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MICROENCAPSULATION OF KETOPROFEN USING W/O/W COMPLEX EMULSION TECHNIQUE

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يتناول هذا البحث حوصلة الكيتوبروفين باستخدام طريقة المستحلب المتعدد المتراكب واستخدام بيوتيرات خلات السيليولوز وعديد ستيرين كمادتى الغلاف وتم دراسة تأثير تركيز عديد ستيرين ونسبة العقار إلى البولمر (المغلف للعقار) على الانتاج من الحويصلات ومتوسط قطر الحبيبات الهندسى والتوزيع الحجمى لها وتحميل العقار - وكذلك دراسة خصائص سطح الحويصلات وانطلاق العقار منها وقد اثبتت الطريقة المستخدمة فعاليتها فيما يتعلق بكمية المنتج من الحويصلات أو المحتوى الدوائى لهذه الحويصلات.

وأظهرت النتائج أن النسبة بين بيوتيرات خلات السيليولوز الى عديد ستيرين ٩٢,٥ الى ٧,٥ فى المائة وجد أنها تزيد انتاج الحويصلات وكذلك المحتوى الدوائى للعقار.

كذلك تم تحليل نتائج انطلاق العقار من حويصلات بيوتيرات خلات السيليلوز على الاسس الكينيتيكية ووجد أنها تتبع نظام التحكم بالانتشار. وقد تم تحضير رقائق البلمرات من بيوتيرات خلات السيليلوز وأيضا من خليط من بيوثيرات خلات السيليلوز مع عديد ستيرين بنسب مختلفة وذلك للمقارنة.

وكذلك تم دراسة تأثير عوامل التحضير مثل تركيز عديد ستيرين والتركيز الكلى للبولمرات وتركيز العقار على النفاذية خلال رقائق البلمرات للعقار.

وقد أثبتت النتائج أن نفاذية العقار خلال رقائق البلمرات وحويصلاته يمكن التحكم فيها بتغيير نسبة البولمرات وأن ثابت النفاذية يقل مع زيادة التركيز الكلى للبولمرات ويتناسب طرديا مع تركيز العقار.

وأخيرا نجد أنه قد تم تحضير الحويصلات بنجاح وكذلك رقائق البلمرات لفحص خصائص بناء ونفاذية الرقائق وتركيبها وخصائص سطح الحويصلات المحضرة ووجد أنها تشرح بدقة خصائص الانطلاق الدوائى منها.

Sustained release cellulose acetate butyrate (CAB) - polystyrene (PS) microcapsules containing Ketoprofen (a non steroidal anti-inflammatory drug) were prepared adopting the modified W/O/W complex emulsion technique. The effect of polystyrene concentration and core/coat ratio on the yield, geometric mean particle diameter dg, size distribution, drug loading as well as release and surface characteristics of the microcapsules were investigated. The results obtained revealed that polystyrene utilization as a wall material play a dominant role to the manufacturing process. A particular composition of 92.5:7.5 (percent) of CAB to PS was found to improve greatly the microcapsule yield and maximize the drug loading. In most of cases, the encapsulation efficiencies increased with increasing microcapsule size and theoretical drug loading. Kinetic analysis of the data shows that the drug release process from CAB microcapsules followed Higuchi model (a diffusion-controlled model for planar matrix), whereas the release behavior actually conforms with Baker and Lonsdale model (a diffusion-controlled model for spherical matrix) for CAB - PS microcapsules. The preparation of free films of CAB and CAB-PS was described for comparison. The effect of processing parameters (Polystyrene concentration, total polymers concentration and permeant concentration) on the permeation of ketoprofen through the polymeric films was discussed. The results demonstrated that ketoprofen permeation through the films and microcapsules could be controlled by modifying the CAB-PS ratio in the polymer matrices. The permeability constants

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decreased with increasing the total polymers concentration up to 5 percent and were proportional to permeant concentration.

To compare kinetics of drug release from polymeric films with those of microcapsules, ketoprofen was incorporated at different concentrations within CAB-PS cast films. These films exhibited timed release of the drug ($t_{0.5}$; 58.22-146.46 hr). Release rates were found to agree with Baker and Lonsdale model, previously suggested for ketoprofen release from CAB-PS microcapsules. In conclusion: to expedite successfully the microencapsulation process, cast films were prepared to examine the build - up and permeability characteristics of the membrane coat structure. The surface characteristics of the prepared microcapsules were found to explain precisely the release profiles.

INTRODUCTION

A variety of microencapsulation techniques are available for the formation of microparticulate drug delivery systems[1-3]. In many instances, the controlled release of an agent from microcapsules[4,5] and the reduction of gastrointestinal tract irritation are desired[6]. The choice of one particular method is primarily determined by the physicochemical properties of the drug and polymer. A popular method for the encapsulation of water - insoluble drugs within water -insoluble polymers is the solvent evaporation method. In most investigations, attention has focused on solid matrix microspheres prepared by a single emulsion process with an external oily phase[7-9]. However, It is easier and more economical to work with aqueous media instead of oils or organic solvents as the external phase with regard to agglomeration of microparticles, clean - up requirements of the final product, recovery of the organic phase and its viscosity[5]. Use of a W/O/W complex emulsion can, however, solve these problems and facilitate the preparation of reservoir - type microcapsules[10]. Numerous polymers such as ethylcellulose[11], poly - B-hydroxy butyrate homopolymers and copolymers thereof with 3 - hydroxyvalerate[12], poly (D,L-Lactide- and poly (D,L-Lactic-Co-glycolic acid)[13], are employed to prepare microspheres by this method. Iso *et al.*[14] used polystyrene and styrene butadiene rubber as wall materials either separately or in mixture to encapsulate lipase using a w/o/w complex emulsion technique. They demonstrated that 2:1 polystyrene-styrene butadiene rubber mixture produced homogenous and tough wall structure suitable for the enzyme protection. A porous polystyrene microcapsules containing sodium dichromate were also prepared[3].

Ketoprofen, a nonsteroidal anti-inflammatory drug, is a good candidate for the development of oral controlled release preparations. Adverse gastrointestinal reactions have been observed and short biological half-lives (1-2 hr) require a three times a day administration[15].

Ketoprofen was encapsulated with Eudragit E,L and S microcapsules adopting the fluidized bed technique[6,16,17] and the emulsion solvent evaporation process in an oil phase[15,18].

Bodmeier and Chen[19] prepared ethylcellulose microspheres containing ketoprofen by an o/w emulsion solvent evaporation method. The results obtained revealed that a maximum incorporation efficiency of 63.2 percent was obtained at 60 percent theoretical drug content.

The selection of a given microcapsule coating can be aided reliably in as short a time as possible by the study of cast films[20-21].

Numerous studies were made to evaluate film-forming polymers of various composition as the coating material[22-24]. Greater changes in film properties may be obtained by the use of additive polymers selected on the basis of hydrophilicity properties such as hydroxy-propylcellulose in polyvinyl acetate films[25] and polycaprolactone with polylactide[26]. Samuelove *et al.*[22] prepared cast films composed of different ratios of polyethylene glycol 4000 and ethylcellulose with salicylic acid, caffeine and tripelennamine as model dispersed drugs, Their results revealed that cast films exhibited sustained release which followed the square root

of time equation.

Mixtures of polymers can have properties significantly better than an individual polymer for achieving sustained release[27].

The objective of the present work was to prepare ketoprofen loaded CAB- PS composite microcapsules with optimum sustained release profile using the modified w/o/w complex emulsion technique. The effect of the following processing variables viz, polystyrene concentration and core/coat ratio on microcapsule properties was evaluated. Cast films were utilized as a mean of examining the permeability characteristics of the coating material. Several factors affecting the diffusion of the drug through cast films were discussed.

EXPERIMENTAL

Materials

Materials used for encapsulation including; ketoprofen (Courtesy of Ameriya-Rhone Poulenc, Alexandria, Egypt); Cellulose acetate butyrate (CAB) (17% butyryl, 29% acetyl and 1.5% hydroxyl content) (Scientific polymer products, Ontario. N.Y); Polystyrene (MW 325000 to 350000), Polyvinyl alcohol (MW 125000) (Polysciences Inc., Worthington, PA); Tween 80 (Sigma Chemical Co., St, Louis, MO 63178 U.S.A.), Dichloromethane (Wako Pure Chemicals, Tokyo, Japan). All other chemicals were of reagent grade and were used as received.

