Bull. Pharm. Sci., Assiut University, Vol. 24, Part 2, December 2001, pp. 115-134.

DEVELOPMENT AND EVALUATION OF VERAPAMIL RESINATES-LOADED CONTROLLED RELEASE MICROCAPSULES USING A BINARY POLYMER SYSTEM IN DRUG RELEASE RATE MODULATION

I. El-Gibaly and M. Fathy

Department of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut, Egypt

لقد تم إستخدام راتنجات التبادل الأيوني الموجبة (في صورة أيونات الصوديوم) لتحضير أنظمة ممتدة المفعول لعقار الفيراباميل (في صورة هيدروكلوريد). واعتمدت كفاءة تحميل العقار والتي قدرت بنسبة ١٩,١٧ إلى ٤٨,٨٦ في المائة على نوع الراتنج ونسبة العقار إلى الراتنج.

وقد أمكن ترتيب هذه الأنظمة على حسب قدرتها على إنطلاق العقار في المحلول المشابه للوسط المعدي والمحلول المشابه للوسط المعوي كما يلي: راتنج (MB-1) > راتنج IRP-69(Na+) ≥ راتنج IR-120(Na+) > راتنج الدواكس 50-W(Na+).

وقد تمت حوصلت راتنجات الـ IR-120(Na+) (المحضرة بنسبة ١ إلى ١ للعقار والراتنج) بغرض زيادة تأخير إنطلاق العقار منها بإستخدام طريقة معدلة (طريقة التبخير والإستخلاص من المستحلب) مع مواد تغليف مختلفة وتشمل إيثيل السليلوز وإيثالات خلات السليلوز وبيوتيرات خلات السليلوز وكذلك أنظمة ثنائية مختلفة من بيوتيرات خلات السليلوز مع عديد الإستيرين. وتمت دراسة تأثير نوع البوليمر وتركيز عديد الإستيرين ونسبة الراتنج إلى الغلاف على حجم وإنتاج الحويصلات وخواص إنطلاق العقار منها وكذلك على الخواص السطحية للحويصلات. وأوضحت النتائج إن إستخدام بيوتيرات خلات السليلوز مع عديد الإستيرين بنسبة ٧٠٪ من الأول إلى ٣٠٪ من الثاني قد حسنت إنتاج الحويصلات وقللت حجمها وعدلت إنطلاق العقار منها. ومن ناحية أخرى قد أدت زيادة نسبة الراتنج إلى الغلاف (المحتوى الدوائي النظري للحويصلات) إلى زيادة كفاءة الحوصلة وتقليل إنطلاق العقار.

وقد أوضحت نتائج دراسة النظام الحركي (الكينيتي) لإنطلاق العقار من الحويصلات الدقيقة أن نظام إنطلاق العقار من حويصلات بيوتيرات خلات السليلوز الخالصة أو المحتوية على عديد الإستيرين بنسبة ٧,٥ في المائة كان بالإنتشار الحركي التابع لقانون فيكس (نموذج أليه الإنتشار المضبوط)، في حين أوضحت قيم العوامل الأسية المحسوبة (قيم n) أن نظام إنطلاق العقار من حويصلات بيوتيرات خلات السليلوز المحتوية على عديد الإستيرين بنسبة ٣٠ في المائة كان بالإنتشار الحركي الغير تابع لقانون فيكس مؤكدا فاعلية آلية نظام الإنتشار والإرتشاف المضبوط.

وقد أوضحت هذه الدراسة أن الحويصلات المحضرة من بيوتيرات خلات السليلوز مع عديد الإستيرين قد أطالت فترة إنطلاق العقار إلى ٢٤ ساعة بالمقارنة مع أقراص الفيراباميل التجارية الممتدة المفعول (Isoptin (SR)).

The application of polystyrene-divinylbenzene sulfonic acid-based ion exchange resins as a carrier system for the sustained delivery of verapamil hydrochloride was primarily evaluated. A large degree of variation in the loading efficiencies (drug loaded: 19.17-48.86%), was observed between the different drug-resin complexes depending on resin type and drug/resin ratio. Upon comparing different carrier resins at drug/resin ratio of 1:1, verapamil release in either 0.1 N HCl or phosphate buffer (pH 7.4) was in the order of Amberlite MB-1 > Amberlite IRP-69 (Na^+) ≥ Amberlite IR-120 (Na^+) > Dowex-50 W (Na^+). For further retardation of the drug release rate, microencapsulation of the strongly acidic cation exchange resin (Amerlite IR-120 (Na^+) loaded with verapamil hydrochloride (drug/resin ratio of 1:1, resinate drug content: 48.86%, core/coat ratio of 1:2) was carried out by means of a modified

Received in 1/1/2001 & Accepted in 21/2/2001

emulsion-solvent evaporation / extraction technique (ESE/E) using different coating polymers, namely ethylcellulose (EC), cellulose acetate phthalate (CAP), cellulose acetate butyrate (CAB) as well as CAB/polystyrene (PS) binary polymer systems. The effect of polymer type, polystyrene concentration and core/coat ratio on the yield, size distribution as well as release characteristics and surface topography of the microcapsules were investigated. The results obtained revealed that polystyrene utilization as a complementary wall material at a particular composition of 70:30 (%) of CAB to PS was found to improve greatly the microcapsule yield, reduce the average microcapsule size and modulate the in-vitro release of the entrapped drug. On the other hand, the entrapment efficiencies increased and the release rate decreased with increasing microcapsule size and/or theoretical drug loading of CAB/PS (30%) - microcapsules. Kinetic assessment of the release data using different mathematical models showed that the drug release from CAB or CAB/PS (7.5%)-microcapsules (core/coat ratio of 1:2) was found to be best explained by a Fickian-diffusion kinetics (a diffusion-controlled model for a planar matrix), whereas the calculated exponential release exponents (n values) of the empirical equation ($M_t/M_\infty = Kt^n$) indicated that the release behaviour of CAB/PS (30%) - microcapsules was a non-Fickian-diffusion kinetics, confirming that a diffusion / chain relaxation-controlled release mechanism was operative. Overall, this study demonstrated that the prepared CAB/PS microcapsules were capable of releasing their drug content gradually for an extended period of time, irrespective of variations in the pH of the gastrointestinal tract and exhibited slower release rates as compared with the commercial sustained-release product (Isoptin(SR) tablets).

INTRODUCTION

Verapamil hydrochloride is a calcium channel blocker used as antianginal, antiarrhythmic and antihypertensive.[1] It is approximately 90% absorbed from the gastrointestinal tract. However, its pharmacokinetics after oral administration are characterized by extensive first-pass metabolism leading to a low oral bioavailability of about 20 to 27%, a relatively short elimination half-life of 2 to 8 hours and interindividual variation in plasma concentrations.[1] In addition, verapamil hydrochloride is a salt of weak base with pH dependent solubility in the physiological pH range which will affect the release of the drug and its bioavailability.[2,3] In light of these problems, the pharmacokinetic properties of this drug warrant the development of controlled release formulations for use in the treatment of hypertension.

As the preparation of a sustained release dosage form of a freely soluble drug is almost a challenge, many formulation studies for controlling verapamil hydrochloride release have been reported. Thus, the drug has been formulated as modified-release matrix tablets press-coated with chiral excipients,[4] floating sustained-release capsules containing a mixture of hydroxypropyl cellulose (HPC) and effervescent,[5] single unit slow-action matrix tablets coated with ethylcellulose / hydroxypropyl methylcellulose film,[6] pH-independent release hydrophilic tablets containing a matrix of sodium alginate and hydroxypropyl methylcellulose[7] and "multiple unit" modified-release systems (film-coated swellable minimatrices).[8] In addition, bioadhesive matrix tablets as controlled release dosage form for verapamil hydrochloride have been prepared.[9] Also, extended release solid dispersions of verapamil hydrochloride in solid polymeric matrices, comprising ethylcellulose and Eudragit L100 were prepared.[10]

Occasionally, microencapsulation of soluble drugs results in microcapsules with unacceptably rapid release due to the likelihood of particles protruding through the microcapsule wall. Upon dissolution of the exposed portion of the drug particle, an opening is created through which the remaining drug can rapidly dissolve.[11]

In a recently published study, microspheres containing verapamil hydrochloride were prepared with three different cellulose esters

(cellulose acetate, cellulose acetate propionate and cellulose acetate butyrate) of approximately similar molecular weights using the emulsion-solvent evaporation method.[12]

Application of ion-exchange resins in drug delivery technology has received particular attention over the last two decades and is primarily dependent on physicochemical binding of drugs by the resins. Ion-exchange resins contain positively or negatively charged sites and are thus classified as either cationic or anionic exchangers. They offer a number of advantages over conventional coating techniques and function for some drugs as reliable controlled drug delivery systems.[13,14] In particular, studies evaluating the loading and release properties of drugs from strong cationic exchange resins (Amberlite and Dowex types) have been conducted in many reports.[15,15,16]

Coating the resin particles with a rate-controlling membrane may effectively solve the release problems and achieve the targeted bioavailability. With this aim, drug-resin complexes were microencapsulated with water-insoluble polymers, such as ethylcellulose,[17,18] cellulose acetate butyrate,[19,19] and polymethyl methacrylate.[20]

However, loading of verapamil hydrochloride on ion-exchange resins and microencapsulation of the prepared resinates have not been prepared before. Given this lack of data, the objectives of this study were primarily to prepare, for the first time, verapamil-resin complexes with sustained release profiles and then encapsulate the selected verapamil resinates within CAB/PS composite microcapsules using a modified emulsion-solvent evaporation method. Thus, the effect of several processing variables viz., type of encapsulating polymers, polystyrene concentration in the binary polymer system and core/coat ratio on microcapsule properties were investigated. The kinetics of drug release from microcapsules were also discussed using different mathematical models.

