Bull. Pharm. Sci., Assiut University Vol. 16, part 2, pp 113-123

MICROENCAPSULATION OF THEOPHYLLINE

A.M. El-Sayed, H. Abdel Monem Sayed, A. Hamed Osman* and M. Fathy

*Pharmaceutics Dept., Faculty of Pharmacy, and *Chest Dept., Faculty of Medicine, Assiut University, Assiut, Egypt*

ABSTRACT: *Theophylline microcapsules were prepared using the solvent evaporation technique. Each of ethylcellulose (EC) and cellulose acetate butyrate (CAB) was used as a coating material. The adopted technique was simple and efficient. The drug release rate from CAB-coated microcapsules was slower than that from EC-coated ones. Increasing the coating polymer concentration, in the internal phase, from 10 to 20% leads to a decrease in the release rate of the drug. Increasing the CAB/drug ratio from 1:1 to 2:1 leads to a decrease in the release rate. Sealant treatment of EC-coated microcapsules was tried in an attempt to lower the drug release rate thereof. The sealant had a pronounced effect on the release rate. The effect was more enhanced by increasing the sealant concentration.*

Three sustained release formulations of the microcapsules were prepared and orally administered to asthmatic patients. The drug serum levels revealed a sustained action of the tested formulations.

INTRODUCTION

.Theophylline is the most widely prescribed bronchodilator for the treatment of chronic asthma and chronic obstructive lung diseases[1]. The effective serum concentrations were considered to be between 10 and 20 μg/ml. Toxic effects of the drug were common above 20 μg/ml serum theophylline concentration[2]. The undesirable toxic effects are gastrointestinal disturbances, central nervous system effects, focal and generalized seizure and cardiovascular toxic manifestations[3,4]. To achieve maximum therapeutic benefit with a minimum incidence of adverse effects, sustained release preparations of the drug have been suggested. These preparations are effective for the acute and chronic maintenance treatment of bronchial asthma[5-8]. They offer the advantages of less frequent dosing with decreased fluctuation in the serum level during the dosing interval[8-10]. Several microencapsulation techniques were adopted to develop the sustained release systems of theophylline[11-17]. The aim of the present work was directed to design a sustained release formulations of theophylline adopting modified microencapsulation techniques.

EXPERIMENTAL

Materials:

Anhydrous theophylline (Sigma Chem. Co., St. Louis, U.S.A.). Cellulose acetate butyrate, CAB (Sci., Polymer products, Inc., Ontario, new York, U.S.A.). Ethylcellulose N 100, EC. (Hercules, Inc., Wilmington, U.S.A.). All other chemicals were analytical reagent grades and were used as received.

Apparatus:

Shimadzu double beam spectrophotometer (UV-150-02, Japan). The USP standard dissolution apparatus with teflon-coated paddle stirrers (Model Dt-06, Erweka, Germany). Scanning electron microscope (model Jem-T 1, Japan electric optics laboratory Co. LTD). Set of standard sieves (USP).

Procedure:

1- Microencapsulation of theophyllin

each of cellulose acetate butyrate (CAB) and ethylcellulose (EC) was used as the coating material. CAB was used at 1:1 and 1:2 core/coat ratio while EC was only used at 1:1 ratio. To prepare microcapsules, the coating polymer was dissolved in acetone. Theophylline was dispersed in the solution of coating polymer. The

dispersion was then emulsified into paraffin oil (1:3). The emulsion was kept stirred at room temperature. After evaporation of acetone, the formed microcapsules were separated, washed with n-hexane and dried at room temperature. The dried microcapsules were fractionated using a set of standard sieves. The coating polymers were used at 10 and 20% w/v concentration.

2- Determination of microcapsule drug content:

100 mg-samples representing the different sieve fractions were crushed in a mortar. Simulated gastric fluid (No enzymes but 0.02% w/v Tween 80 was added) was added to the mortar content. The content was filtered to remove coat fragments and quantitatively transferred to a volumetric flask. The flask was completed to volume by simulated gastric fluid. The drug concentration was measured spectrophotometrically at 270 nm[11,12].

3- *In-Vitro* release studies :

Release studies were carried out at 37°C in 900 ml of dissolution media. The USP standard apparatus with teflon-coated paddle stirrers at 50 rpm was used. Each of simulated gastric fluid and simulated intestinal fluid was used separately as the dissolution medium. Each medium was used without enzymes but 0.02% w/v Tween 80 was added to overcome the poor wettability of microcapsules and make the solution more closely resemble to the surface tension of gastrointestinal fluid. Accurately weighed samples of microcapsules (100 mg) were added to the dissolution medium. Five ml aliquots were withdrawn at intervals and replaced with fresh medium. The amount of drug released was determined spectrophotometrically at 270 nm for simulated gastric fluid and 271 nm for simulated intestinal fluid[11-12,17].

4- Sealant treatment of the prepared theophylline microcapsules:

In an attempt to prolong the release time of theophylline from its ethylcellulose-coated microcapsules, sealant treatment was tried. The treatment was done as follows :

An accurately weighed sample (0.1 gm) of microcapsules (Fraction size 90-200 μm, ethylcellulose concentration in acetone 20% w/v) was added to 10 ml of beeswax solution in n-hexane. The system was stirred at 150 rpm for 10 minutes, filtered and dried overnight. Different concentrations of beeswax namely; 2.5, 5, 7.5 and 10% w/v in n-hexane, were tested.

5- *In-Vivo* evaluation of theophylline microcapsules :

I-Tested formulations: Three sustained release formulations of the drug were prepared. Each formulation contains a calculated amount of the plain drug (initial dose) in addition to an amount of microencapsulated drug (maintenance dose) equivalent to 100 mg of theophylline[18]. The calculated amount of drug was filled into a hard gelatin capsule. The prepared formulations were denoted as B,C and D.

Formulation B: 36.1 mg of plain drug + EC-coated microcapsules (core/coat 1:1 & 20% polymer concentration).

Formulation C: 60.3 mg of plain drug + microcapsules (As B but sealed by using 7.5% w/v beeswax).

Formulation D: 47.8 mg of plain drug + CAB-coated microcapsules (core/coat 1:1 & 20% polymer concentration).

100 mg of plain drug was filled into hard gelatin capsule and denoted as formulation A (control).

The sustained release formulations were tested at two, three and four capsule-dose levels.

II- Administration of the tested formulations:

Ten hospitalized patients; 6 men & 4 women; 17-80 years of age and 45-70 kg of body weight were participated in this study. Of these patients, five had bronchial asthma and five had chronic bronchitis. There was no evidence of heart, liver or kidney diseases. All patients were non smokers. No other drugs were administered before and during the study. After a light breakfast, the tested doses were administered at 9.00 a.m. with 50 ml of water. No solid food was allowed to be taken for at least 3 hours after drug administration.

III-Blood sampling:

Venous blood samples (blank) were immediately taken before drug intake, then after 1,3,5,7,9,11 & 12 hours. The blood samples were immediately centrifuged and the separated serum was kept frozen until analysis.