Methods

Preparation of microcapsules

A modified method in which two-step emulsification procedure was adopted[28]. At the first emulsification step, 3 ml distilled water containing 0.5 g of finely powdered ketoprofen were emulsified in the polymer solution (10% w/v of cellulose acetate butyrate or a mixture of cellulose acetate butyrate and polystyrene in dichloromethane). Stirring was effected with mechanical stirrer (MLW, ER10, (GDR) for 10 minutes and the temperature was kept constant at 45°C during this step. The obtained W/O emulsion was then added while stirring to the external aqueous phase containing 0.5% W/V polyvinyl alcohol and 0.02% Tween 80 to yield W/O/W emulsion. The temperature was elevated to 55°C and then kept constant till the formation of microcapsules. The obtained microcapsules were filtered off, washed with purified water (3 x 70 ml) and allowed to dry at 37°C in an incubator for 24 hours.

The particle size of the microcapsules was determined by sieving with JPX standard sieves and it was ranged from 250 to 600 μm.

The effect of polystyrene concentration and core / coat ratio on the yield, particle size and drug loading of the microcapsules was investigated.

Determination of drug loading

Twenty five milligrams microcapsules were accurately weighed and crushed in a clean mortar, then pulverized by the aid of a small amount of simulated intestinal fluid (S.I.F, pH 7.4). The pulverized microcapsules were transferred into a 100 ml volumetric flask and completed with S.I.F to the appropriate volume. An aliquot was withdrawn, filtered and suitably diluted and assayed spectrophotometrically at 260 nm using the same medium as a blank. The drug content for every fraction size of the prepared microcapsules was determined.

In-Vitro release study

The USP rotating paddle dissolution apparatus (Model Dt-06, Erweka (Germany)) was used at 50 r.p.m. Twenty-Five milligrams of microcapsules were accurately weighed and added to 500 ml of the dissolution medium (simulated gastric fluid (S.G.F, pH 1.2) or S.I.F (pH 7.4) containing 0.02 % w/v Tween 80) maintained at 37°C. Five milliliter samples were withdrawn at specified time intervals, and were replaced by an equivalent volumes of dissolution medium kept at 37°C. The concentration of ketoprofen at 258 nm and 260 nm was determined for S.G.F and S.I.F respectively. All dissolution studies were run at least in duplicate for each experiment. The dissolution behavior of the drug powder was similarly studied.

Scanning electron microscopy

Scanning electron microscopy[12] was conducted using JEOL (JSM- T200) electron microscope as follows: Microcapsules were

mounted on specimen studs using a double - sided adhesive tape, then coated with gold for 10 minutes at 60 milliamperes by using SPI sputter TM coating unit (SPI supplies, Division of structure Probe, Inc., west chester, PA, USA). Scanning electron micrographs were taken at 20 K.V. The magnification power on the screen ranged from 100 to 3500.

Preparation of cast films

Free films, of composition listed in table 5, were cast from dichloromethane solution containing the polymers by a casting technique[29] employing circular teflon plates (Area 38.5 cm^2) for casting. However, medicated films containing varying ketoprofen concentrations were cast from dichloromethane solutions containing 5 % w/v total polymers concentration (92.5:7.5 CAB: PS). The film thickness was determined after drying by the use of a micrometer (B.D.H. LTD., Poole, England),. The resulting films possessed a uniform thickness prior to testing.

Permeability study

A permeability cell consists of two conical chambers separated by the tested film was used[30]. The capacity of each chamber was 250 ml. and the experiment was conducted in thermostatically controlled water bath at 37°C±0.5 with shaking at 50 r.p.m.. Phosphate buffer pH 7.4 (150 ml) containing 25 mg of the drug as an initial concentration and an equivalent volume of drug-free buffer were introduced into the donor and acceptor chambers, respectively. The effective area of the film between the donor and acceptor chambers was 4.9 cm^2. Aliquots (5 ml) were withdrawn from the receiver solution at specific time intervals and were replaced by an equivalent volumes of fresh media. The amount of drug penetrated was determined spectrophotometrically at 260 nm.

Partition coefficient determination

Partition coefficient were determined by a solution depletion technique[31] in which 50 ml of drug solution in phosphate buffer (pH 7.4) was allowed to equilibrate with a known volume of the film. The drug equilibrium concentration in the bulk aqueous solutions was determined and partition coefficients were obtained from the ratio of the concentrations in the film and in the bulk aqueous phase.

Determination of drug release from medicated films

The release from medicated films was conducted in USP dissolution paddle apparatus using 250 ml of phosphate buffer pH 7.4 as the release medium. The test was done at 37°C±0.5 and 50 r.p.m. Aliquots (5 ml) were withdrawn at specified time intervals and replaced by equivalent volumes of release medium. The amount of drug released was determined spectrophotometrically at 260 nm.

RESULTS AND DISCUSSION

The described w/o/w complex emulsion technique proved to be reliable and efficient for encapsulating Ketoprofen using cellulose acetate butyrate (CAB) or a mixture of CAB and polystyrene (PS) as the coating material. The adopted method produced free - flowing, non - aggregated and spherical microcapsules.

Some formulation and processing variables viz, polystyrene concentration in polymer blends and core/coat ratio, which many have their influence on the physical characteristics of microcapsules and in-vitro release rate of drug were studied.

Table (1) depicts the effect of using CAB either separately or in mixture with PS on the microcapsule properties. Polystyrene was used at concentrations of 7.5, 15 and 25 percent w/w of the total polymers concentration. It is evident that addition of polystyrene to the polymer matrix improved greatly the microcapsule yield and maximized the drug content within the microcapsules. The effect was more prominent on using polystyrene at 7.5 percent w/w concentration, which increased the microcapsule yield significantly from 63.35 to 85.15 percent and the drug content by about 10.47 to 22.32 percent depending on microcapsule size. In the w/o/w complex emulsion method, the organic or

middle phase separates the internal water droplets from each other and from the external aqueous phase. Ketoprofen is soluble in a solution of polymers in methylene chloride and hence may diffuse from the organic polymer solution into the external aqueous phase and/or the drug may be lost with polymer debris resulting from breakdown of primary emulsion droplets. Presence of polystyrene may stabilize the primary emulsion during the second emulsification step resulting in a high yield and drug content. Alex and Bodmeie[5] explained that the drug could be lost from the microparticles to the external aqueous phase in several ways: First, The drug was lost from internal water droplets coming in contact with the external phase during the second emulsification step followed by diffusion of the drug through the organic polymer solution.

Figure (1) shows the typical size distribution of CAB and CAB-PS microcapsules. It is clear that utilization of polystyrene as wall material reduced the microcapsule size. The higher concentration of PS (25 percent w/w) was noted to produce a narrow particle size distribution with more than 70 percent of microcapsules in the range of 150 to 250 um. The geometric mean particle diameter d_g, decreased with increasing PS concentration on an absolute scale (table 1) This indicates that the fluidity of the polymer solution can be easily adjusted by use of mixtures of CAB and PS and thus provides a practical means to control the microcapsule size. Particle size can also be largely controlled by the density of the microcapsule materials and interfacial tension at the water/oil interface[26]. Iso *et al.*[14] studied the microencapsulation of lipase by a w/o/w complex emulsion technique using polystyrene and styrene - butadiene rubber as wall materials either separately or in mixture. They found that the average diameter of microcapsules becomes smaller as the content of polystyrene in the wall increases.

The dissolution of ketoprofen powder compared to the dissolution of ketoprofen from CAB and CAB-PS microcapsules is presented in figures 2,3 and 5. It is evident that the applied microencapsulation process resulted in a marked delay in the rate of ketoprofen dissolution in S.I.F (pH 7.4) and S.G.F (pH 1.2).

Table 1: Effect of polystyrene concentration on characteristics of ketoprofen-loaded CAB-PS microcapsules.