EXPERIMENTAL

Materials

The following reagents were purchased from suppliers, as indicated: verapamil hydrochloride (Sigma Chemical Co., St. Louis, MO 63178, USA); Dowex-50 W (Na^+), 100-200 mesh (Dow Chemical Co., Midland, MI); Amberlite IRP-69 (Na^+), Amberlite IR-120 (Na^+), Amberlite MB-1 (mixture of strong acid and base) (Röhm and Haas Company, Philadelphia, PA, USA); cellulose acetate butyrate (CAB 171-15S, 29.5% w/w acetyl, 17% w/w butyryl and 1.5% w/w hydroxyl content; MW= 65000); cellulose acetate phthalate (CAP) (Eastman Chemical Co., Kingsport, TN, USA); polystyrene (PS) (Polyscience Inc., Worthington, PA); ethylcellulose (EC) (BDH Chemicals Ltd., Poole, England); polyethylene glycol 4000 (Fluka AG, CH-9470 Buchs, Switzerland); sorbitan trioleate (Span 85) (ICI Surfactants, Cleveland, UK); acetone, n-hexane and liquid paraffin (J.T. Baker, Phillipsburg, NJ) and magnesium stearate (Fisher Scientific, Atlanta, GA). All other chemicals were of reagent grade and were used as received.

Methods

Purification of the ion-exchange resins

The ground resin particles were purified prior to drug binding and microencapsulation by successively rinsing about 20 g of wet resin with 2x300 ml portions of deionized water, 2x300 ml of 95% ethanol, 2x300 ml of 50% ethanol then 2x300 ml of deionized water. Each stage of treatment lasted 2 hr. under magnetic stirring. The resin was then activated by recycling the ion exchanger twice between the H^+ and the Na^+ form, with 300 ml of 2 M NaOH and 300 ml of 2M HCl, and washing with deionized water after each treatment. Finally, the resin in the Na^+ form was recovered by vacuum filtration, washed thoroughly with deionized water until the supernatant was neutral and then dried to constant weight at 50°.

Preparation of the drug-resin complex

Different complexes of 0.5:1, 0.75:1, 1:1 and 2:1 drug/resin ratios were prepared by a batch process in which an accurately weighed amount of the resin (300 mg) was suspended in the charging solution (solution of verapamil hydrochloride in deionized water), and the system was stirred using a magnetic stirrer (J.P.

Slecta, S.A., Spain) at room temperature for 24 hr. The complex was separated from the supernatant by filtration, washed with deionized water to remove any unreacted drug and counter ions, dried to constant weight and placed in a dessicator. To determine the actual loading capacity, the amount of free drug in the filtrate was assayed spectrophotometrically (Shimadzu double-beam spectrophotometer 150-02, Japan) at 278 nm.[21] The amount of drug bound to the resin was calculated from the difference between the initial and the remaining amount of drug in the filtrate.

Preparation of microcapsules

A variation of the technique used by Sprockel and Price[20] was employed to encapsulate the verapamil-loaded resins (Amberlite IR-120 (Na^+) at a drug/resin ratio of 1:1) by an emulsion-solvent evaporation / extraction (ESE/E) method, according to the following basic procedures: a sufficient amount of each of the following polymers: CAB (10% w/v), EC (10% w/v), CAP (12.5% w/v) was dissolved separately in acetone. Polyethylene glycol 4000 at 5% w/w concentration was added as a plasticizer. The complex particles were dispersed in 10 ml of the polymer solution (internal phase) at a core/coat ratio of 1:2, followed by emulsification of this phase in 100 ml of liquid paraffin containing 1.0% w/v sorbitan trioleate and 0.5% w/v magnesium stearate. The resulting emulsion was maintained at 25° and agitated at 500 r.p.m with a propeller stirrer (Wheaton Instruments, North Tenth Street, Millville, N.J, USA). After emulsification for 1 hr., 25 ml of n-hexane (non-solvent) was added dropwise at a constant rate of 1 ml/min to extract acetone and precipitate the coat around the resin particles. Agitation was continued until the complete evaporation of acetone was accomplished (2 hr.). The microcapsules were collected by filtration, washed with n-hexane and allowed to dry at 37° in an incubator for 24 hr.

In another set of experiments, CAB/PS composite microcapsules were prepared by a modification of the emulsion-solvent evaporation / extraction (ESE/E) method as follows: CAB was dissolved in acetone to form a 10% w/v solution. Prior to microencapsulation, the appropriate quantity of polystyrene (PS) solution (10% w/v in methylene chloride) was added to CAB solution and mixed thoroughly with gentle agitation by a magnetic stirrer to form binary polymer system solutions having various PS concentrations. The required amount of the drug-resin complex was uniformly suspended in the corresponding polymer solution and the rest of the encapsulation process was performed as described for ESE/E method.

The microcapsules were sized through standard sieves (IPX) and they ranged from 90-710 μm. The fraction of microcapsules remaining on each sieve was collected for further study.

The effect of polystyrene concentration [7.5 to 30% w/w (based on total polymers weight) at a core/coat ratio of 1:2] and core/coat ratios of 1:1 and 2:1 (at 30% w/w polystyrene) on the yield, particle size, drug loading, surface morphology and release characteristics of the microcapsules were investigated.

Determination of drug loading

Twenty five milligrams of the loaded resins or 100 mg of verapamil resinates-loaded microcapsules were accurately weighed and comminuted in a clean mortar, then pulverized by the aid of a small amount of 0.1 N HCl. The pulverized resin particles or microcapsules were transferred into a 100 ml volumetric flask and completed with 0.1 N HCl to the appropriate volume. An aliquot was withdrawn, filtered and suitably diluted and assayed spectrophotometrically at 278 nm using the same medium as a blank. The drug content for every fraction size of the prepared microcapsules and the commercial product (Isoptin SR tablets) was also determined similarly.

In-vitro release studies

The USP rotating paddle dissolution apparatus (Model DT-06, Erweka F.R.G.) was used at 50 r.p.m. Fifty milligrams of the drug resinates complexes were accurately weighed

and added to 250 ml of the dissolution medium (0.1 N HCl or $Na_2HPO_4.2H_2O$ / $NaH_2PO_4.12H_2O$ buffer (pH's 5.2 and 7.4 at 0.154 M Na^+ ions) containing 0.02% w/v Tween 80) maintained at 37°±0.2. Five milliliter samples were withdrawn at specified time intervals, and were replaced by equivalent volumes of dissolution medium kept at 37°±0.2. The drug released from the resin particles was determined spectrophotometrically at 278 nm for the acidic medium (0.1 N HCl) or isotonic phosphate buffers. All dissolution studies were run at least in duplicate for each experiment.

Release studies of verapamil from the drug resinates-loaded microcapsules (200 mg) were similarly performed. The dissolution behaviour of Isoptin (SR) tablets was conducted with 900 ml of the selected dissolution medium for comparison.

Differential scanning calorimetry (DSC)

Differential thermal analysis of the untreated drug, unloaded ion exchange resins, the prepared drug-resin complexes (drug/resin ratio of 1:1), drug free-CAB/PS microcapsules (PS concentration: 30% w/w), and verapamil resinate-loaded CAB/PS microcapsules (core (Amberlite IR-120): coat ratio of 1:1 and 2:1) was carried out with a computer-interfaced Shimadzu differential scanning calorimeter (DSC-50 model, Kyoto, Japan). Samples (5 mg) were scanned in aluminum pans over a temperature range of 0-250° at a scanning rate of 10°/min. All tests were run in duplicate and in a nitrogen atmosphere (40-50 ml/min.).

Scanning electron microscopy

The surface morphology of the untreated drug, loaded resins (Dowex-50 W (Na^+) and Amberlite IR-120 (Na^+)) and verapamil resinate-loaded CAB/PS microcapsules was examined using a JEOL scanning electron microscope (JSM-5200, Japan) as follows: Samples were coated with gold for 10 min at 60 milliampers (under a nitrogen atmosphere) by using SPI Sputter ™Coating Unit (SPI Supplies, Division of Structure Probe, Inc., West Chester, PA, USA). Scanning electron micrographs were taken at 15 kV.