IV-Determination of theophylline serum level:

A modified version of the Schack and Waxler[19] method by El-Yazigi & Sawchuk[20] was adopted. The serum sample was extracted with chloroform containing 5% v/v isopropyl alcohol after the addition of 0.4 ml of 0.1 N HCl/ml of serum. The chloroformic layer was then back extracted with 0.1 N NaOH. The absorbance of the alkaline solution was read at 271 and 310 nm. The corrected absorbance of the sample was calculated as

$$A_{sample} = (A_{271}-A_{310})_{sample} - (A_{271}-A_{310})_{blank}$$

where A is the absorbance.

RESULTS AND DISCUSSION

Theophylline microcapsules were prepared by an emulsion-solvent evaporation method. The adopted procedure are simple and reproducible. The electron micrographs of the prepared microcapsules (Figure 1) show monodispersed spheres. Microscopical examination of the monodispersed spheres indicated that each one is surrounded by a cohesive and continuous film provided by the coating polymer.

Table 1 shows that by increasing the CAB concentration or the coat/core ratio, the microcapsule size was found to be decreased. A result which can be attributed to the enhanced viscosity of coating solution. An effect which keeps the drug particles in a monodispersed state as small aggregates during emulsification and while stirring. In case of using EC a coating material; there is no significant variation in the microcapsule size upon increasing EC concentration.

The determined drug content of the prepared microcapsules (Table 2) confirms the efficiency of the adopted procedure.

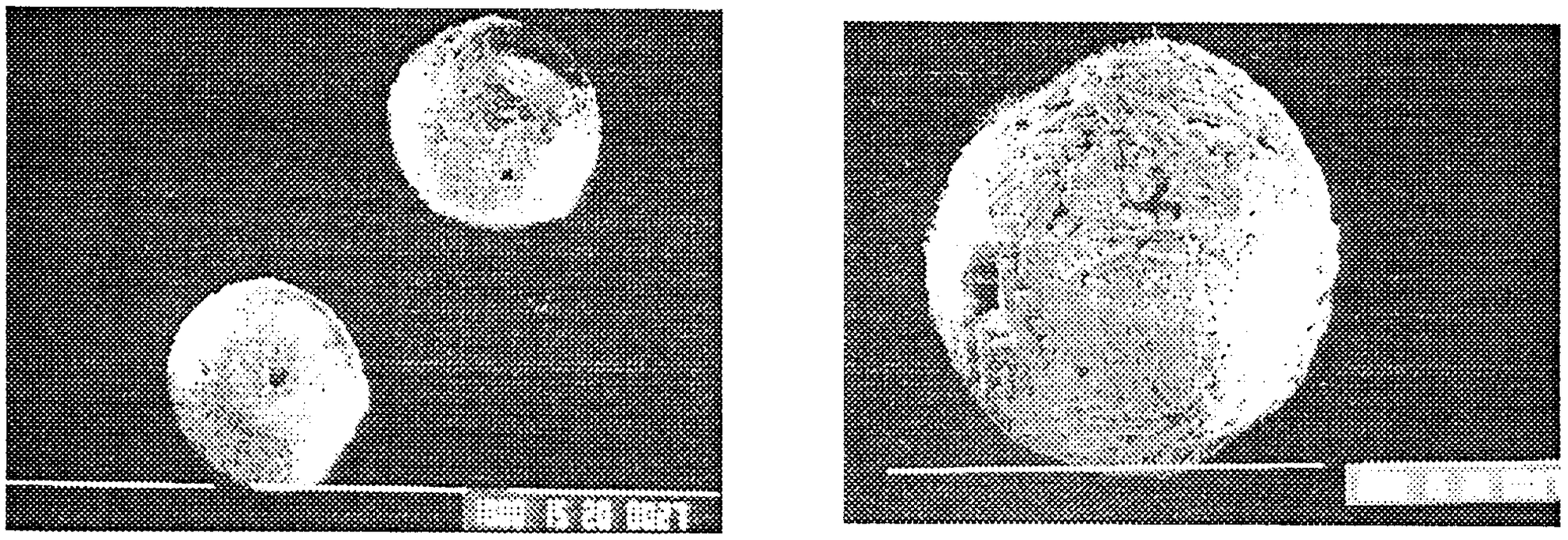

Fig. 1: Electron Micrographs of Theophylline Microcapsules Prepared by the Use of Cellulose Acetate Butyrate as the Coating Material.

Table 1: Frequency Distribution of Theophylline Microcapsules Prepared by Using Different Coating Materials.

Microcapsule Fraction size	Amount of microcapsules in each fraction using the following coating materials					
	EC 1:1 *	EC 1:1 **	CAB 1:1 *	CAB 1:2 *	CAB 1:1 **	CAB 1:2 **
μm						
< 63	--	4.63	--	--	--	--
63-90	39.24	18.11	--	--	1.62	1.96
90-200	--	60.73	--	36.03	48.35	62.82
200-315	60.76	14.34	23.01	33.03	48.05	31.83
315-400	--	1.07	52.47	9.64	3.90	2.09
400-630	--	1.12	22.09	16.75	1.08	1.30
630-710	--	--	2.43	4.55	--	--

* The coat concentration: 10% w/v.
** The coat concentration: 20% w/v.

Table 2: Drug Content of Theophylline Microcapsules Prepared by Using Different Coating Materials.

Microcapsule Fraction size	Drug content (w/w) using the following coating materials					
	EC 1:1 *	EC 1:1 **	CAB 1:1 *	CAB 1:2 *	CAB 1:1 **	CAB 1:2 **
μm						
63-90	49.73	51.21	--	--	--	--
90-200	51.84	51.67	49.14	31.21	50.42	31.40
200-315	--	52.14	49.29	32.48	50.64	31.57
315-400	--	--	50.89	32.91	51.20	32.70
400-630	--	--	--	--	--	--

* The coat concentration: 10% w/v.
** The coat concentration: 20% w/v.

The *in-vitro* release studies (Figures 2-7) revealed the following: In case of CAB-coated microcapsules, large sized microcapsules showed a slower rate of release compared to those of smaller size. A result that can be attributed to the decrease in the surface/volume ratio by increasing the microcapsule size. The release rate of the drug from CAB-coated microcapsules was found to be slower than that from EC-coated ones. The high release rate of theophylline from EC-coated microcapsules confirms the poor capability of EC as a coating