Polystyrene conc. % W/W	Fraction size (μm)	Average Size (μm)	d_g (μm)	σ_g	Yield (%)	Drug loading (%)		Encapsulation Efficiency (%)
						theoretical	actual	
0	355-500	427.5	316.23	2.066	63.35	30.37	13.76	45.31
	500-600	550					13.44	44.25
	600-710	655					13.40	44.12
7.5	355-500	427.5	309.02	1.57	85.15	30.37	15.37	50.61
	500-600	550					15.89	52.32
	600-710	655					17.25	56.80
15	355-500	427.5	288.40	1.58	78.04	30.37	14.73	48.50
	500-600	550					14.60	48.07
	600-710	655					14.70	48.40
25	355-500	427.5	204.20	2.09	81.96	30.37	13.58	44.72
	500-600	550					14.12	46.50
	600-710	655					14.53	47.84

- Core/Coat ratio 1:2. - d_g Geometric mean particle diameter, um. - σ_g Geometric standard deviation.

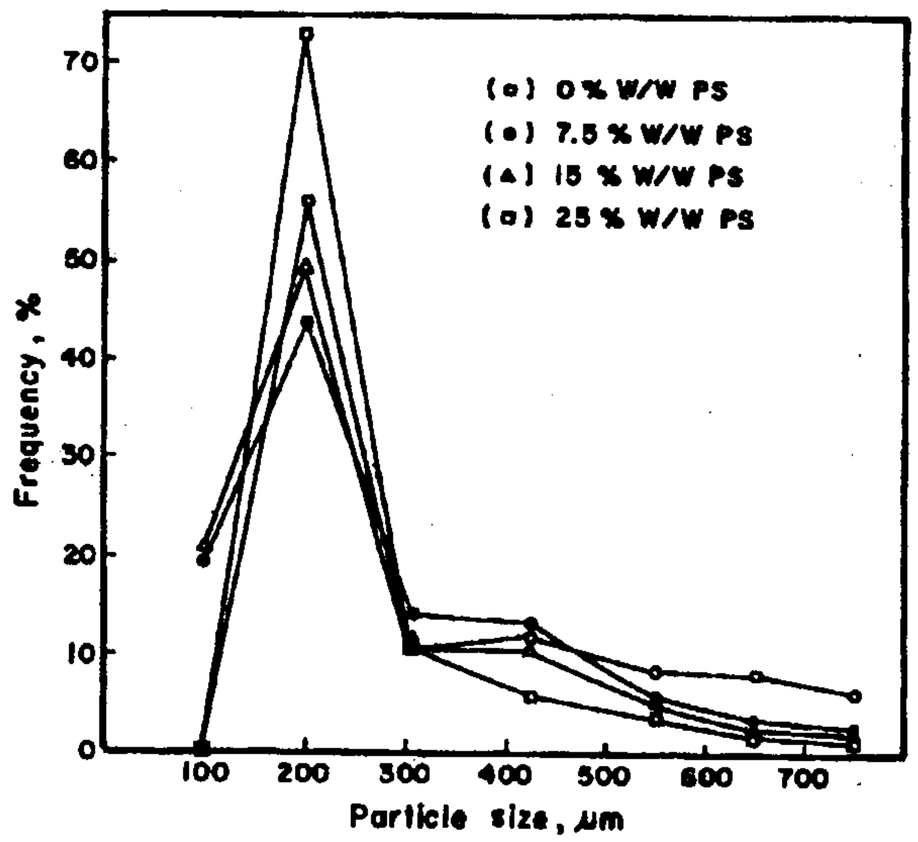


Fig. 1: Effect of polystyrene concentration on particle size distribution of CAB-PS microcapsules containing ketoprofen (Core/Coat ratio 1:2).

The effect of polystyrene concentration in polymer blends on the drug release rate is presented (in table 2) and (figures 2 and 3). Obviously, the release patterns were easily changed by using a mixture of CAB and PS. An increase in polystyrene content of the polymer microcapsule matrix brought about an increase in the release rate ; but a particular composition of 92.5:7.5% of CAB to PS seemed to approach the lowest dissolution extreme for the CAB - PS system. Thus, the drug release rates ($K_1 x 10^{-1}$) from CAB microcapsules and CAB-PS microcapsules (600-710 um, S.I.F) prepared using polystyrene at 7.5% concentration of the polymer matrix were found to be 1.750 and 1.804 respectively (table 2). The variations in the release properties of microcapsules can be verified by the scanning electron micrographs given in plate 1. A representative CAB microcapsule is less spherical in shape and has relatively smooth and slightly wrinkled surface which is covered by discrete micropores (plate 1 a, x 100). High magnification (x 1000) shows the microporous and the sponge-like morphology of the outer wall and the absence of drug crystals on the microcapsule surface. The porous structure is probably introduced by rapid vaporization of the solvent resulting in subsequent formation of bubbles during the fabrication process and puncturing the microcapsule membrane[27,3].

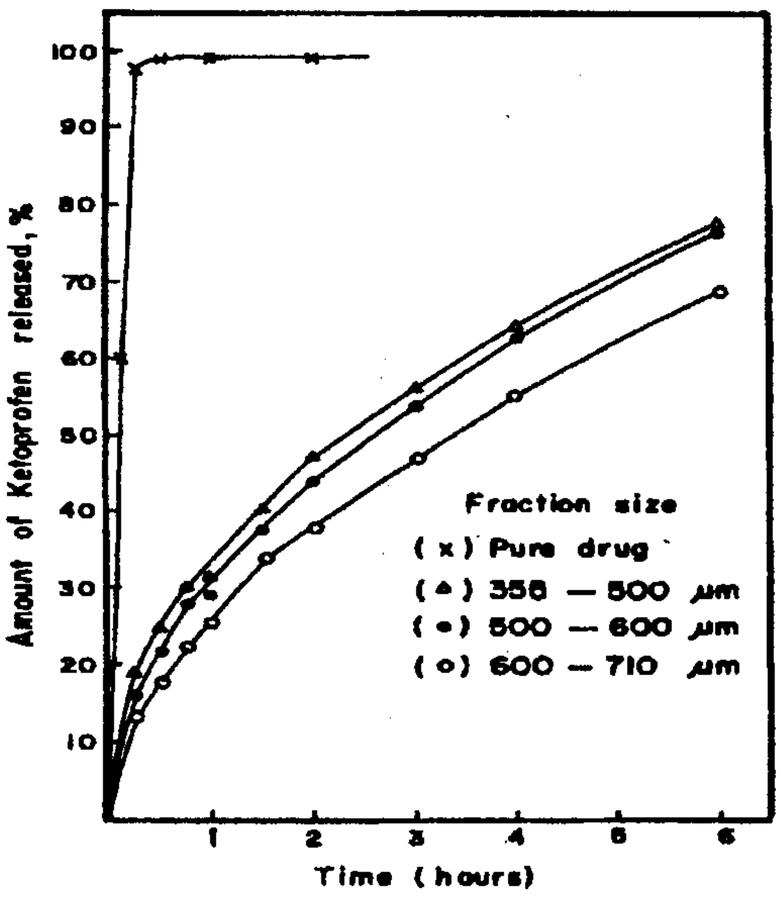
CAB-PS microcapsules appeared to have different surface morphologies. Using polystyrene at 7.5% concentration of the coat-forming polymer solution produced an excellent yield of mostly spherical particles having relatively rough surface (plate 1 b, x 100) At high resolution (x 1000, a few number of drug crystals are clearly observed within a less - porous, wrinkled and shrivelled microcapsule membrane. Increasing polystyrene concentration to 15% produced rough and spherically shaped microcapsules as shown in (plate 1 c, x 100). Higher magnification, x 1000, shows the appearance of a significant proportion of drug crystals within a less porous and shrivelled microcapsule wall. The surface appeared to have many indentations and depressions which might be formed during vaporization of solvent and contraction of polymer matrix. Embleton and Tighe[12] reported that low viscous polymers usually give rise to wrinkled, non-porous, and spherical particles due to polymer precipitation as a more mechanically stable gel. Consequently the forces caused by contraction, as solvent extraction progresses, are therefore unable to rupture the developing wall. Instead, the wall shrinks as a continuous film during the final stage of polymers precipitation and emerges intact, but with a shrivelled appearance.