RESULTS AND DISCUSSION

Characterization of the prepared verapamil hydrochloride-resin complexes

Table (1) shows the relation between the drug/resin ratio and the amount of drug that reacted with the resin. In most of cases, the percentage of drug reacted was increased by increasing the initial drug concentration as the protonated drug species competes with and displaces the sodium counter-ion from the sulfonic acid functional groups on the resin particle. It was also found that the strong cation exchange resin in the Na^+ form (Amberlite IR-120) exhibited the highest loading capacity (drug content: 30.03-48.86%, depending on drug/resin ratio), whereas Dowex-50 W (Na^+) showed the lowest amounts of drug loaded (19.17-29.25%). With higher drug/resin ratio (2:1), only a slight increase in the amount of drug content was observed (Table 1). Thus, the increase of drug concentration produced an increased counter-ion concentration through exchange, which, increased the competition between the ionized drug and the sodium ion for the remaining binding sites, leading to a reduced adsorption efficiency at higher drug/resin ratios.[30]

The release profiles of the drug-resin complexes (drug/resin ratio of 1:1) were conducted in 0.1 N HCl and in phosphate buffers (pH's: 5.2 and 7.4 at 0.154 M Na^+ ions) as shown in Figure 1. It is obvious that all resins showed delayed release profiles but to a variable extent. The maximum release rate was found to be in the following order: Amberlite MB-1 > Amberlite IRP-69 (Na^+) ≥ Amberlite IR-120 (Na^+) > Dowex-50 W (Na^+).

Figure 2 shows the influence of drug/resin ratio in resinates (Amberlite IR-120 and Dowex-50 W) on verapamil release in 0.1 N HCl. The obtained results revealed that the rate of drug release from the Dowex type resinates was directly related to the initial drug concentration and only 7.41-58.76% of verapamil (depending on drug/resin ratio) was released in the first 2 hr. These results point out that the uncoated Dowex-type resinates alone in a ratio of 0.5:1 or 0.75:1 can be considered as a sustained release drug delivery system for verapamil hydrochloride. In contrast, an inverse correlation

Table 1: Loading characteristics of verapamil hydrochloride on the tested ion-exchange resins as a function of its concentrations.

Resin type	Character	Form	Active group	Verapamil/ resin ratio	Loading capacity (mg/gm)	Estimated verapamil content (%)
Amberlite IRP-69	strong acid	Sodium	$-SO_3^-$	0.50:1	341.02	25.43
				0.75:1	598.21	37.89
				1:1	651.25	39.44
				2:1	708.81	41.48
Amberlite IR-120	strong acid	Sodium	$-SO_3$	0.50:1	429.18	30.03
				0.75:1	706.80	41.41
				1:1	955.42	48.86
				2:1	(–)	(–)
Amberlite MB-1	mix. of strong acid & base	Acid & base	$-SO_3^-$ $+N-(CH_3)_3$	0.50:1	424.50	29.80
				0.75:1	473.19	32.13
				1:1	462.42	31.62
				2:1	509.21	33.74
Dowex-50 W(X8)	strong acid	Sodium	$-SO_3^-$	0.50:1	237.19	19.17
				0.75:1	311.16	23.73
				1:1	413.43	29.25
				2:1	(–)	(–)

Notes: Equilibrium time: 24 hours, (–): not-determined.

Resin: 300 mg

existed between percentage of drug released and initial drug concentration for Amberlite IR-120 resinates, with only 25.0-78.87% of verapamil (depending on drug/resin ratio) was released within 2 hr.

Characterization of the prepared microcapsules containing verapamil-resin complexes

Microencapsulation

During initial trials, it was observed that CAB or EC microcapsules were free-flowing, non-aggregated and fairly spherical. Thus, the effect of polystyrene utilization as a complementary wall material on microcapsule characteristics was studied using a mixture of PS with CAB as a binary polymer system for the coating process.

Physicochemical characteristics of microcapsules containing verapamil-resin complexes

Table 2 depicts the effects of using a binary polymer system (CAB/PS) on the microcapsule properties. It is evident that addition of polystyrene at concentrations of 7.5, 15 and 30% w/w to the polymer matrix improved greatly the yield of microcapsules (yield: 81.00, 83.00 and 91.39-95.32%, respectively).

The effect of polymer type and core/coat ratio on microcapsule yield and drug loading of microcapsules containing verapamil-loaded resins are shown in Table 2. The use of CAP as the coating polymer was found to reduce the microcapsule yield by about 12.62% as compared with CAB alone or EC.

Figure 3 shows the typical particle size distribution of CAP, EC, CAB and CAB/PS

Table 2: Characteristics of verapamil resinates-loaded microcapsules

Polymer type	Polystyrene concentration % w/w	Core/coat ratio	Fraction size (μm)	Average size (μm)	Yield (%)	Drug loading %		Entrapment efficiency (%)	Amount of drug released, % (after 24 h)
						Theoretical	Actual		
CAP	0·0	1:2	150-250	200	68.12	16.33	10.21	62.54	–
EC	0.0	1:2	150-250	200	78.26	16.33	9.97	61.07	-
CAB	0.0	1:2	150-250	200	77.65	16.33	9.80	60.04	–
CAB/PS	7.5	1:2	150-250	200	81.00	16.33	9.97	61.07	–
CAB/PS	15	1:2	150-250	200	83.00	16.33	9.69	59.36	-
CAB/PS	30	1:2	150-250	200	94.54	16.33	9.20	56.36	72.08
CAB/PS	30	1:1	150-250	200.0	95.32	24.50	14 06	57.39	92.24
			250-355	302.5			14.82	60.52	79.80
			355-500	427.5			17.18	70.13	54.88
CAB/PS	30	2:1	150-250	200.0	91.39	32 67	19.57	59.91	68.89
			250-355	302.5			23.13	70,81	50.88
			355-500	427.5			24.28	74.33	44.67

Notes: Resin: Amberlite IR-120 (Na^+); drug/resin ratio· 1.1, (–). not-determined.

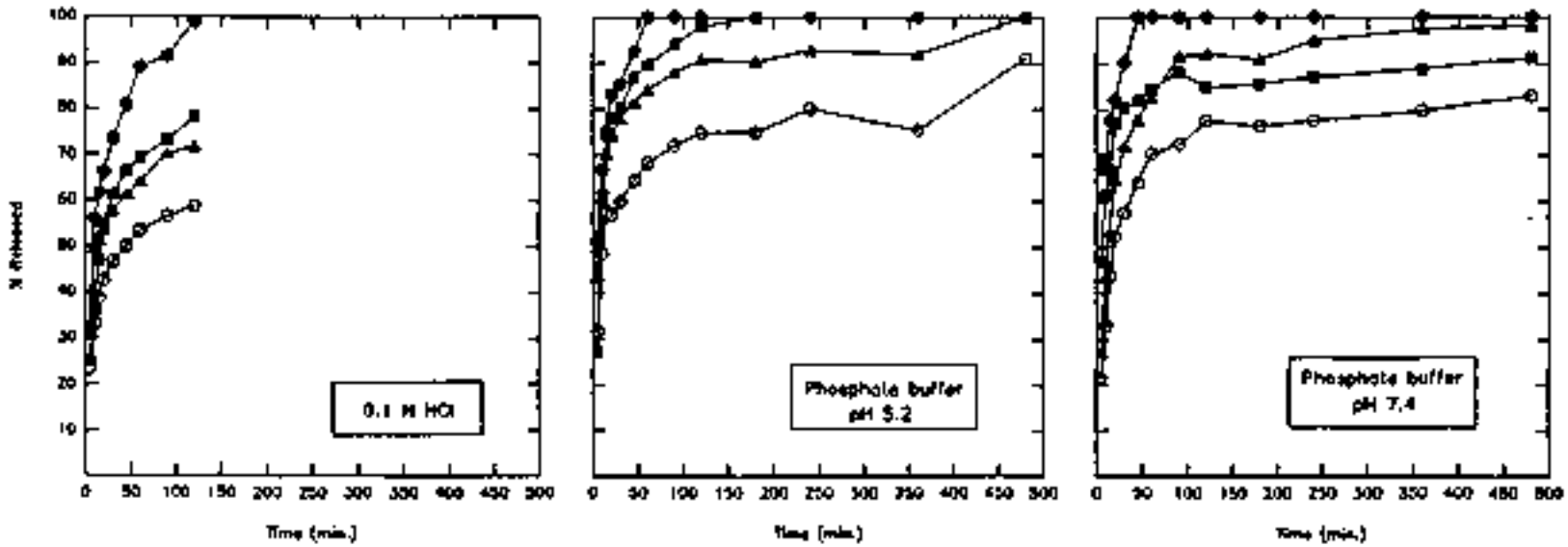

Fig. 1: *In-vitro* release of verapamil hydrochloride from its resinates prepared at a drug/resin ratio of 1:1. (■) Amberlite MB-1, (▲) Amberlite IRP-69, (●) Amberlite IR-120, (○) Dowex-50W.

