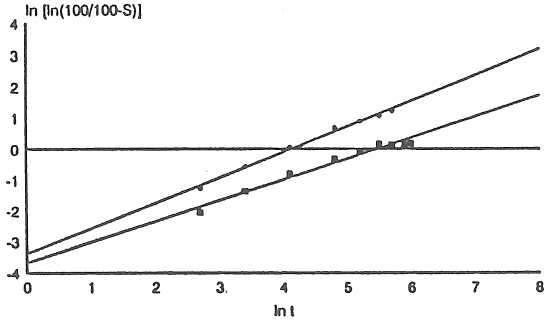

Fig 7. RRSBW distributions of nitrofurantoin:gelatin microcapsules and nitrofurantoin:gelatin/CMC dual microcapsules. —●—, nitrofurantoin:gelatin, —■—, nitrofurantoin:gelatin/CMC

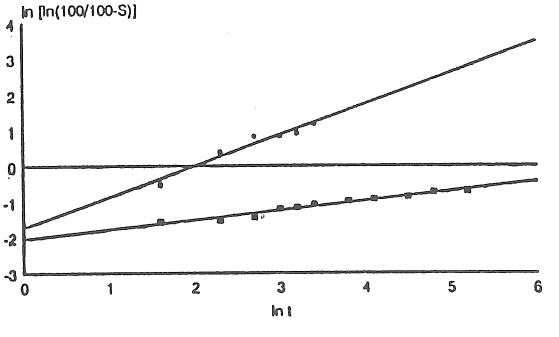

Fig. 10. RRSBW distributions of oxolamine citrate:EC microcapsules and oxolamine citrate:EC/EC dual microcapsules. —●— , oxolamine citrate:EC, —■—, oxolamine citrate:EC/EC

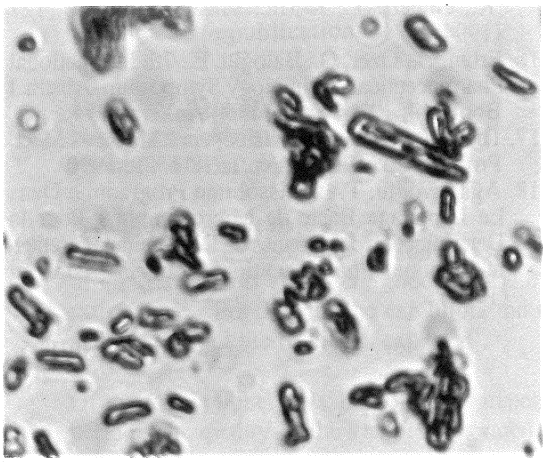

Fig.11.(a) Photograph of the uncoated oxolamine citrate crystals (x1100)

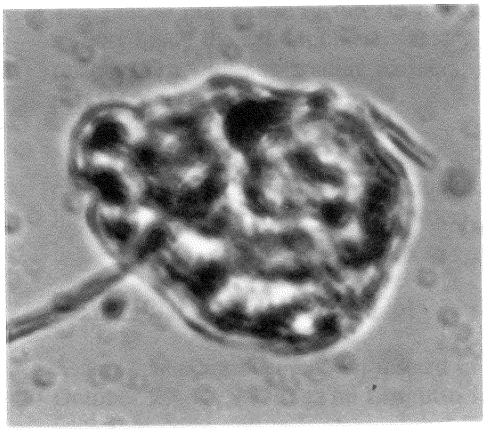

Fig.11. (b_1) Cross sections of the dual encapsulated oxolamine citrate microcapsules (x1100);

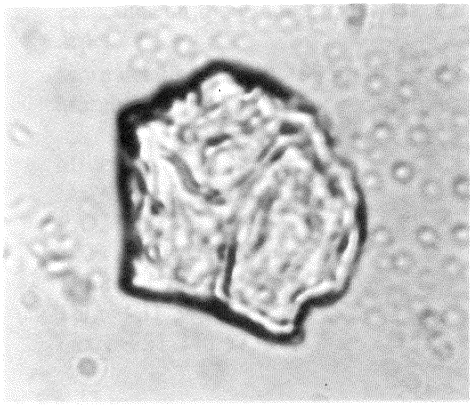

Fig.11.(b_2) Three dual microcapsules together

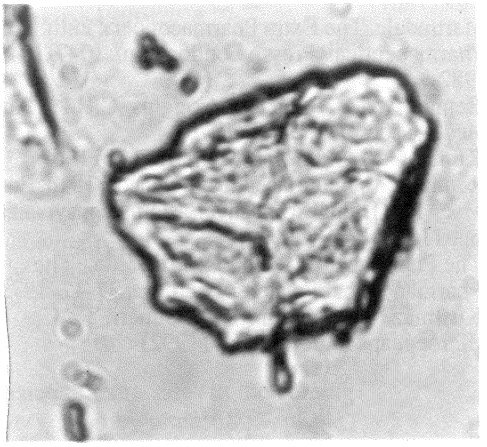

Fig.11.(b_3) Four dual microcapsules together respectively

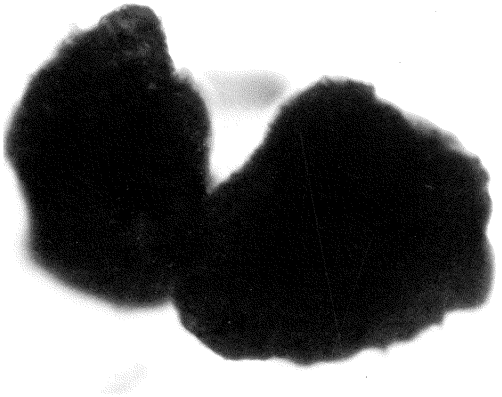

Fig.11.(c). Top view of the dual microcapsules (x1100).

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