The high concentration of polystyrene (25% w/w) was noted to produce microcapsules bearing a similar morphological features. However, the representative microcapsule shown in plate 1d, x 100 is less spherical in shape and has a porous and very rough surface. At high magnification, x 1000, the surface was nearly covered by drug crystals and appeared to be loosely bound giving rise to a heavily structured and macroporous morphology (plate 1 d, x 1000). The remarkable existence of drug crystals on the surface of CAB-PS microcapsules and their absence on

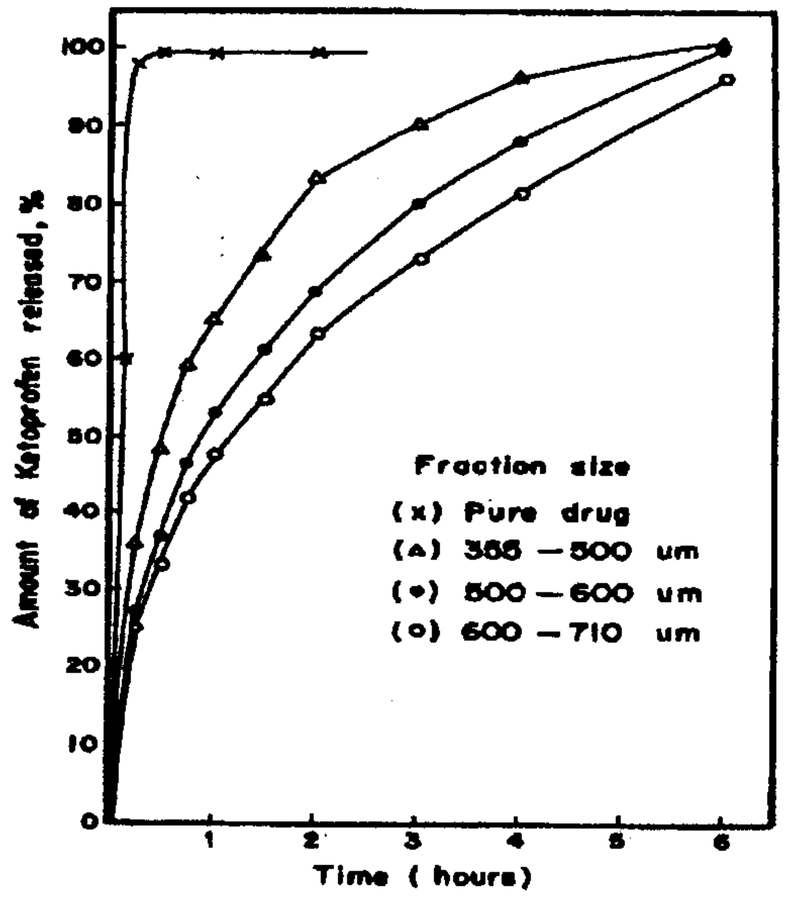
Table 2: Kinetics assessment of release data from ketoprofen-loaded CAB-PS microcapsules prepared at different polystyrene concentrations (S.I.F.).

Polystyrene Conc. % W/W	Average Size of microcapsules (μm)	Zero order		First order			Diffusion models						
							Planar matrix				Spherical matrix $3/2(1-(1-F)^{2/3})-F$ vss. t		
							Q vss $t^{1/2}$		log Q vss. log t				
		r	K_o ($mg.hr^{-1}$)	r	$k_1 x10^{-1}$ (hr^{-1})	$t_{0.5}$ (hr.)	r	K_H ($mg.hr^{-1/2}$)	r	slope	r	$K_{BL} x10^{-2}$ (hr^{-1})	$Dx10^{-2}$ ($cm^2.hr^{-1}$)
0	427.5	0.9817	11.66	0.9968	2.131	3.25	0.9980	30.49	0.9970	0.4480	0.9925	2.33	
	550	0.9846	11.98	0.9989	2.166	3.199	0.9990	31.34	0.9983	0.4987	0.9958	2.26	
		(0.9938)	(10.39)	(0.9973)	(1.810)	(3.83)	(0.9978)	(29.97)	(0.9966)	(0.6322)	(0.4877)	(1.75)	(1.113)
	655	0.9860	10.90	0.9985	1.750	3.96	0.9988	28.70	0.9987	0.5275	0.9975	1.592	
7.5	427.5	0.9602	13.47	0.9829	6.50	1.066	0.9965	35.26	0.9959	0.3994	0.9970	6.803	
	550	0.9533	12.84	0.9778	2.88	2.406	0.9888	33.54	0.9943	0.4290	0.9993	3.144	
		(0.9804)	(12.05)	(0.9959)	(1.972)	(3.514)	(0.9994)	(31.27)	(0.9980)	(0.5784)	(0.9992)	(1.962)	(1.476)
	655	0.9810	11.67	0.9937	1.804	3.842	0.9993	27.00	0.9986	0.4535	0.9987	1.785	
15	427.5	0.9438	18.87	0.9971	7.162	0.9676	0.9820	36.39	0.9909	0.3598	0.9980	10.98	
	550	0.9631	15.50	0.9988	4.733	1.464	0.9955	34.02	0.9960	0.4130	0.9977	6.17	
		(0.9974)	(14.45)	(0.9959)	(3.758)	(1.844)	(0.9998)	(–)	(0.9991)	(0.6165)	(0.9966)	(3.58)	(2.474)
	655	0.9676	14.35	0.9801	4.737	1.463	0.9991	33.33	0.9984	0.4238	0.9992	4.88	
25	427.5	0.9422	21.91	0.9485	10.28	0.6740	0.9891	36.40	0.9942	0.2518	0.9931	11.90	
	550	0.9779	15.91	0.9962	5.105	1.357	0.9995	35.25	0.9984	0.2998	0.9958	7.184	
		(0.9922)	(14.60)	(0.9968)	(3.944)	(1.757)	(0.9996)	(–)	(0.9993)	(0.5490)	(0.9985)	(3.844)	(2.569)
	655	0.9794	14.68	0.9950	3.30	2.10	0.9988	33.00	0.9996	0.3613	0.9993	4.070	

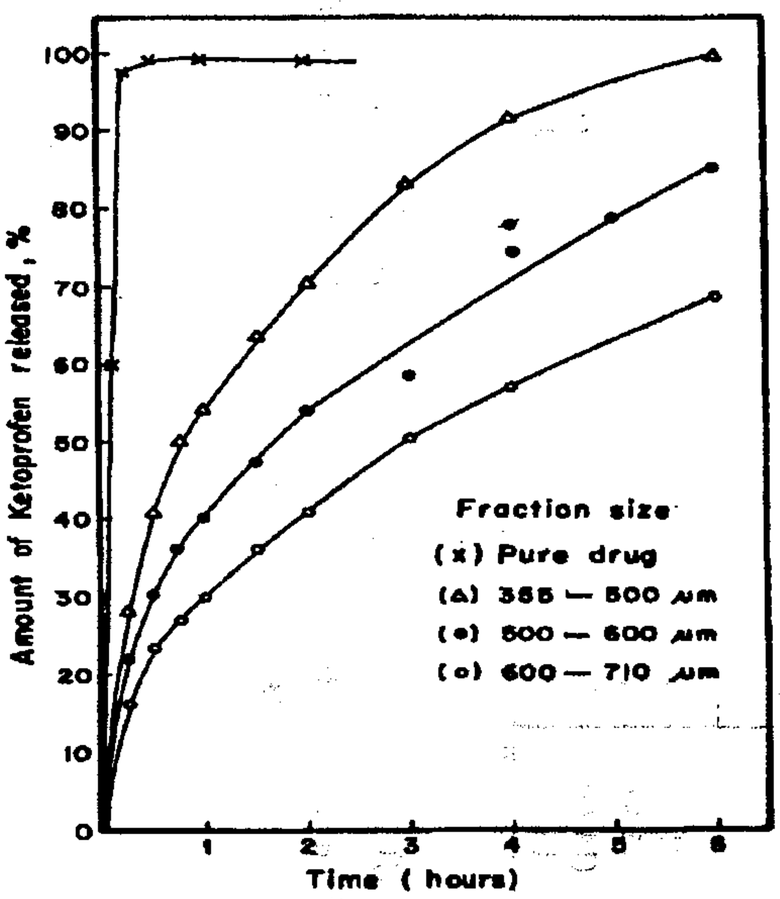
- Core/Coat ratio: 1:2.
- Q: amount of drug released after time t; K_{BL}: Baker and Lonsdale's model constant and D: Diffusion coefficient ($cm^2.hr^{-1}$).
- $F= M_t/M_\alpha$ where M_t and M_α are the amounts of drug released at t and at infinity time α.
- Data between parantheses indicate release in S.G.F.