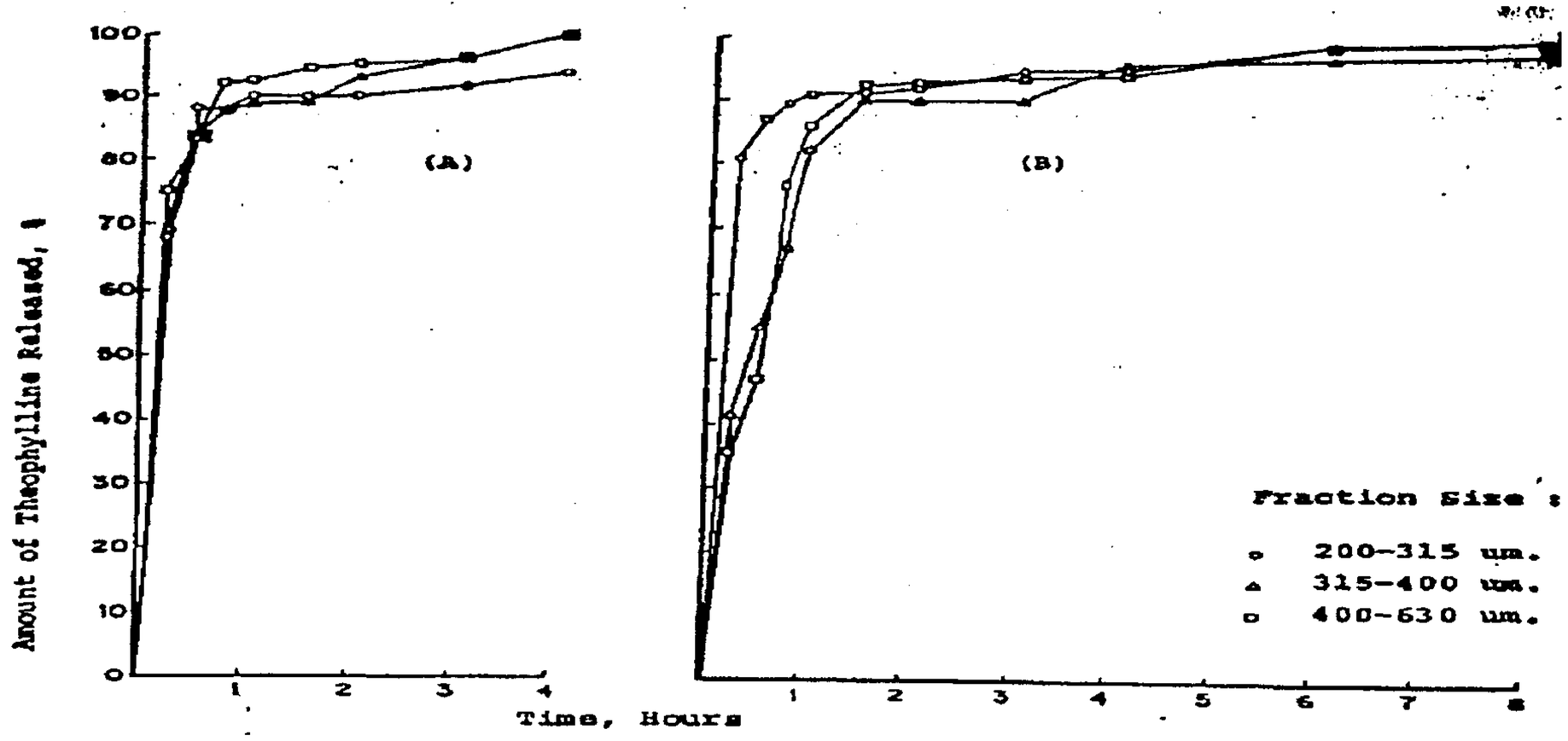

Fig. 2: *In-Vitro* Release of Theophylline from its Microcapsules Prepared by Using Cellulose Acetate Butyrate as the Coating Material at 10% Concentration and 1:1 Core/Coat Ratio.

Key: (A) in S.G.F. (B) in S.I.F.

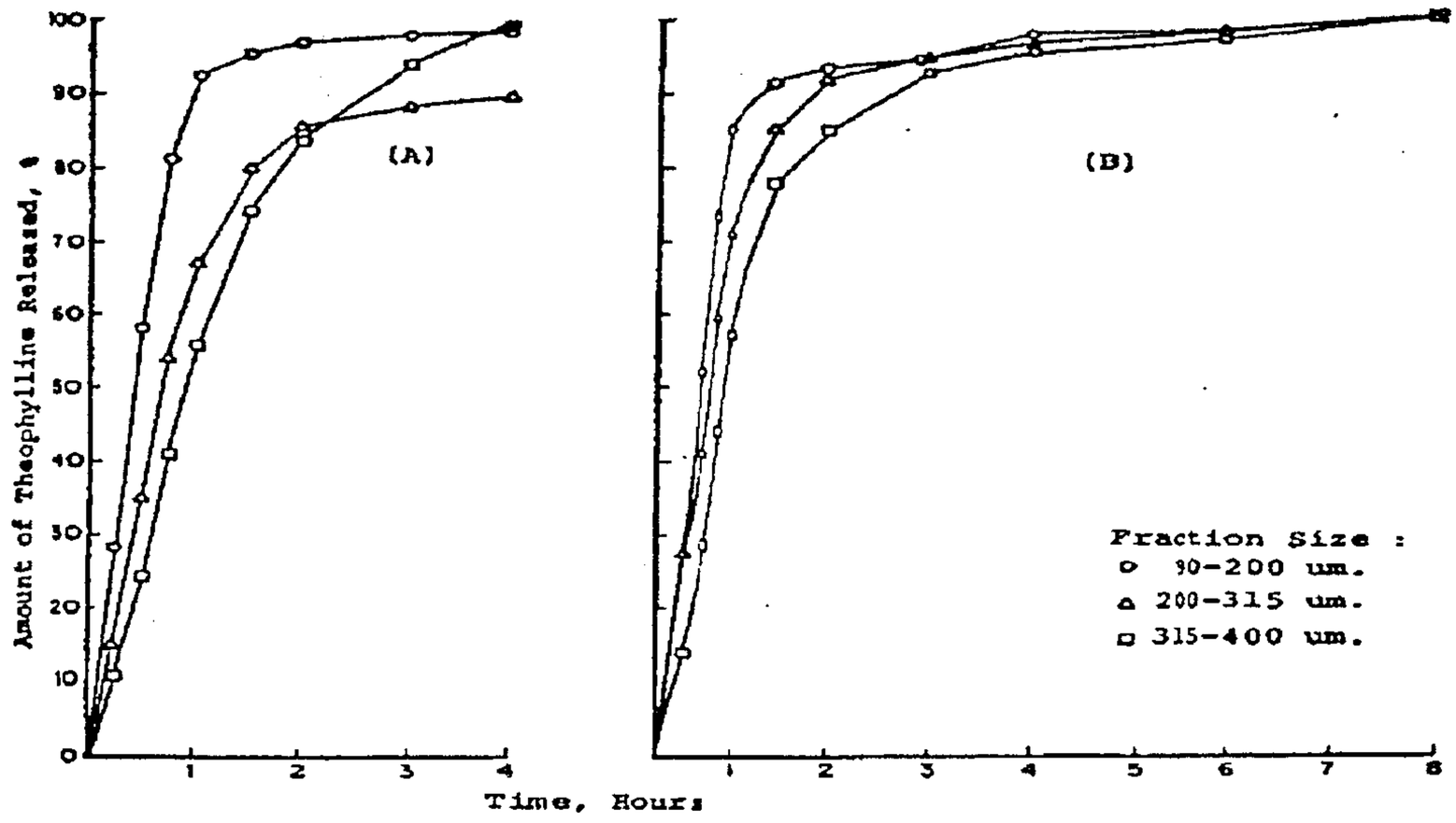

Fig. 3: *In-Vitro* Release of Theophylline from its Microcapsules Prepared by Using Cellulose Acetate Butyrate as the Coating Material at 10% Concentration and 1:2 Core/Coat Ratio.

Key: (A) in S.G.F. (B) in S.I.F.