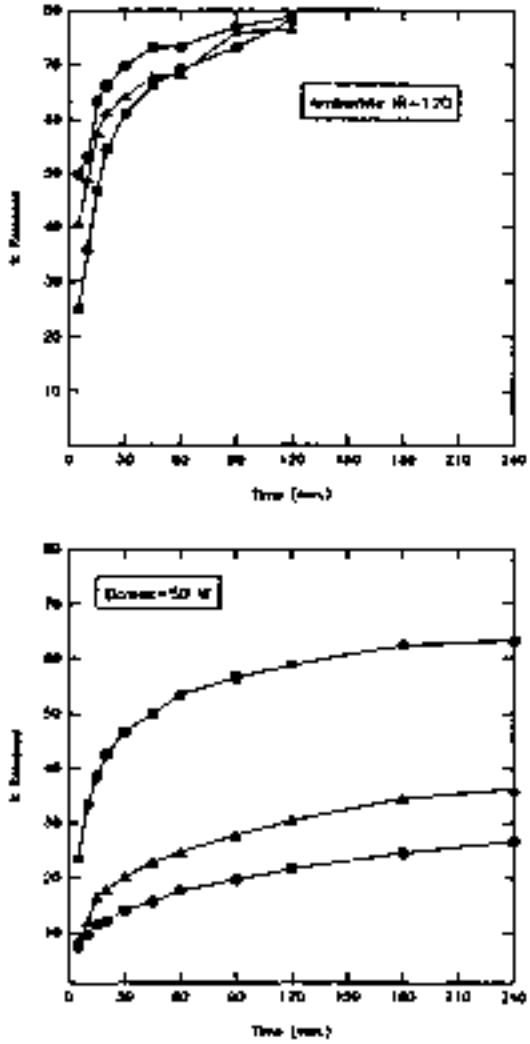

Fig. 2: Effect of drug/resin ratio on release of verapamil hydrochloride from its resinates in 0.1 N HCl: (■) 0.5:1, (▲) 0.75:1, (●) 1:1.

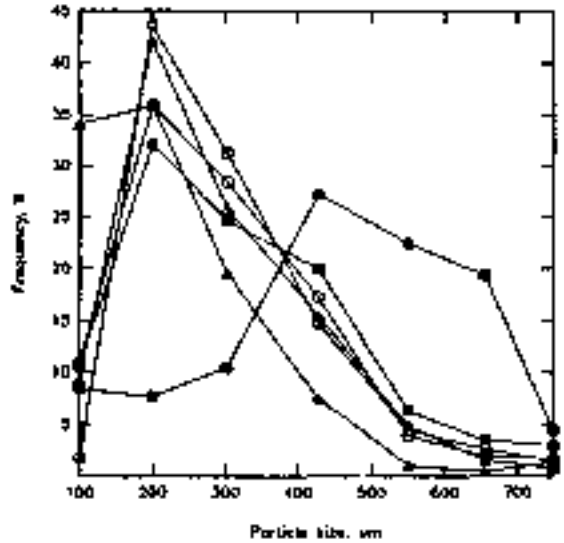

Fig. 3: Effect of coating polymer type on particle size distribution of verapamil resinates-loaded microcapsules. (resin : Amberlite IR-120 (Na^+), core/coat ratio: 1:2). (■) CAP, (▲) EC, (●) CAB, (○) CAB/PS (7.5%), (△) CAB/PS (15%), (□) CAB/PS (30%).

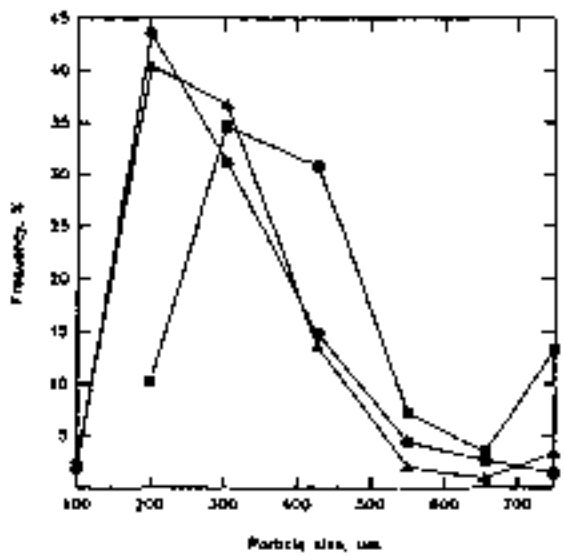

Fig. 4: Effect of core/coat ratio on particle size distribution of CAB/PS microcapsules containing verapamil resinates. (resin : Amberlite IR-120 (Na^+), PS concentration: 30% w/w). (■) 1:2, (▲) 1:1, (●) 2:1.

microcapsules prepared at a drug/resin ratio of 1:2. Obviously, microencapsulation using CAP as the coating polymer yielded the highest percent of microcapsules (41.79%) in the size range of 500-710 μm, whereas EC produced the highest percent (34.16%) of microcapsules smaller than 150 μm.

The utilization of CAB/PS as binary polymer systems resulted in reducing the mean size of coated complexes to a higher degree than CAB alone. Thus, the higher concentration of PS (30% w/w) was noted to produce a narrower particle size distribution with more than 74% of microcapsules in the range of 150-355 μm. The results obtained can be explained on the basis that the fluidity of the polymer solution can be easily adjusted by use of mixtures of CAB and PS and thus provides a practical mean to control the mean microcapsule size.[22] In addition, methylene chloride in which PS was dissolved, is miscible with both CAB solvent (acetone), liquid paraffin and n-hexane, and this facilitates partitioning of polymer solvents into and diffusion through the external phase. An effect which might influence the deposition of the particulate film (CAB/PS) around the complex and make coalescence more difficult, perhaps by preventing close contact between the droplets. The reduction in microcapsule size with increasing PS concentration and amount of methylene chloride supports these suggestions. The results are consistent with those of Iso *et al.*[23] who studied the microencapsulation of lipase by a w/o/w complex-emulsion technique using mixtures of PS and styrene-butadiene rubber as wall material and found that the average diameter of microcapsules becomes smaller as the content of PS in the wall increases.

When related factors such as emulsification stirring speed, polystyrene concentration, and surfactant concentration were kept constant, an increase in the drug loading elicited a change in microcapsule particle size distributions. As shown in Figure 4, an increase in the drug loading from 16.33 to 32.67% w/w resulted in larger microcapsules. This effect can be attributed to the corresponding increase in viscosity of resinate-polymer dispersion comprising the internal phase of the emulsion. Therefore, the viscosity increase within the internal phase results in the generation of a coarser emulsion with larger droplets, leading eventually to the formation of larger microcapsules.[22]

Differential thermal analysis of empty CAB/PS microcapsules (PS concentration: 30% w/w), verapamil-resin complexes and verapamil resinates-loaded CAB/PS (30%)-microcapsules was carried out to characterize the nature of the drug encapsulated in the microcapsules (Figure 5). In the case of the melting phase transition of the drug-resin complexes (drug/resin ratio of 1:1), the maxima of the peak of drug-resin complexes were broader and shifted to lower temperatures of approximately 85.8 to 93.60° than those of the drug melting point (a sharp endotherm at 143.6°C) and resins alone (broad endotherms at 96.3 to 110.6°) (Figure 5,a-i). This may be attributed to the presence of the drug in the complex form as a solid solution state.[24,25] However, the analytical method revealed no thermal events during the examination of empty microcapsules, whereas broad endotherms were observed at 82.1° and 94.1° for verapamil resinates (Amberlite IR-120)-loaded microcapsules of 1:1 and 2:1 core/coat ratios, respectively (Figure 5,j-l). These results can be attributed to the presence of a considerable portion of the drug in the microcapsules in a resinate form.