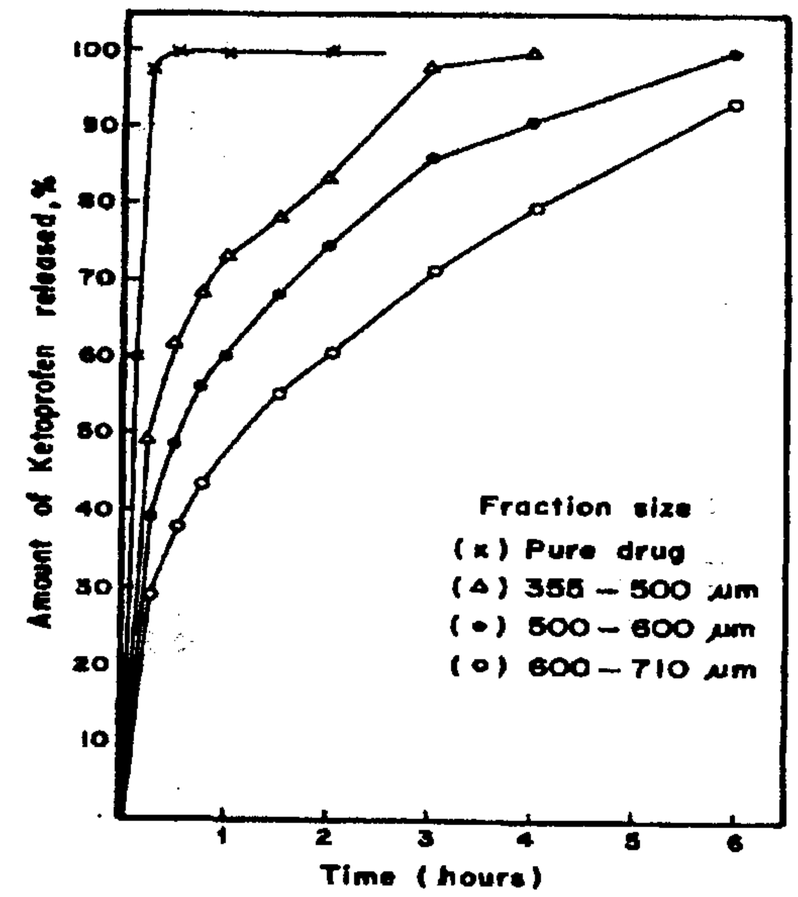
0% PS



15% PS



7.5% PS



25% PS

Fig. 2: In-vitro release of ketoprofen from CAB-PS microcapsules prepared at different polystyrene concentrations (Core/Coat ratio 1:2, S.I.F. pH 7.4).

CAB microcapsules can be explained on the basis of the rates of polymer and drug precipitation during microcapsule formation[19]. Thus when CAB was selected as the wall material, the polymer might be precipitated before the drug and drug crystals were not observed. When mixtures of CAB and PS were used as the matrix, the drug precipitated prior to the polymer and ketoprofen crystals were visible on the microcapsule surface. The reasonable factor may be the reduction in polymer viscosity with increasing polystyrene content in the matrix which resulted in non precipitated polymer at the time of the drug precipitation.

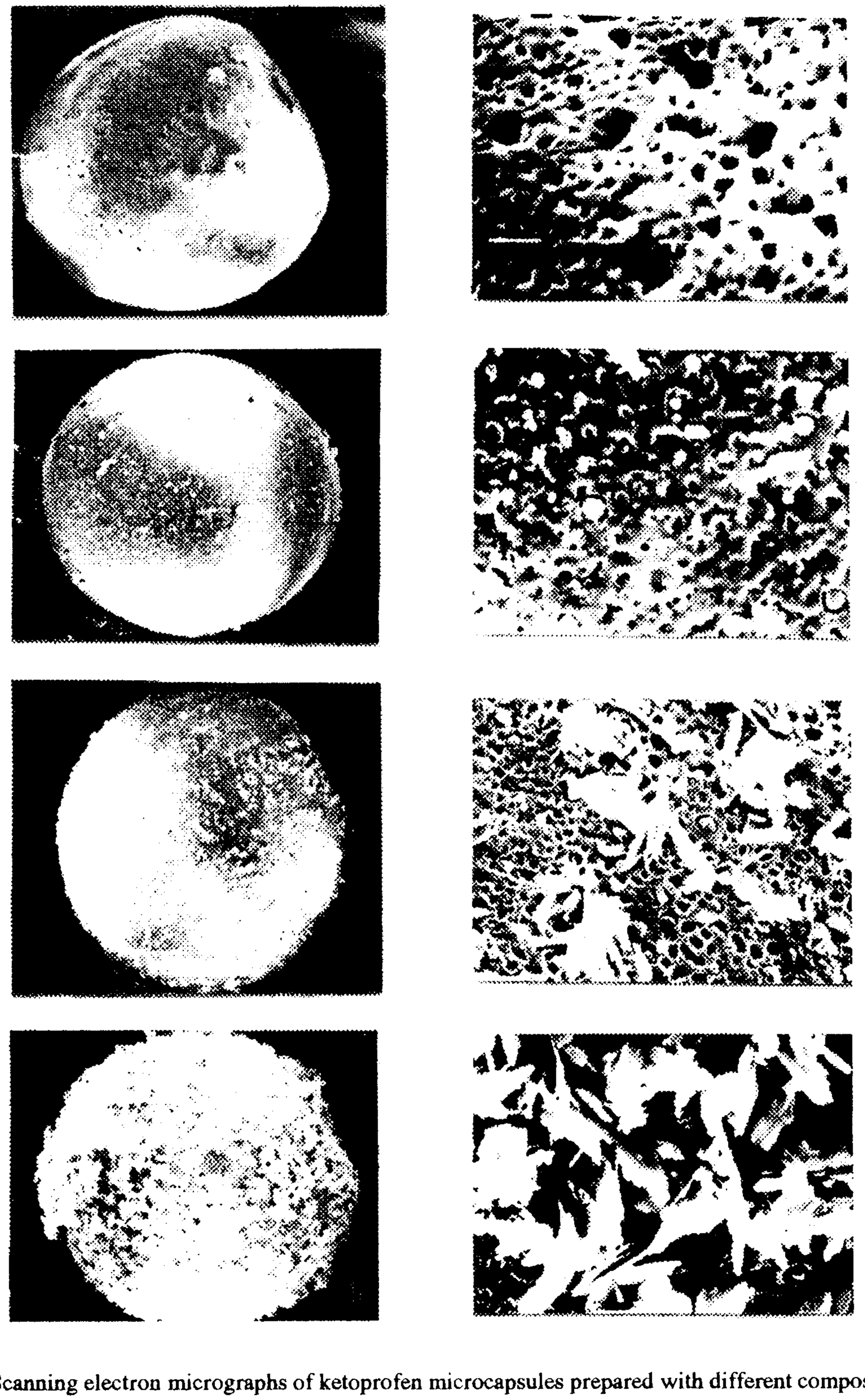


Plate 1: Scanning electron micrographs of ketoprofen microcapsules prepared with different composition of wall materials:
(a) CAB (100%) (b) CAB:PS (92.5:7.5(%))
(c) CAB:PS (85:15(%)) (d) CAB:PS (75:25(%))
- Core/Coar ratio: 1:2.