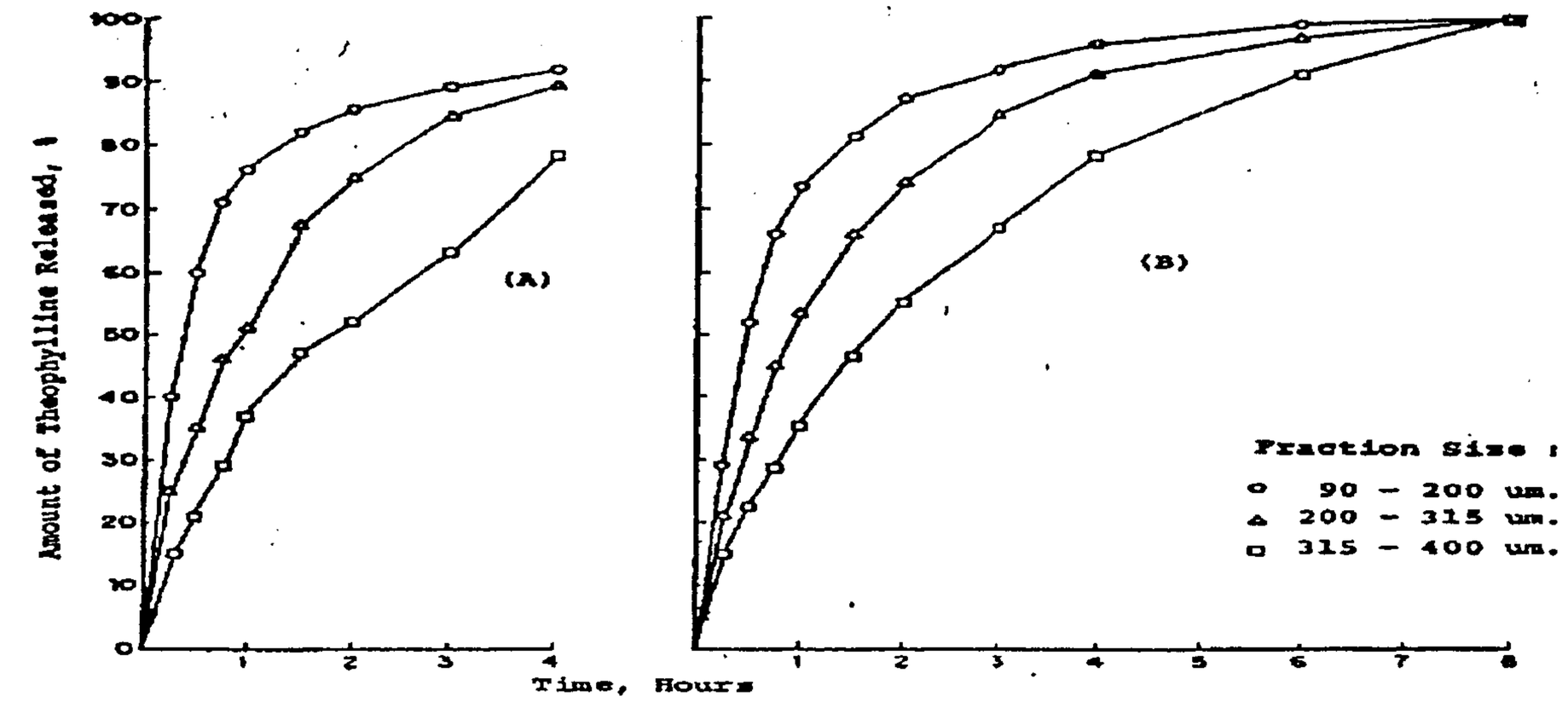

Fig. 4: *In-Vitro* Release of Theophylline from its Microcapsules Prepared by Using Cellulose Acetate Butyrate as the Coating Material at 20% Concentration and 1:1 Core/Coat Ratio.
Key: (A) in S.G.F. (B) in S.I.F.

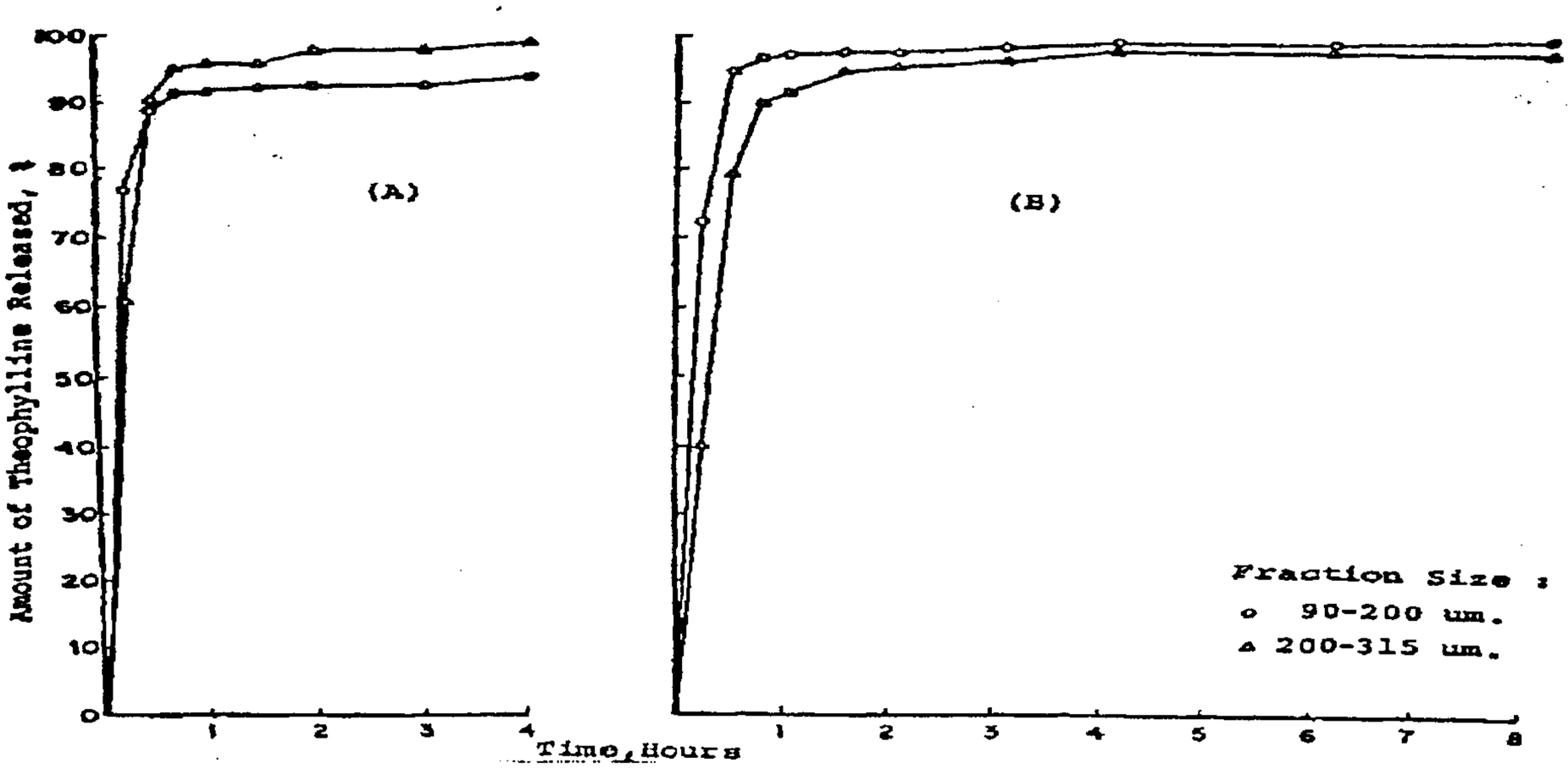

Fig. 5: *In-Vitro* Release of Theophylline from its Microcapsules Prepared by Using Cellulose Acetate Butyrate as the Coating Material at 20% Concentration and 1:2 Core/Coat Ratio.
Key: (A) in S.G.F. (B) in S.I.F.