Drug release from microcapsules containing verapamil-resin complexes

Figure 6 shows the effect of polymer type employed in the microencapsulation on drug release from resinates (Amberlite IR-120)-loaded microcapsules (200 μm average diameter) with about 9.81% w/w drug loading. The release rate studies in 0.1 N HCl and in phosphate buffer (pH 7.4) demonstrated that drug release was the fastest from microcapsules prepared with CAP (12.5% w/v), which exhibited a substantial burst effect followed by complete dissolution and drug release within the first hour in phosphate buffer (pH 7.4). This contrasted to approximately 8%

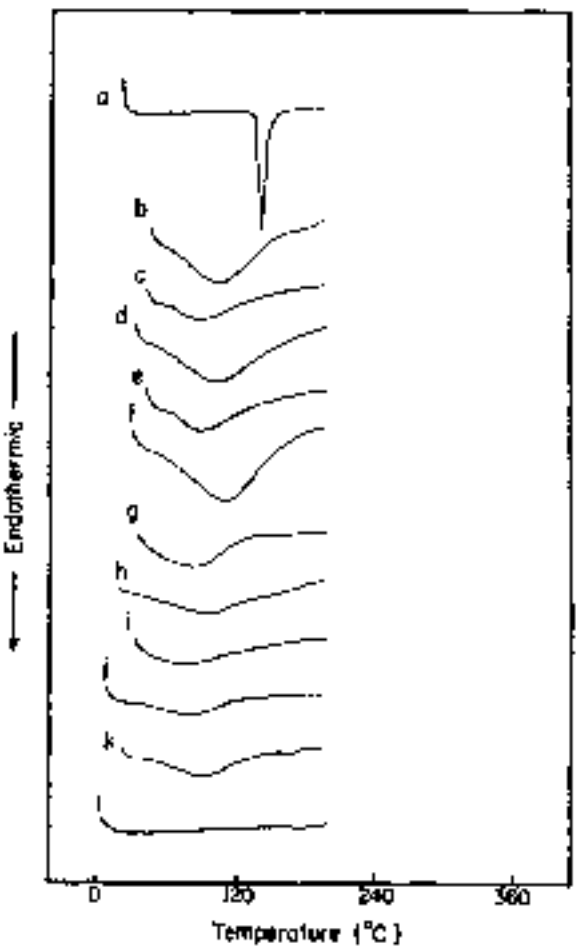

Fig. 5: DSC thermograms of (a) verapamil hydrochloride alone; (b,c) Amberlite MB-1 (Na^+) alone and its resinates, respectively; (d,e) Amberlite IRP-69 (Na^+) alone and its resinates, respectively; (f,g) Amberlite IR-120 (Na^+) alone and its resinates, respectively; (h,i) Dowex-50W (Na^+) alone and its resinates, respectively; (j,k) verapamil resinates-loaded CAB/PS (30%)-microcapsules prepared at core/coat ratios of 1:1 and 2:1 respectively (resin:Amberlite IR-120 (Na^+)); (l) empty CAB/PS (30%)-microcapsules.

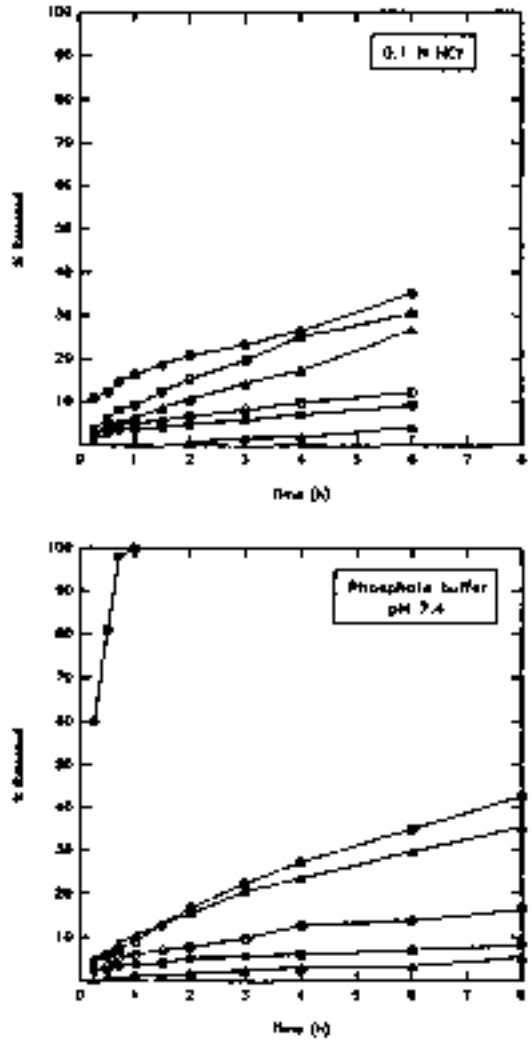

Fig. 6: Effect of coating polymer type on drug release from verapamil resinates-loaded microcapsules prepared at core/coat ratio of 1:2 (resin : Amberlite IR-120 (Na^+), microcapsules fraction size: 150-250 μm). (●) CAP, (▲) EC, (■) CAB, (○) CAB/PS (7.5%), (△) CAB/PS (15%), (□) CAB/PS (30%).

release from CAB microcapsules in 8 hr. The divergence in release profiles illustrates performance differences between cellulose ester polymers (CAP, CAB) whereby CAP as an enteric coating polymer dissolves rapidly in alkaline pH media and CAB has butyryl groups that have been postulated to increase polymer hydrophobicity, depending mainly on the type and extent of substitution. Bhardwaj *et al.*[12] reported that similar trends may be operative in determining verapamil hydrochloride (unloaded on resin) release from cellulose ester microspheres. This has been experimentally confirmed via water-vapour transmission rate studies conducted on cast films of CA, CAP and CAB[28] that established a rank-order relationship based on decreasing polymer hydrophobicity, which are summarized as CAB > CAP > CA. However, coating the resin particles with EC at a core/coat ratio of 1:2 resulted in undesired retardation in the drug release (4-5% within 8 hr), regardless of pH of the dissolution medium (Figure 6). This could be a result of the higher viscosity grade of EC used which might increase the coating thickness of the microcapsules.

With the objective of modulating drug release from the selected CAB-microcapsules, three formulations were prepared by combining CAB with a more permeable polymer, the polystyrene (PS) in the proportions: 92.5:7.5, 85:15 and 70:30% (CAB/PS). Obviously, the release patterns were easily changed by using a mixutre of CAB and PS (Figure 6). Thus an increase in PS content of the microcapsule matrix (core/coat ratio of 1:2) brought about an increase in the release rate (Table 3 and Figure 6).

The variations in the release properties of the microcapsules and their resinates can be verified by the scanning electron micrographs given in Figures 7 and 8. Verapamil resinates of the Dowex type are smooth, completely spherical and have a dense structure, whereas those of the Amberlite type that have higher release rates are irregular and having rough surfaces (Figure 7(B,C), X 100). Therefore, microencapsulation of the Amberlite-type resinates is prerequiste for achieving optimum controlled release profiles. Representative CAB microcapsules (core/coat ratio of 1:2) containing Amberlite IR-120 resinates are relatively spherical in shape and have highly wrinkled surfaces and shrivelled membranes (Figure 7(D) X 100, X 1000). Higher magnification (X 3,500) shows the sponge-like and less porous morphology of the outer wall and the absence of resin particles or smaller microcapsules (spherules) on the microcapsule surface. This correlated well with the decreased release rates of CAB microcapsules (Table 3 and Figure 6).

CAB/PS microcapsules (core/coat ratio of 1:2) appeared to have different surface morphologies. Using polystyrene at 15% w/w concentration of the coating polymer produced free-flowing microcapsules with a better spherical shape and characteristically smooth surface in contrast to CAB microcapsules (Figure 7(E), X 100). In addition, discrete micropores and numerous spherules as well as resin particles are clearly seen on the microcapsule surfaces (Figure 7(E), X 1000). Higher resolution (X 3,500) showed a more porous structure for such microcapsules with dispersed resin particles embeded in the microcapsule membranes. The higher concentration of PS (30% w/w) was used to produce an excellent yield of mostly spherical particles bearing a similar morphological features (Figure 8(A), X 100, X 1000). At higher magnifications (X 3,500, X 7,500), the micrographs evidenced the porous nature of microcapsules and the existence of numerous micropores within the microcapsule wall, thus explaining the relatively faster release rates of CAB/PS (30%)-microcapsules (Table 3 and Figure 6). 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.[27,28] On the other hand, the presence of distinct spherulitic structures and resin particles on CAB/PS microcapsules surface and their absence with CAB microcapsules supports an evidence for rapid polymer crystallization on using a rigid polymer (PS) and an oily miscible solvent (dichloromethane) for

Table 3: Kinetic assessment of release data from verapamil resinates-loaded (CAB/PS) microcapsules prepared at different core/coat ratios (phosphate buffer, pH 7.4).