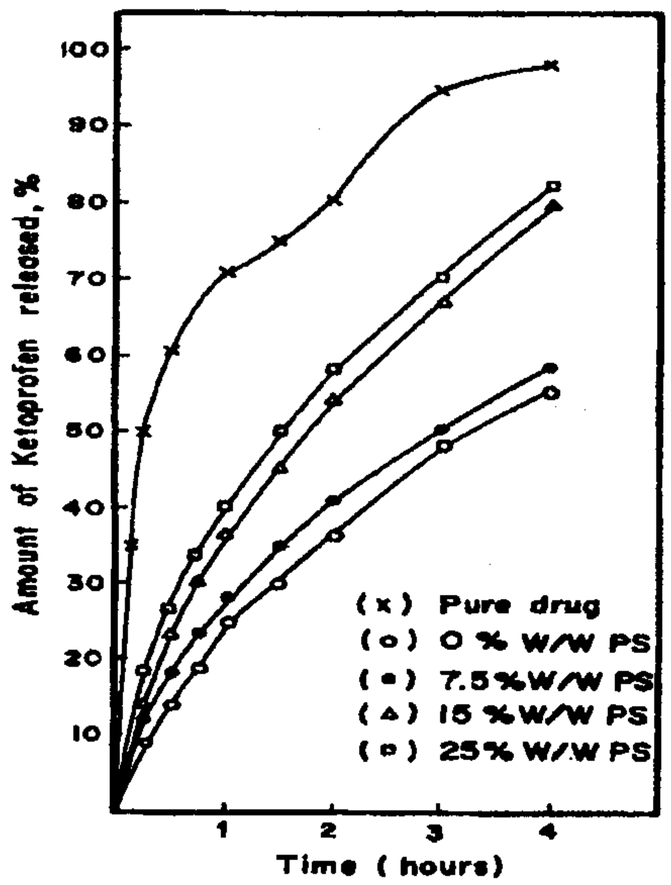


Fig. 3: In-vitro release of ketoprofen from CAB-PS microcapsules prepared at different polystyrene concentrations (Core/Coat ratio 1:2, S.G.F. pH 1.2).

The effect of microcapsule size on the drug release rate was shown in (table 2) and (figures 2). It is obvious that the smaller the microcapsule, the more rapid the drug release rate due to the greater effective surface area.

The drug release rates were found to be higher in S.I.F (pH 7.4) than in S.G.F (pH 1.2) because of the acidic nature of the drug, being propionic acid derivative (table 2 and figures 2,3). Solubility of Ketoprofen in S.I.F and S.G.F at 37°C was determined to be 7.415 and 0.13315 mg/ml, respectively. The results obtained are consistent with those of El - Khodairy *et al.*[32] who prepared Eudragit RL/RS microcapsules containing Ketoprofen and found that the dissolution rate of Ketoprofen in 0.1 N hydrochloric acid was very low, but when the pH of the medium changed to pH 7.6 the release rate increased rapidly. However, Goto *et al.*[18] reported that the dissolution patterns of Ketoprofen from Eudragit E, L and S microcapsules were dependent on the pH of the dissolution medium. In Eudragit E microcapsules Ketoprofen was completely dissolved within 30 minutes after the start of dissolution test in acidic medium.

The effect of core/coat ratio viz: 1:2, 1:1 and 2:1 on the physical characteristics of CAB-PS microcapsules prepared using polystyrene at 7.5 percent w/w concentration is shown in (table 3). It appeared that increasing the core/coat ratio from 1:2 to 1:1 was

Table 3: Effect of core/coat ratio on characteristics of ketoprofen-loaded CAB-PS microcapsules.

Core/coat ratio	Fraction size (μm)	Average Size (μm)	d_g (μm)	σ_g	Yield (%)	Drug loading (%)		Encapsulation Efficiency (%)
						theoretical	actual	
1:2	355-500	427.5	309.02	1.57	85.15	30.37	15.37	50.61
	500-600	550					15.89	52.32
	600-710	655					17.25	56.80
1:1	355-500	427.5	376.00	1.42	68.63	46.63	20.76	44.52
	500-600	550					25.15	53.94
	600-710	655					23.03	49.40
2:1	355-500	427.5	331.13	1.45	72.00	63.60	43.27	68.04
	500-600	550					46.85	73.66
	600-710	655					44.50	69.67

- Polystrene concentration: 7.5% W/W.
- d_g Geometric mean particle diameter, μm.
- σ_g Geometric standard deviation.

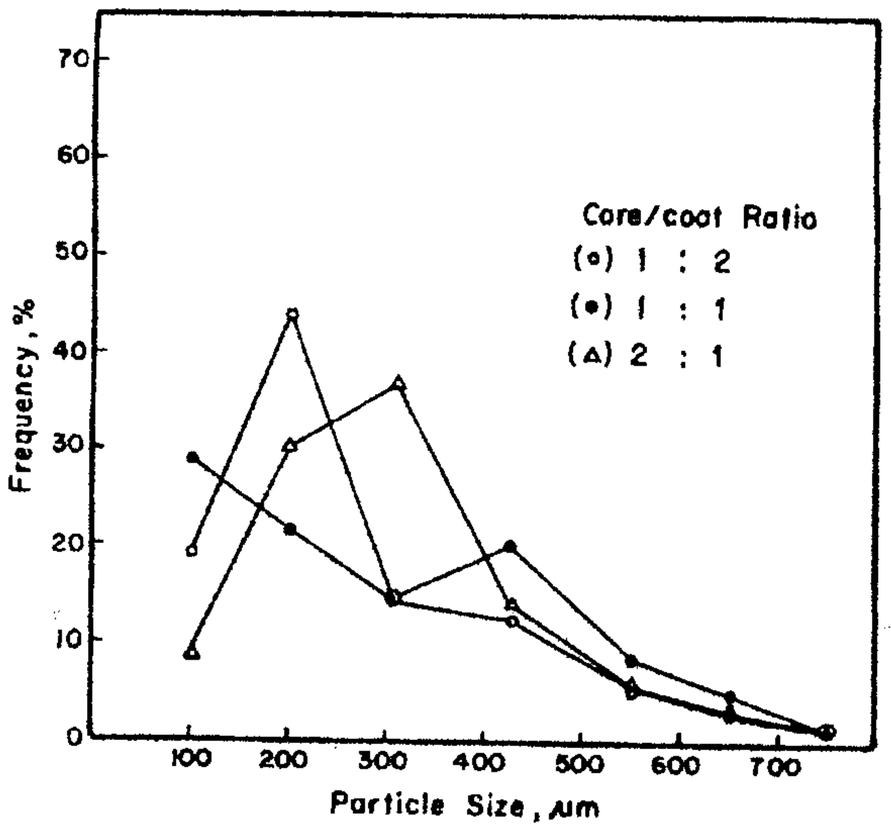


Fig. 4: Effect of core/coat ratio on particle size distribution of CAB-PS microcapsules containing ketoprofen (CAB-PS; 92.5:7.5 (%)).

accompanied by an increase in drug loading and geometric mean particle diameter and a decrease in microcapsule yield and geometric standard deviation and encapsulation efficiencies of most of fraction size ranges. The decrease in encapsulation efficiencies may be attributed to drug loss during encapsulation process. Alex and Bodmeier[5] illustrated that osmotic pressure difference increased with increasing drug loading, possibly resulting in a more intimate mixing of the internal and external aqueous phase and hence a higher drug loss.

A core/coat ratio of 2:1 was found to elevate greatly the encapsulation efficiencies. Thus a maximum drug loading and encapsulation efficiency close to 46.85 and 73.66 respectively were achieved (table 3). This can be explained on the basis that a constant drug fraction was expected to be lost to the aqueous phases and therefore, on a relative scale, a smaller loss of drug with increasing theoretical loading resulting in a higher encapsulation efficiencies.

Figure 4 shows that increasing the core/coat ratio was accompanied by an increase in microcapsule size. A particle size distribution with more than 35 percent of microcapsules in the range of 250-350 μm was observed at 2:1 core/coat ratio.

The effect of core/coat ratio on the release patterns of Ketoprofen from CAB-PS microcapsules is shown in table 4 and figure 5. It is evident that increasing the core/coat ratio from 1:2 to 2:1 resulted in a great increase in the drug release rate (K1 X 10-1) from 2.88 to 11.0 respectively. mainly due to the increase in the drug loading and subsequent decrease in wall thickness of microcapsules. This is clearly illustrated by the surface topography of the microcapsules which indicated that microcapsules of 1:1 and 2:1 core/coat ratio are spherically shaped particles but have wrinkled and very rough walls (plate 2 a, b x 100) in comparison with those of 1:2 core/coat ratio (plate 1b, x 100). A closer view of the walls is shown at higher magnification (plate 2a, b. x 1000). The micrographs revealed the appearance of a significant amount of drug crystals within ruptured and loosely bound walls which leads to rapid drug release. The results obtained are in agreement with those of Goto *et al.*[33].