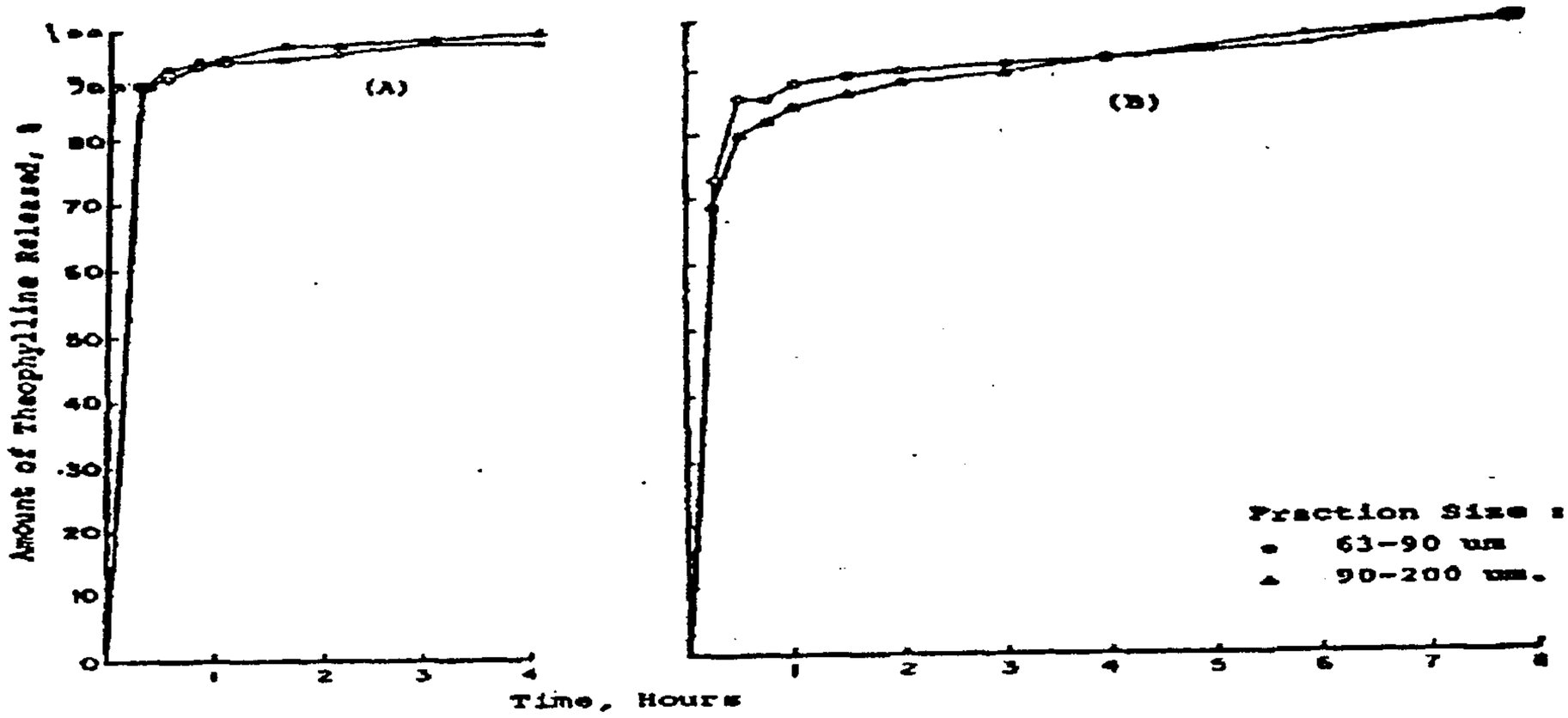

Fig. 6: *In-Vitro* Release of Theophylline from its Microcapsules Prepared by Using Ethylcellulose as the Coating Material at 10% Concentration and 1:1 Core/Coat Ratio.

Key: (A) in S.G.F. (B) in S.I.F.