Core/ coat ratio	Polystyrene conc. in the binary polymer system (% w/w)	Average size of micro-capsules (μm)	Zero-order		First-order			Diffusion models				Ritger-Peppas model M_t / M_∞ vs t^n	
								Planar matrix (Q vs. $\sqrt{t}$)		Spherical matrix $3/2\,(1-(1-F)^{0.66})$-F vs. t			
			r^2	K_o (%/h)	r^2	$K_1 \times 10^{-2}$ (h^{-1})	$t_{0.5}$ (h)	r^2	K_h(%/$\sqrt{h}$)	r^2	$K_{BL} \times 10^{-3}$	r^2	n
1:2	0.0	200	0.9622	0.6413	0.9646	0.684	–	0.9877	2.399	0.980	0.1347	0.9887	0.368
1:2	7.5	200	0.9613 (0.9885)	1.504 (1.405)	0.9652 (0.9911)	1.688 (1.55)	41.04 (44.71)	0.9803 (0.9914)	5.609 (5.196)	0.9787 (0.9934)	0.5938 (0.4293)	0.9805 (0.986)	0.4689 (0.513)
1:2	15	200	0.981 (0.9415)	3.624 (3.11)	0.9916 (0.9448)	4.686 (3.74)	14.79 (18.54)	0.9985 (0.970)	13.51 (11.65)	0.9942 (0.9359)	3.223 (2.346)	0.9984 (0.9890)	0.5904 (0.713)
1:2	30	200	0.982 (0.978)	4.247 (4.356)	0.996 (0.987)	6.40 (5.42)	10.83 (12.79)	0.999 (0.995)	18.548 (14.541)	0.9842 (0.9921)	6.039 (3.295)	0.996 (0.997)	0.725 (0.656)
1:1	30	200	0.976 (979)	5.836 (5.978)	0.9981 (0.9928)	11.50 (8.20)	6.035 (8.45)	0.998 (0.9981)	25.52 (19.98)	0.9834 (0.995)	13.959 (6.560)	0.998 (0.998)	0.692 (0.672)
1:1	30	302.5	0.979 (0.989)	4.865 (4.574)	0.998 (0.9957)	7.77 (5.69)	8.91 (12.16)	0.9980 (0.996)	21.263 (15.204)	0.9832 (9891)	7.933 (3.442)	0.9952 (0.995)	0.774 (0.700)
1:1	30	427.5	0.987 (0.976)	3.123 (2.658)	0.995 (0.981)	4.012 (3.00)	17.27 (23.11)	0.997 (0.990)	13.576 (8.869)	0.981 (0.990)	2.679 (1.097)	0.998 (0.994)	0.819 (0.696)
2:1	30	200	0.966 (0.968)	4.116 (4.537)	0.990 (0.980)	6.30 (5.70)	11.0 (12.15)	0.999 (0.996)	18.092 (15.247)	0.996 (0.997)	6.130 (3.383)	0.996 (0.992)	0.654 (0.719)
2:1	30	302.5	0.9861 (0.970)	3.172 (2.942)	0.996 (0.975)	4.25 (3.36)	16.33 (20.63)	0.9963 (0.9942)	13.805 (9.866)	0.979 (0.994)	3.176 (1.320)	0.9971 (0.991)	0.690 (0.697)
2:1	30	427.5	0.970 (0.914)	2.353 (2.475)	0.982 (0.933)	2.90 (2.72)	23.9 (25.43)	0.997 (0.971)	10.326 (8.544)	0.994 (0.962)	1.662 (0.906)	0.995 (0.971)	0.680 (0.767)

Notes: Q: amount of drug released after time t; K_{BL}: Baker and Lonsdall's model constant, $F = M_t/M_\infty$ where M_t and M_∞ are the amounts of drug released at t and at infinity ∞; n: diffusional release exponent; data between parantheses indicate release in 0.1 N HCl.

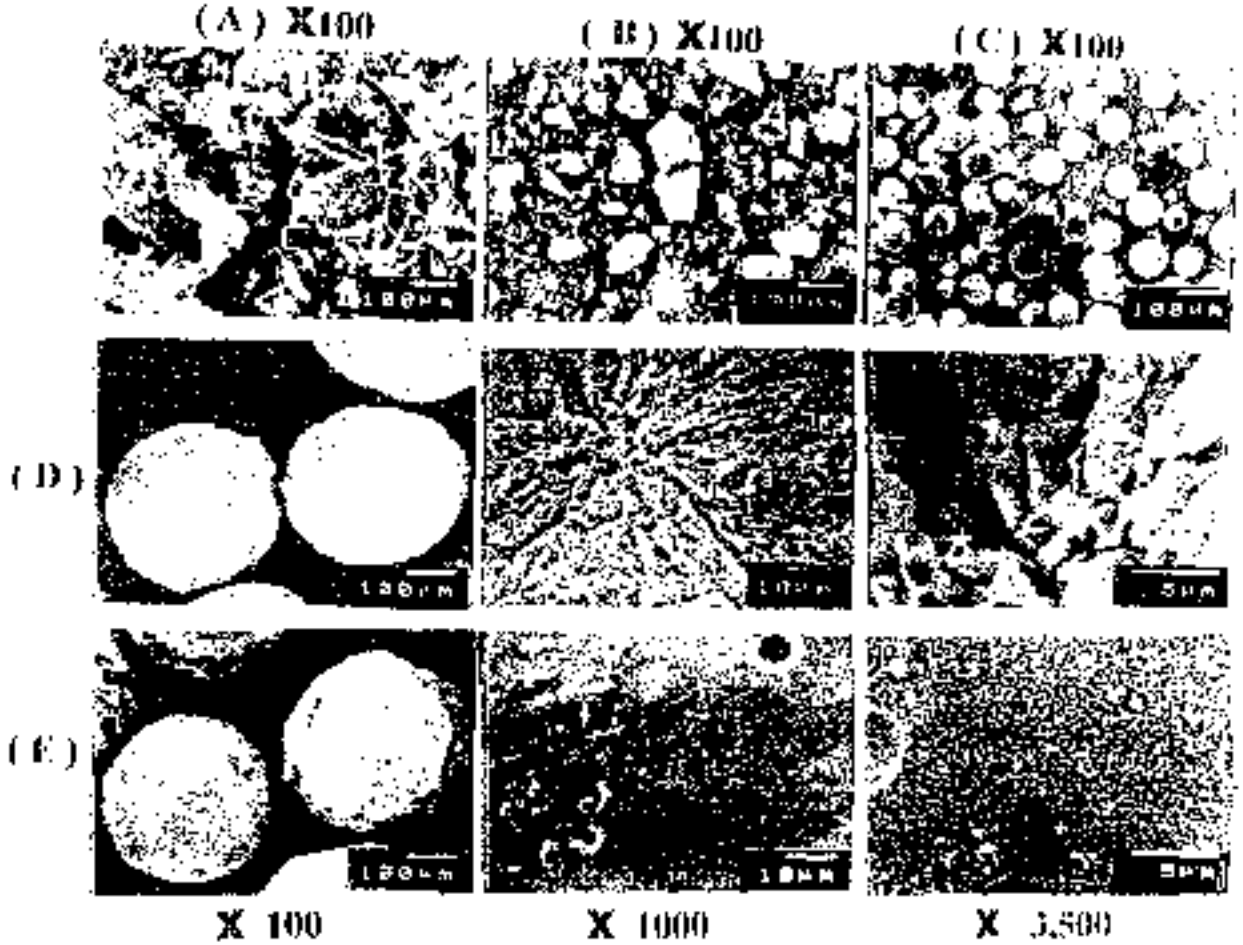

Fig. 7: Representative scanning electron micrographs of (A) verapamil hydrochloride crystals; (B) verapamil resinates (drug:resin (Amberlite IR-120 Na^+) ratio: 1:1); (C) verapamil resinates (drug:resin (Dowex-50W Na^+) ratio: 1:1), (D, E) verapamil resinates-loaded CAB microcapsules; and verapamil resinates-loaded CAB/PS (15%)-microcapsules, respectively: (Resin: Amberlite IR-120 (Na^+), drug/resin ratio: 1:1 and core/coat ratio of 1:2).