To examine the build-up and permeability characteristics of the microcapsules membrane in more detail, drug transport experiments through CAB and CAB-PS cast membranes were done. The process variables such as polystyrene concentration in the polymer matrix, total polymers concentration and permeant concentration had a marked effect on the permeation of Ketoprofen through the polymeric films. The permeability constants (Pm) were easily changed by using a mixture of CAB and PS as the matrix. As shown in table 6, the Pm values increased from 0.1463 x 10-3 to 2.628 x 10-3 with increasing polystyrene concentration from 7.5 to 15 percent w/w. polystyrene may have permeabilizing features such as plasticizing properties which could increase the release rate abruptly at a critical porosity value. The Pm values were proportional to permeant concentration (table 7) and lowered greatly with increasing the total polymers concentration up to 5 percent (table 8).

Table 9 shows that increasing amount of Ketoprofen incorporated in CAB-PS films resulted in an increase in drug release rates.

Kinetics of drug release

Analysis of the release data of Ketoprofen microcapsules was carried out according to zero

Table 4: Kinetics assessment of release data from ketoprofen-loaded CAB-PS microcapsules prepared at different core/coat ratios (S.I.F.).

Core/ Coat ratio	Average Size of micro-capsules (μm)	Zero order		First order			Diffusion models						
							Planar matrix				Spherical matrix $3/2(1-(1-F)^{2/3}-F$ vss. t		
							Q vss $t^{1/2}$		log Q vss. log t				
		r	K_o ($mg.hr^{-1}$)	r	k_1x10^{-1} (hr^{-1})	$t_{0.5}$ (hr.)	r	K_H ($mg.hr^{-1/2}$)	r	slope	r	$K_{HL}x10^{-2}$ (hr^{-1})	$Dx10^{-2}$ ($cm^2.hr^{-1}$)
1:2	550	0.9533 (0.9804)	12.84 (12.05)	0.9778 (0.9959)	2.88 (1.972)	2.406 (3.514)	0.9888 (0.9994)	33.54 (31.27)	0.9943 (0.9980)	0.4290 (0.5784)	0.9993 (0.9992)	3.144 (1.962)	(1.476)
1:1	550	0.9985 (0.9735)	- (12.37)	0.9642 (0.9954)	4.286 (2.12)	1.6 (3.27)	0.9967 (0.9971)	31.04 (30.0)	0.9669 (0.9992)	0.2701 (3820)	0.9977 (0.9992)	3.02 (2.51)	(2.988)
2:1	550	0.9696 (0.9560)	19.67 (14.09)	0.9899 (0.9990)	11.0 (3.024)	0.630 (2.292)	0.9879 (0.9995)	34.85 (-)	0.9970 (0.9973)	0.2356 (0.610)	0.9972 (0.9986)	14.05 (3.040)	(6.742)

- Polystyrene Concentration: 7.5% W/W. - Data between parantheses indicate release in S.G.F.

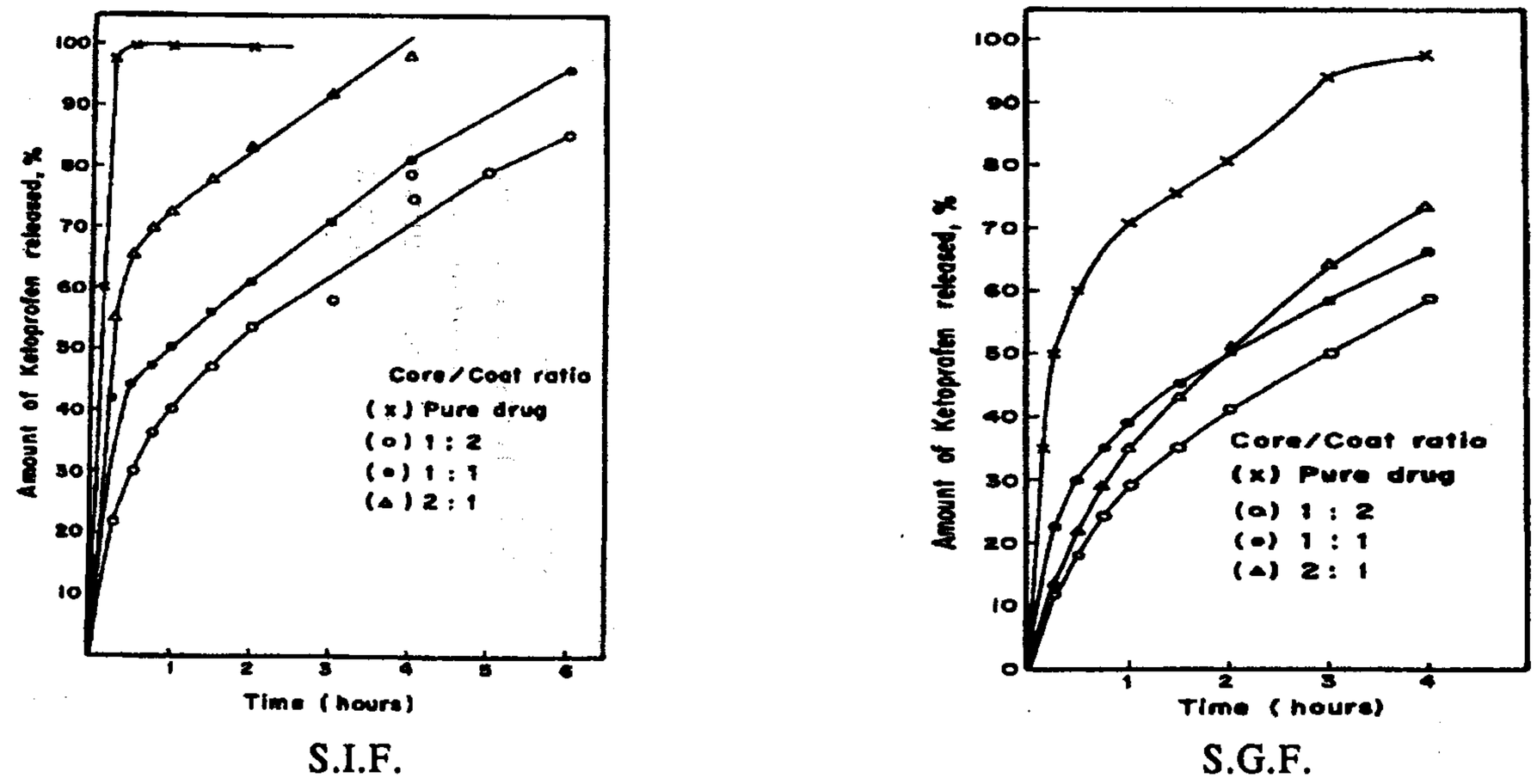


Fig. 5: In-vitro release of ketoprofen from CAB-PS microcapsules prepared at different core/coat ratios (CAB-PS; 92.5:7.5 (%)).

Table 5: Film preparation and composition selected for permeation studies.

Composition of film forming solusion (gm)		Polystyrene concentration % W/W	Total polymers concentration %W/V	Casting solvent (ml)
Cellulose acetate butyrate	Polystrene			
5.00	0.00	0.00	5.00	Methylene Chloride, 100
4.625	0.3750	7.500	5.00	Methylene Chloride, 100
4.250	0.7500	15.00	5.00	Methylene Chloride, 100

Table 6: Characteristics of ketoprofen premeability through CAB-PS films as a function of polystyrene concentration.

Polystyrene conc. % W/W	Correlation coefficient (r)	Penetration flux rate (Slope)	Permeability constant $P_m x10^{-3}(cm^2.hr^{-1})$	Diffusion coefficient $Dx10^{-3}(cm^2.hr^{-1})$	Lag time (h)	Film thickness (mm)
0.00	0.9988	0.62487	0.06086	1.8890	0.3417	0.100
7.50	0.9928	1.50000	0.14625	4.5394	0.00255	0.100
15.00	0.9843	13.49000	2.62800	81.5670	0.03895	0.200

- Total polymers concentration; 5% W/V and drug concentration of 0.1666 mg/ml.

Table 7: Characteristics of ketoprofen premeability through CAB-PS films as a function of drug concentration.