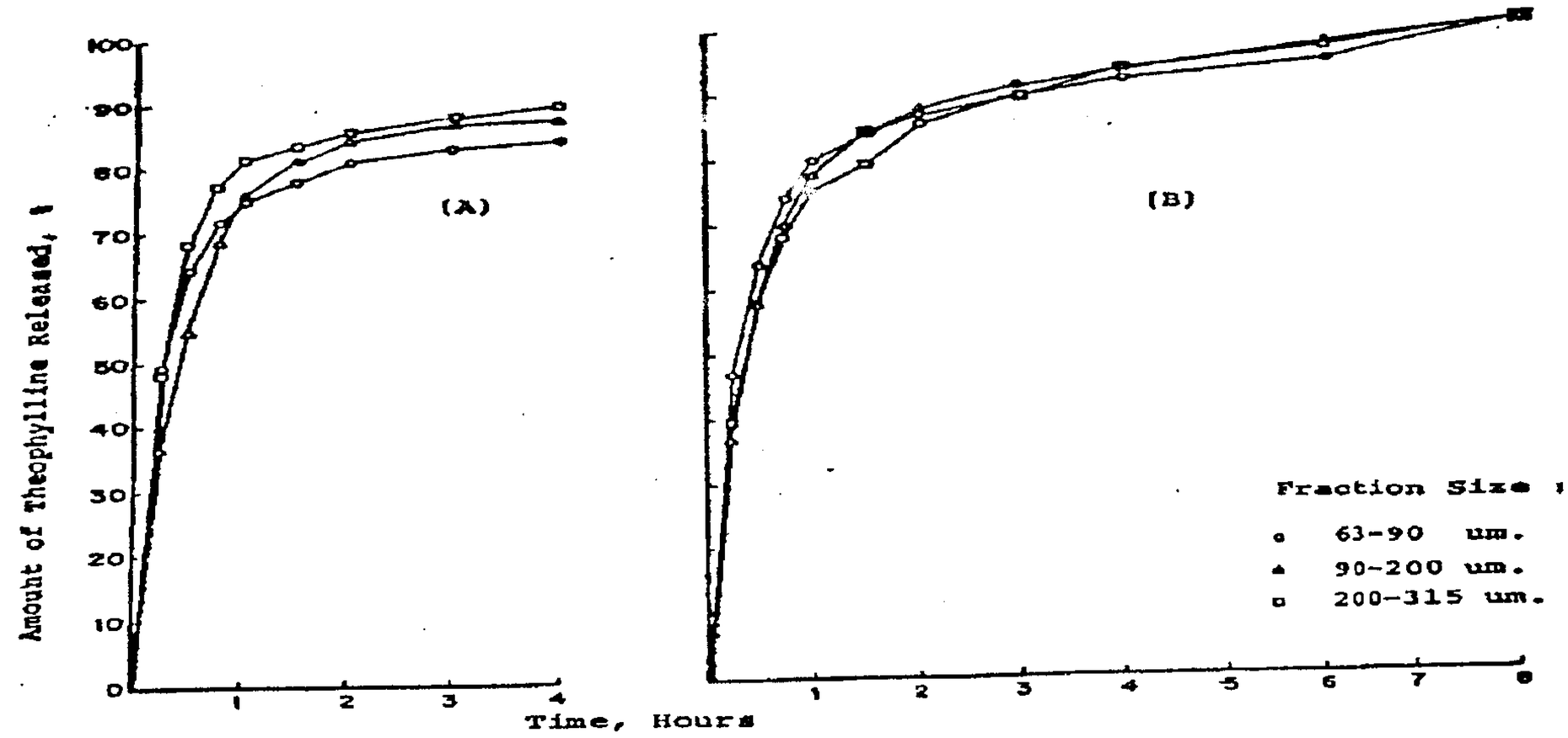

Fig. 7: *In-Vitro* Release of Theophylline from its Microcapsules Prepared by Using Ethylcellulose as the Coating Material at 20% Concentration and 1:1 Core/Coat Ratio.

Key: (A) in S.G.F. (B) in S.I.F.

material to retard the dissolution of sparingly water soluble drugs from microcapsules, a result which can be attributed to EC swelling in the dissolution media with pore induction[21]. The drug release rate from CAB-coated microcapsules in simulated gastric fluid was found to be slightly higher than that in simulated intestinal fluid. This can be attributed to the basic nature of the drug. Similar results were found by Nakano[22,23] *et. al.* working on theophylline release from dried konjac gel and sustained release tablets of the drug. The use of coating polymer at 20% concentration was found to give microcapsules with slower release rates than those prepared at polymer concentration of 10%. A result that can be attributed to the high viscosity of coating solution which helps the formation of more cohesive and more continuous film of the coating polymer around the core particles. Increasing the CAB/drug ratio from 1:1 to 2:1 was found to be accompanied by a decrease in the release rate. An effect which is mainly attributed to the increase in coat thickness by increasing coat/core ratio. The effect was only found on using CAB at 10% concentration. However, at 20% concentration, increasing the coat/core ratio leads to microcapsules with higher release rates. A result which suggests the formation of imperfect microcapsules due to the inability of the highly viscous coating solution to form a continuous film around the drug particles. Similar findings were noted by Madan *et. al*[24].

The sealing treatment of EC-coated microcapsules resulted in retardation of drug release. The effect was more enhanced upon increasing the concentration of sealing solution (Figure 8). The release of theophylline from its microcapsules can be best described by the diffusion controlled mechanism (Higuchi's model)[25].

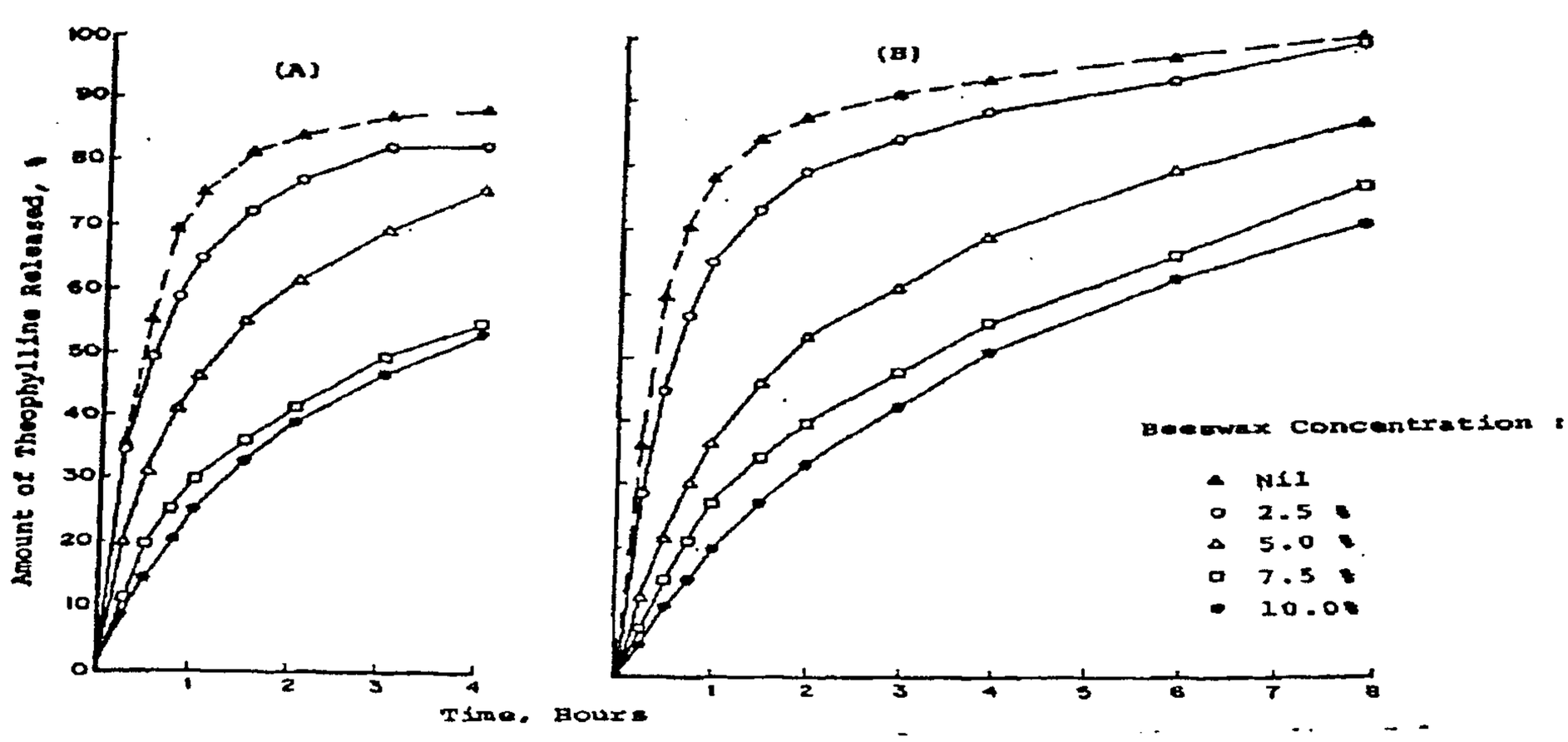

Fig. 8: Effect of Different Concentration of Beeswax on the *In-Vitro* Release of Theophylline from its Microcapsules Prepared by Using Ethylcellulose as the Coating Material at 20% Concentration and 1:1 Core/Coat Ratio.

Key: (A) in S.G.F. (B) in S.I.F.