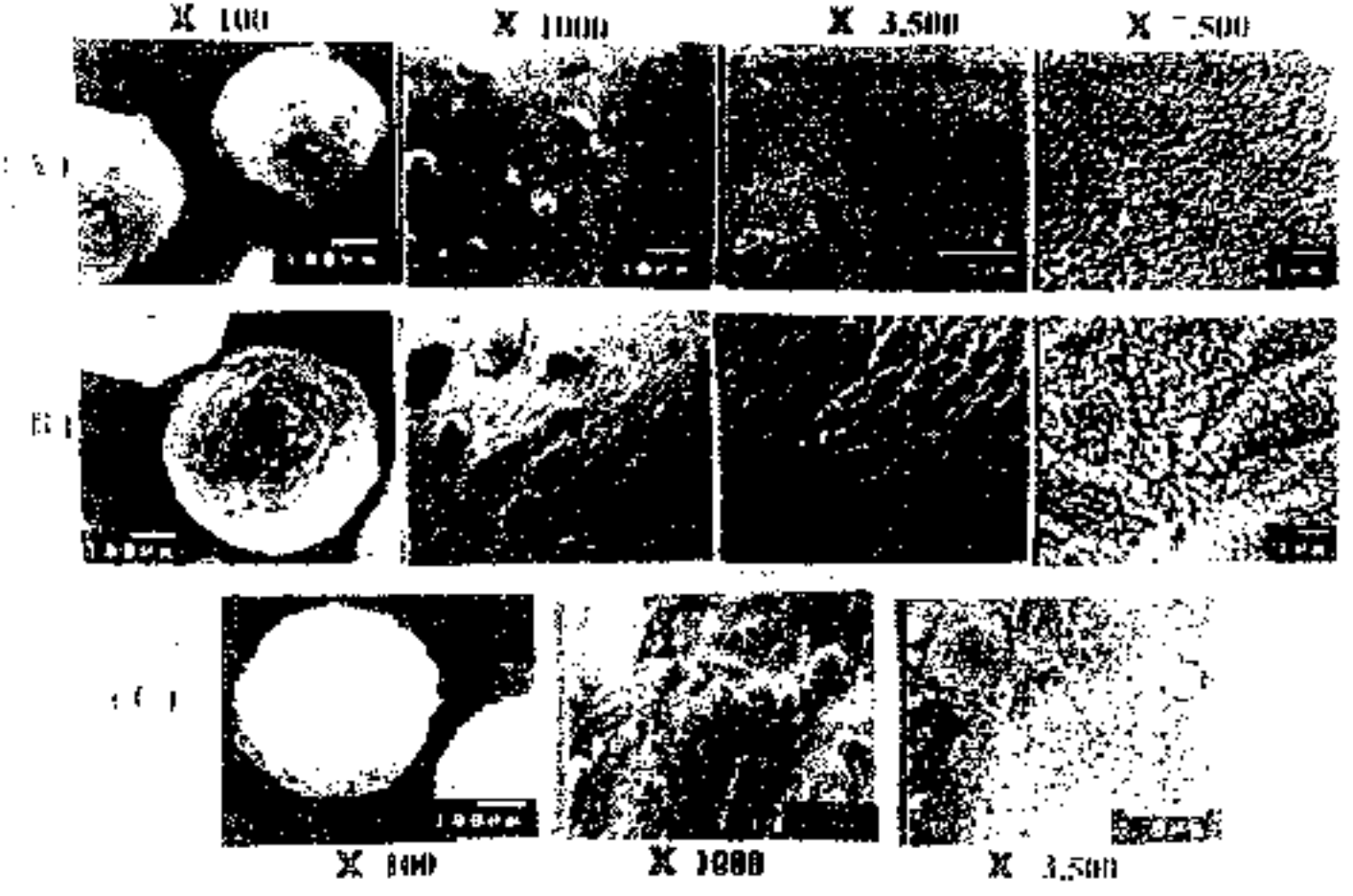

Fig. 8: Representative scanning electron micrographs of verapamil resinates-loaded CAB/PS (30 %)-microcapsules prepared at different core/coat ratios: (A) 1:2; (B) 1:1 and (C) 2:1. (Resin:Amberlite IR-120 (Na^+) and drug/resin ratio of 1:1).

dissolving the styrene polymer. This resulted in better mixing of solvents system and the continuous phase and, hence rapid microcapsule formation. Similar morphological structures were observed when rapid crystallization of polymer blends such as poly (ε-caprolactone)/synperonic L61[29] and polyvinyl chloride/poloxamer 188[30] occurred in organic solvents.

Increasing the core/coat ratio from 1:2 (average drug loading: 9.203%) to 1:1 (average drug loading: 14.45%) increased the amount of drug released from the CAB/PS microcapsules (200 μm or 302.5 μm) prepared with 30% w/w PS concentration as shown from Table 2 and $t_{0.5}$ values in Table 3. Thus, an increase in drug loading by about 35% resulted in decreasing the $t_{0.5}$ values by a factor of 1.05 to 1.8, depending on microcapsule size and pH of the dissolution medium (Table 3 and Figure 9). This may be attributed to the decrease in wall thickness of microcapsule with increasing resinate loading. This is clearly illustrated by the surface topography of the microcapsules which indicated that microcapsules with a core/coat ratio of 1:1 are spherically shaped particles but have wrinkled and rough as well as microporous walls in comparison with those of 1:2 core/coat ratio (Figure 8(A,B), X 100, X 1000). A closer view of the walls is shown at higher magnifications (Figure 8(B), X 1000, X 3500, X 7500). The micrographs revealed the higher porosity of the 1:1 core/coat ratio microcapsules and the existence of some macroscopic pores and resin particles embeded within loosely bound walls, which lead to a relatively rapid drug release.

However, increasing the core/coat ratio from 1:2 to 2:1 (drug loading: 19.57%) in case of 200 μm diameter microcapsules had no marked effect on the $t_{0.5}$ values (Table 3 and Figure 9). Interestingly, it can be seen also from Tables 2 & 3 and Figure 9 that CAB/PS (30%) - microcapsules prepared at a core/coat ratio of 2:1 (drug loading: 19.57-24.28%, depending on microcapsule size) exhibited lower release rates ($t_{0.5}$: 11.0-25.43 hr, depending on microcapsule size and pH of the dissolution medium) than those obtained with microcapsules prepared at 1:1 core/coat ratio ($t_{0.5}$: 6.04-23.11 hr). These results were a contrast to the observed increase in drug release with increasing the initial drug loading described in similar formulations containing ketoprofen[25] and such as those of cellulose ester microspheres containing verapamil hydrochloride.[12] In fact, an increase in drug loading without increasing the amount of the barrier polymer will lead to faster drug release rates as a result of the presence of less amount of barrier polymer at higher drug loadings. However, this did not occur in our case when the drug was fixed on the ion-exchange resins because the extent of the increase in microcapsule porosity as well as the presence of numerous surface resin particles and macroscopic pores with increasing the resinate loadings (as observed in the scanning electron micrographs (Figure 8(C), X 1000, X 3500)), did not compensate well for the higher drug content.

The effect of microcapsule size on the drug release from CAB/PS microcapsules prepared at 30% w/w PS concentration is shown in Tables 2 & 3 and Figure 9(A,B). It is clear that the smaller the microcapsule, the more rapid the drug release rate due to the greater effective surface area.

The performance as prolonged release preparation of verapamil resinate-loaded CAB/PS (30%)-microcapsules was compared with the action of commercial sustained release tablets (Isoptin-(SR) containing 240 mg of verapamil hydrochloride) (Figure 9(A,B)). Generally the release profiles revealed that the described verapamil formulations exhibited slower release rates in 0.1 N HCl and phosphate buffer (pH 7.4) than the conventional tablets which showed a complete drug release after 10 hr in phosphate buffer (pH 7.4). This contrasted to approximately 30.9-75.10% release (depending on core/coat ratio and microcapsule size) from CAB/PS (30%)-microcapsules containing drug fixed onto the resin in a time frame of 12 hr (Figure 9(A,B).

Despite the solubility of verapamil hydrochloride is higher in the pH range of 2.3 to 6.4, where the ionized species predominates,