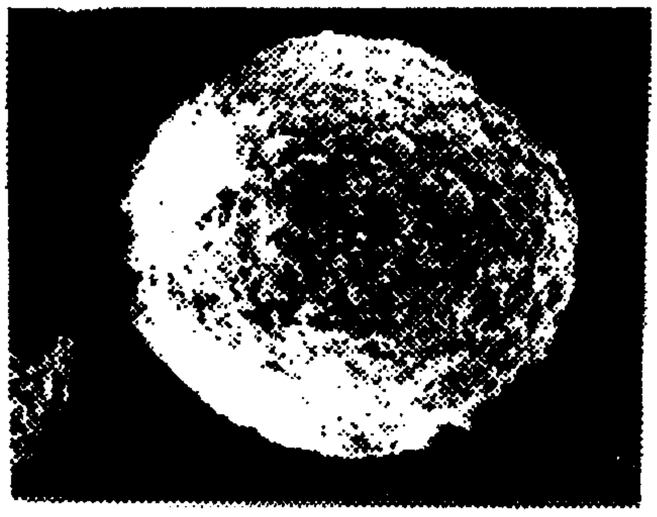
Drug conc. mg/ml %W/W	Correlation coefficient (r)	Penetration flux rate (Slope)	Permeability constant $P_m x10^{-3}(cm^2.hr^{-1})$	Diffusion coefficient $Dx10^{-3}(cm^2.hr^{-1})$	Lag time (h)	Film thickness (mm)
0.1666	0.9928	1.5000	0.14625	4.5394	0.00255	0.100
0.2666	0.9801	6.7850	0.41305	12.8200	0.38250	0.100
0.4000	0.9850	11.2800	0.45780	14.2100	0.35220	0.100

- Polystyrene concentration, 7.5% W/W.

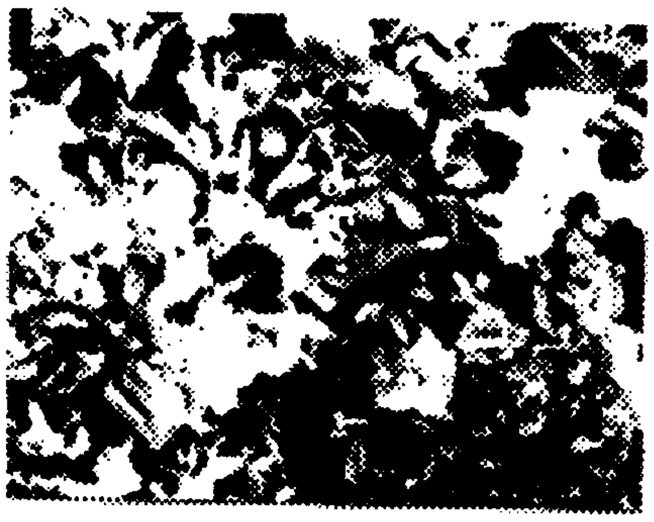
Table 8: Characteristics of ketoprofen premeability through CAB-PS films as a function of total polymers concentration.

Total polymers conc. %W/V	Correlation coefficient (r)	Penetration flux rate (Slope)	Permeability constant $P_m x10^{-3}(cm^2.hr^{-1})$	Diffusion coefficient $Dx10^{-3}(cm^2.hr^{-1})$	Lag time (h)	Film thickness (mm)
2.5	0.9989	1.4060	0.13690	4.2510	0.2557	0.100
5.0	0.9849	1.4760	0.14380	4.4620	0.4520	0.100
7.5	0.9888	0.1442	0.01404	0.4358	0.5463	0.100

- Polystyrene concentration, 7.5% W/W and drug concentration of 0.1666 mg/ml.



X 100



X 1000

Plate 2: Scanning electron micrographs of ketoprofen microcapsules prepared at core/coat ratio of (a) 1:1 and (b) 2:1.

- CAB-PS (92.5:7.5 (%)).

order kinetics, first-order kinetics[34], Higuchi model, a diffusion-controlled model for planar matrix[35] and Baker and Lonsdale model, a diffusion-controlled model for spherical matrix[36]. The correlation coefficients of the plots of the rate (dQ/dt) as a function of Q and 1/Q for first order kinetics and Higuchi diffusion model respectively were used for differentiation between the two mechanisms (table 10). The results revealed that Higuchi diffusion treatment predominates over first-order treatment.

Tables 2 and 4 show the kinetic assessment of release data from CAB microcapsules and CAB-PS composite microcapsules. The diffusion models were sufficiently linear and the differences between them were noted to be minimal. However it appeared that the release pattern of Ketoprofen from CAB microcapsules obeyed Higuchi model, while in almost all cases of CAB-PS microcapsules, the release data were found to follow Baker and Lonsdale model. The spherical matrix model has been applied successfully to chlorpromazine release from cellulose acetate butyrate-polycaprolactone composite microcapsules[27]. It has been observed from table 2 and 4 that the diffusion coefficients calculated from the spherical matrix model were obtained with S.G.F only due to the higher solubility of the drug in S.I.F which exceeded the initial drug loading of microcapsules[36]. It is quite interesting to note that Ketoprofen has been released from the medicated CAB-PS cast films by the spherical matrix model previously suggested for the release from CAB-PS composite microcapules (table 9).

A CAB-PS composite microcapsules formulation with high yield and drug loading and with optimum sustained release profile was prepared employing the modified w/o/w complex emulsion technique.

Table 9: Kinetics assessment of release data from CAB-PS films prepared at different drug concentrations.

Drug conc. mg/ml of polymer solution	Zero order		First order			Diffusion models							
						Planar matrix					Spherical matrix $3/2(1-(1-F)^{2/3}-F$ vss. t		
						Q vss $t^{1/2}$		log Q vss. log t					
	r	$K_o x10^{-2}$ ($mg/cm^2.hr^{-1}$)	r	$k_1 x10^{-2}$ (hr^{-1})	$t_{0.5}$ (hr.)	r	$K_H x10^{-2}$ ($mg/cm^2.hr^{-1/2}$)	r	slope	Lag t (hr)	r	$K_{SE} x10^{-5}$ (hr^{-1})	$Dx10^{-5}$ ($cm^2.hr^{-1}$)
1.6	0.8886	0.2406	0.8895	0.4715	146.96	0.9519	0.7753	0.9330	1.05200	0.4422	0.9601	2.568	0.2828
3.2	0.9542	0.8817	0.9529	0.8624	80.36	0.9884	2.0480	0.9879	0.74402	1.9180	0.9866	4.853	1.0680
4.8	0.9858	1.8090	0.9876	1.1900	58.22	0.9967	4.0990	0.9978	0.75060	2.2450	0.9982	8.868	2.9300

- Total polymers concentration: 5% W/V and polystyrene concentration of 7.5% W/W.

Table 10: Corrrelation coefficient analysis for differentiation between first-order kinetics and Higuchi diffusion model.

Polystyrene conc. % W/W	Core/coat ratio	Average size (μm)	Correlation coefficients	
			dQ/dt vss. Q	dQ/dt vss. 1/Q
0	1:2	427.5	0.8562	0.9884
		550	0.8629	0.9930
			(0.9471)	(0.9671)
		655	0.8691	0.9919
7.5	1:2	427.5	0.9544	0.9935
		550	0.8849	0.9931
			(0.9573)	(0.9807)
		655	0.9193	0.9925
15	1:2	427.5	0.9702	0.9951
		550	0.9462	0.9962
			(0.9468)	(0.9835)
		655	0.9218	0.9971
25	1:2	427.5	0.9355	0.9885
		550	0.9110	0.9885
			(0.9389)	(0.9946)
		655	0.8866	0.9913
7.5	1:1	427.5	-	-
		550	0.7145	0.8273
			(0.9222)	(0.9977)
		655	-	-
7.5	2:1	427.5	-	-
		550	0.9180	0.9720
			(0.9739)	(0.9554)
		655	-	-

- Data between parantheses indicate release in S.G.F.

The permeability of the microcapsule wall can be modified over a wide range by changing the CAB-PS ratio. Consequently, varieties of microcapsules with different dissolution patterns of Ketoprofen could be prepared.

A correlation was found to exist between the drug release pattern from microcapsule and its diffusion through films.

The suggested microcapsules provide a system in which the overall release rate is determined mainly by a diffusion - controlled process in which the dissolution process plays an important role.

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