From the *in-vivo* studies (Figure 9,10 & 11) the following can be deduced: Sustained release formulations maintained a nearly constant serum theophylline levels for a longer period of time in comparison to the plain drug. The effect is more pronounced at 2 capsule-dose level. Increasing the sustained dose from 2 capsules to 3 or 4 capsules was found to be accompanied by an increase in the theophylline serum levels. However, the increase in the serum level was not proportional with the increase in the dose. A result which can be explained on the basis that theophylline renal clearance may show concentration dependence due to the diuresis produced by the drug soon after administration[26]. Similar results were obtained by Jenne *et. al*[2]. A 2 capsule-dose of the drug seemed to be economical and sufficient to produce the desired therapeutic concentration. Also, it is worthy to note that there is no observed side effects reflecting the absence of dose dumping.

Finally, the tested microcapsules are suitable for formulating sustained action products.

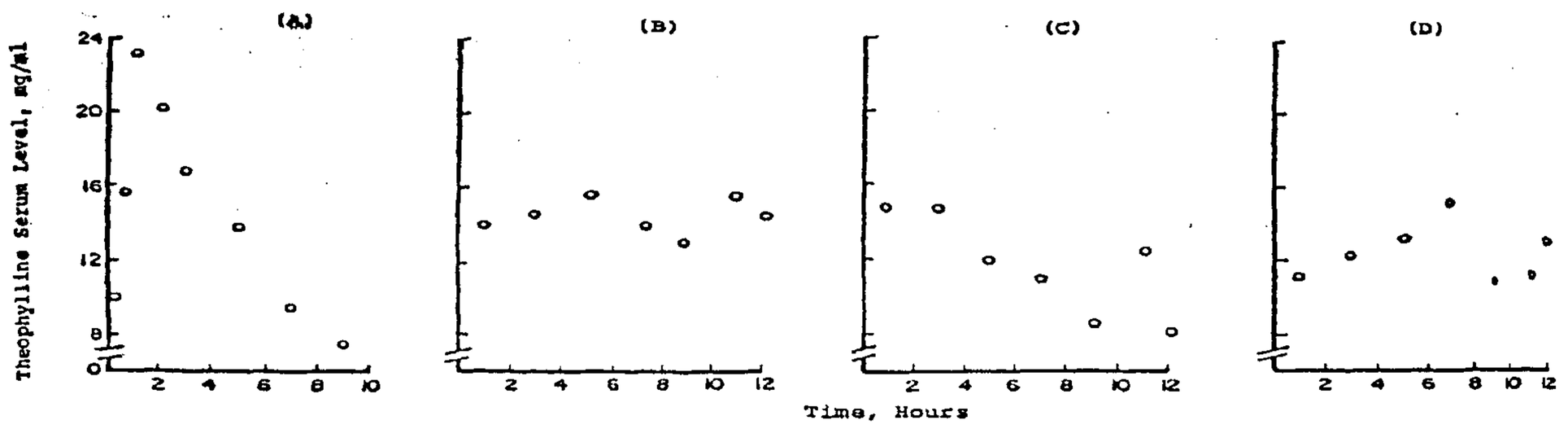

Fig. 9: Theophylline Serum Level after Oral Administration (2 Capsule-Dose) of Plain Drug (A) and Different Sustained Release Formulations (B, C & D).

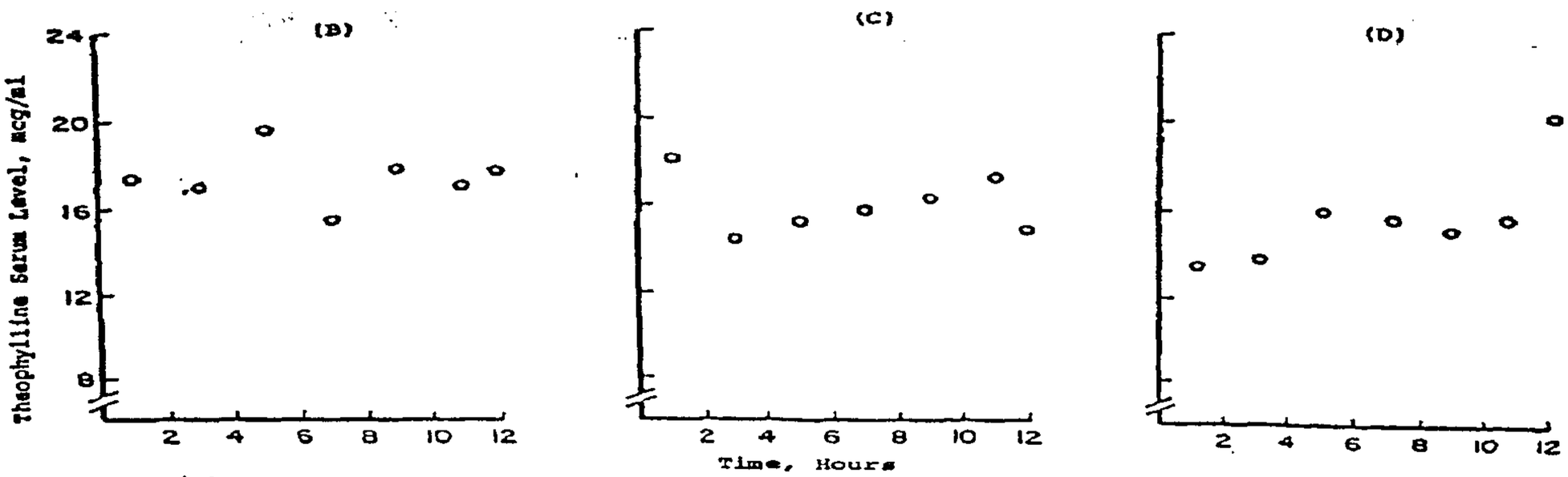

Fig. 10: Theophylline Serum Level after Oral Administration (3 Capsule-Dose) of Different Sustained Released Formulations.

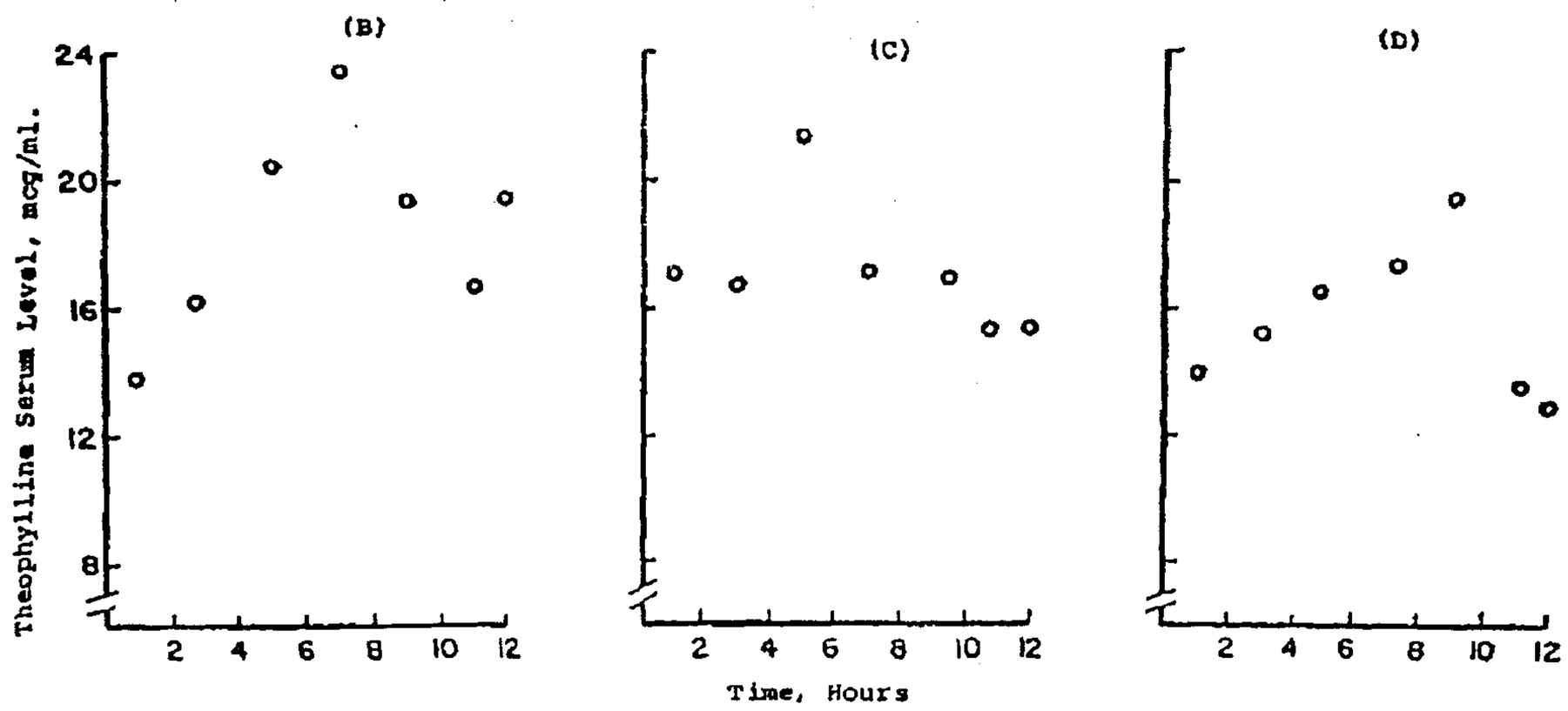

Fig. 11: Theophylline Serum Level after Oral Administration (4 Capsule-Dose) of Different Sustained Released Formulations.

REFERENCES

1- Hendeles and M. Meinberger, Pharmacotherapy, 3,2 (1983).
2- J.W.Jenne, E.Wyze, F.S.Roadand and F.M.MacDonald, Clin. Pharmacol. Ther., 13, 349 (1972).
3- Martindale, "The Extrapharmacopoeia", 29th Ed., The Pharmaceutical Press, London, 1989, p. 1526.
4- R.Baptista and D.F.Driscoll, Am. Pharm. Assoc., NS 24, 285 (1984).
5- M.Bukowskyj, K.Nakatsu and P.W.Munt, Ann. Inter. Med., 101, 63 (1984).
6- N.Svedmyr, Scand. J. Resp. Dis., 101 (Suppl.), 125 (1977).
7- G.Lonnerholm, T.Foncard and B.Lindstrom, Br. Med. J., 282, 1029 (1981).
8- M.M.Weinberger, Pharmacotherapy, 4, 181 (1984).
9- J.M.Cummiskey and V.Popa, J. Asthma, 21, 243 (1984).
10- R.A.Dederich, S.J.Szeffer and E.R.Green, J. Allergy Clin. Immunol., 61, 465 (1981).
11- S.Motycka, C.J.Newth and J.G.Nairn, J. Pharm. Sci., 74, 643 (1985).
12- S.Y.Lin and J.C.Yang, ibid., 67, 219 (1987).
13- Y.Koida, H.Takahata, M.Kobayashi and M.Samejima, Chem. Pharm. Bull. 35, 1538 (1987).
14- S.Y.Lin, J. Pharm. Sci., 77, 229 (1988).
15- Y.Pongpaibul, K.Maruyama and M.Iwatsuru, J. Pharm. Pharmacol., 40, 530 (1988).
16- R.Bodmeier and H.Chen, ibid, 754 (1988).
17- A.Shukla and J.C.Price, Pharm. Res., 6, 418 (1989).
18- M.Robinson, in "The Theory and Practice of Industrial Pharmacy", Lachman, L., Lieberman, H.A. and Kanig, J.L.,Eds., Lea & Febiger, Philadelphia, 1975, p, 439.
19- J.A.Schack and S.H.Waxler, J. Pharmacol. Exp. Ther., 97, 283 (1949).
20- A.El-Yazigi and R.J.Sawchuk, J. Pharm. Sci., 70, 452 (1981).

21- P.B.Deasy, M.R.Brophy, B.Ecnaow and M.M.Joy, J. Pharm. Pharmacol., 32, 15 (1980).
22- M.Nakano, K.Takikawa, K.Juni and T.Arita, Chem. Pharm. Bull., 27, 2834 (1979).
23- M.Nakano, N.Nakazono and N.Inotsume, Chem. Pharm. Bull., 35, 4346 (1987).
24- P.L.Madan, L.A.Luzzi and J.C.Price, J. Pharm. Sci., 61, 1586 (1972).
25- T.Higuchi, ibid, 52, 1143 (1963).
26- M.Rowland and T.N.Tozer, Eds. "Clinical Pharmacokinetics Concepts and Applications", 2nd Ed., Lea & Febiger, Philadelphia, 1989, p. 376.

الحوصلة الدقيقة للثيوفلين

أحمد مصطفى السيد - حسين عبد المنعم سيد - أحمد حامد عثمان*.
قسم الصيدلانيات - كلية الصيدلة - جامعة اسيوط
*. قسم الأمراض الصدرية - كلية الطب - جامعة أسيوط

تمت الحوصلة الدقيقة لعقار الثيوفلين بطريقة تبخير الوسط المنتشر للمستحلب باستخدام كل من ايثيل السيليلوز وخلات بيوترات السيليلوز كمواد مغلفة. وبدراسة الصفات الانطلاقية للحويصلات المحضرة فى المحاليل المشابهة للوسط المعدى والمعوى اتضح ان معدل الانطلاق ابطأ فى حالة الحويصلات الاكبر حجما أو من تلك المغلفة بخلات بيوترات السيليلوز كما اتضح أن زيادة تركيز مادة الغلاف من ١٠ – ٢٠ ٪ يؤدى الى ابطاء فى معدلات انطلاق العقار كما وجد أيضا أن زيادة نسبة مادة الغلاف / العقار من ١:١ الى ١:٢ فى حالة خلات بيوترات السيليلوز تؤدى الى تقليل معدلات الانطلاق. وبمعالجة حويصلات اثيل السيليلوز بتركيزات مختلفة من شمع النحل لوحظ حدوث ابطاء فى معدلات انطلاق العقار تزداد قيمته بزيادة التركيز المستخدم.

كما حضرت صياغات ممتدة المفعول من الحويصلات موضوع الدراسة وتم اعطاؤها الى مرضى الربو الشعبى وتم متابعة تركيز العقار فى مصل هؤلاء المرضى. وقد اثبتت هذه الصياغات صلاحيتها كأشكال ممتدة المفعول.

Received in 9/1/1993 & Accepted in 5/6/1993