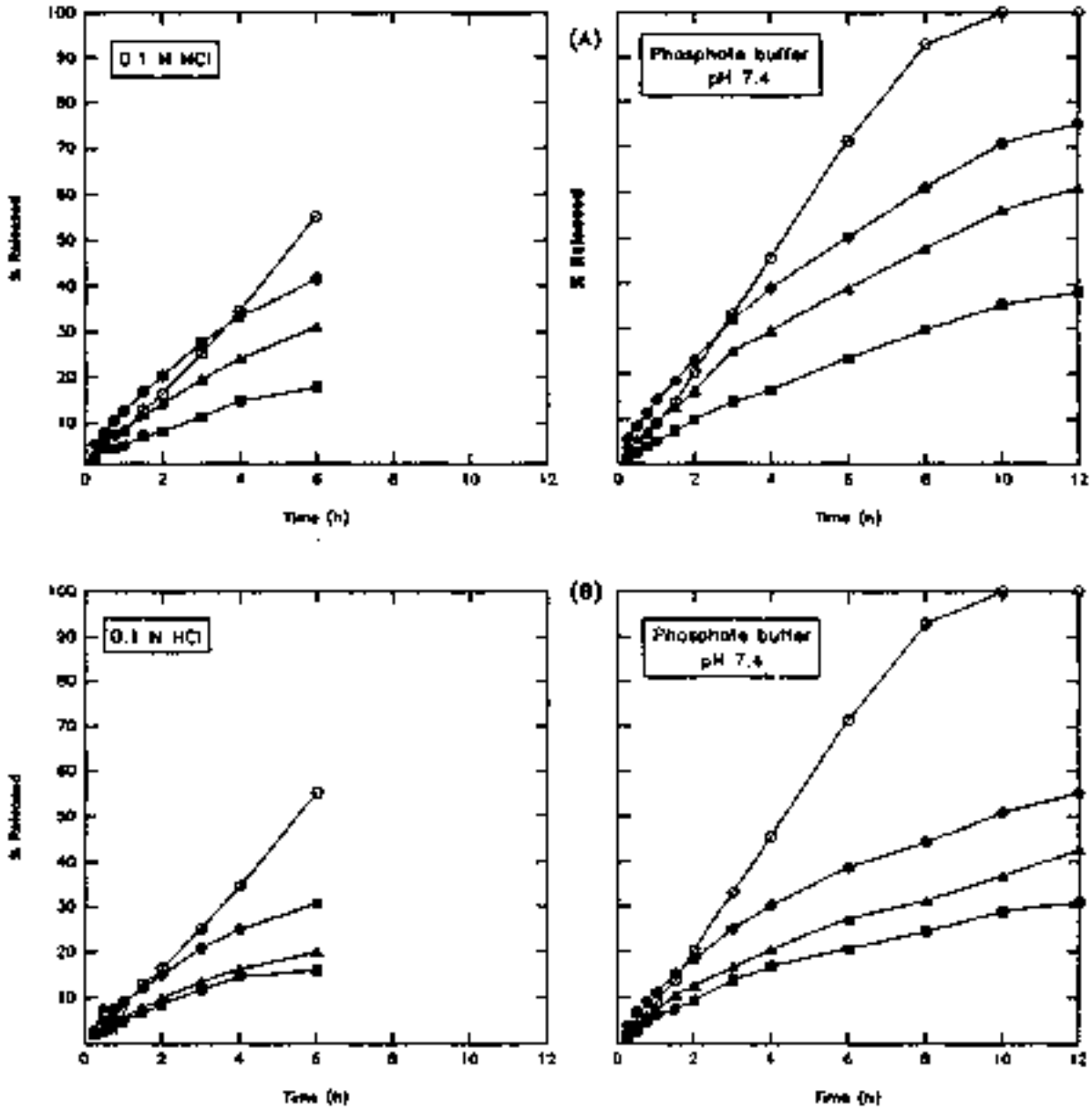

Fig. 9: Comparison of drug release profiles of verapamil resinates-loaded CAB/PS (30%)-microcapsules prepared at a core/coat ratio of (A) 1:1 and (B) 2:1 with isoptin-SR tablets / Resin : Amberlite IR-120 (Na^+), (○) Isoptin-SR tablets, microcapsules fraction size: (●) 150-250 μm; (▲) 250-355 μm, (■) 355-500 μm.

than at higher pH values,[23] the drug release rates were found to be higher in phosphate buffers (e.g pH 7.4) than in 0.1 N HCl (Table 3 and Figures 1 & 9). It is known that the resin containing a strongly acidic functional group (sulphonic acid) will have a greater affinity for hydrogen ions compared to sodium or potassium ions, hence, a faster cation exchange and drug release may be expected in a more acidic environment.[31] However, the unexpected results obtained could be presumably inferred from the difference in the concentration of different counter-ions in eluting media. This was also evident from the extent of drug release with uncoated complexes in the presence of each counter-ion (Figure 1). Also, the change in release profiles was less pronounced at higher pH values (5.2 and 7.4) even though the ionic strength was kept constant at 0.154 (data not shown). The results obtained are consistent with those of Sprockel and Prapaitrakul,[31] who observed that the influence of media pH at constant ionic strength on drug release from CAB microspheres containing phenylpropanolamine loaded onto sulfonic acid cation exchange resin (Amberlite IRP-69) was less dramatic, especially at higher pH values (5-7), than the effect of counter-ion type.

Kinetics interpretation of the release data

Analysis of the release data of verapamil resinates-loaded CAB or CAB/PS microcapsules was carried out according to zero-order kinetics, first-order kinetics, Higuchi model, a diffusion-controlled model for planar matrix[32] and Baker and Lonsdale model, a diffusion-controlled model for spherical matrix.[33] A simple empirical exponential relation (Eqn. 1) was also proposed by Peppas[34] to describe the general solute release behaviour of controlled release polymeric devices;

$$\frac{M_t}{M_\infty} = K t^n \qquad \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

where M_t/M_∞ is the fractional release of the drug, t is the release time, K is a constant incorporating structural and geometric characteristics of the controlled release device, and n is the release exponent, indicative of the mechanism of drug release. Reportedly, the value of n for a spherical sample is 0.43 ± 0.007 for Fickian diffusion, 0.85 ± 0.02 for case II transport (zero-order kinetics) and < 0.85 and > 0.43 for anomalous (non-Fickian) transport.[35] The following equation was derived for quantifying the approximate amount of a drug released by a non-Fickian (diffusion/relaxation) controlled release mechanism.[36]

$$\frac{M_t}{M_\infty} = K_1 t^{1/2} + K_2 t \qquad \ldots\ldots\ldots\ldots \quad (2)$$

where K_1 and K_2 are the diffusion (Fickian)-controlled and the relaxation-controlled release mechanism constants, respectively.

The values of n, release rate constants and the corresponding determination coefficients (r^2) for the release data of microcapsules are listed in Table 3. Generally, the applied models were sufficiently linear and the differences between them were noted to be minimal. However, it appeared that the release pattern of verapamil from CAB or CAB/PS (7.5%)-microcapsules was found to be best explained by a Fickian-diffusion kinetics with n values ranging from 0.368 to 0.513. This indicates that the square root of time relationship for a matrix diffusion-controlled mechanism (Higuchi model) was operative.[34,35] The suggested model has been applied successfully to drug release from CAB microcapsules.[32] Also, the results obtained are consistent with those of Moldenhauer and Nairn[37] who found that microencapsulated ion-exchange resins containing theophylline fitted a t^n plot, when M_t/M_∞ is < 0.3, thereby, suggesting particle diffusion control.[32] It is also evident from Table 3 that Ritger-peppas model showed the highest correlation coefficients and the calculated (n) values ranged from 0.589 to 0.819 in almost all the cases of CAB/PS microcapsules prepared at higher resinate/polymer ratios and/or PS concentrations (15, 30%), thus confirming a non-Fickian-type kinetics controlled by a combination of a

diffusion and a chain relaxation mechanism.

What is perhaps more interesting, is the unusual release behaviour of verapamil in these controlled release microcapsules; especially those with higher resin content. This is because significant amounts of core usually interfere with the macromolecular chain relaxation process, thus leading to a suppression of the relaxation mechanism and observation of only a diffusional mechanism.[36,37] However, the unexpected relaxation mechanism for the new dosage form of verapamil hydrochloride may be the result of the relatively slow swelling of the device (containing higher resin and PS content) which leads to a transition of the overall system from the glassy to the rubbery state.[35] In fact, the swelling behaviour of resinate/CAB/PS system could be explained on the basis that higher PS content increased the membrane permeability and number of water-filled pores as evidenced from the scanning electron microscopy (Figure 9). Consequently, the hydration of resin (Amberlite IR-120) increased which, in turn, affects the swelling capacity and volume expansion of resin particles in the microcapsules, resulting in an overall swelling of the system. The swelling capacity of the ion exchange resins when wetted has been put to practical use with resins such as Amberlite IRP-88 used as a tablet disintegrating agent.[14]

CONCLUSION

For the first time, verapamil hydrochloride was successfully complexed with sulfonic acid-cation exchange resins and the complexes were microencapsulated by a modified emulsion-solvent evaporation / extraction technique using different coating polymers and binary polymer systems (CAB/PS). By virtue of the adopted method, complete evaporation of solvent and microcapsule formation were accomplished within 1.5-2 hr. The prepared microcapsules offered a further prolongation of the drug release rates of Amberlite-type resinates and improved their microscopic properties, whereas, the uncoated Dowex-type resinates which have better surface properties showed potential as a sustained release drug delivery system for verapamil hydrochloride.

Of special concern should be the advantageous sustained release properties of verapamil complex-loaded microcapsules prepared using CAB/PS binary polymer systems in drug release rate modulation. Thus, the permeability of microcapsules wall which controls overall mass transfer processes and/or microcapsule particle size can be modified over a wide range by changing the CAB/PS ratio. Consequently, varieties of microcapsules with varying release profiles could be obtained. The variations in drug release rates with pH of dissolution media indicate a potential for *in-vivo* variability. Drug release data of such microcapsules fitted better to the diffusion / relaxation-controlled release mechanism (non-fickian-diffusion kinetics).

REFERENCES

1- Martindale, The Extrapharmacopoeia, Thirty-first Ed., E. F. Reynolds (ed.). The Pharmaceutical Press, London (1996), pp. 961-964.

2- K. Naonori, H. Yatabe, K. Iseki, and K. Miyazaki, International Journal of Pharmaceutics, 68, 255 (1991).

3- K. Thomma and T. Zimmer, International Journal of Pharmaceutics, 58, 197 (1990).

4- L. Maggi, G. Massolini, E. De-Lorenzi, U. Conte and G. Caccialanza, International Journal of Pharmaceutics, 136, 43 (1996).

5- C. Gun-Lan and H. Wei-Hua, Drug Development and Industrial Pharmacy, 24, 1067 (1998).

6- M. Marvola, A. Kannikoski, J. Taskinen and P. Ottoila, Journal of Pharmacy and Pharmacology, 37, 766 (1985).

7- S. Ugarkovic, G. Trendovska-Serafimovska, B. Sapkareva, *et al.*, Acta Pharmaceutica, 46, 155 (1996).

8- A. Gazzaniga, M. E. Sangalli, U. Conte, C. Caramella, P. Colombo and A. La-Manna, International Journal of Pharmaceutics, 91, 167 (1993).

9- S. A. Elkeshen and E. A. Hosny, Die Pharmazeutische Industrie, 61, 666 (1999).

10- M. S. Nagarsenker and R. Govindarajan, Pharmacy and Pharmacology Communications, 4, 331 (1998).

11- W. Prapaitrakul, and C. W. Whitworth, Journal of Microencapsulation, 6, 213 (1989).
12- S. B. Bhardwaj, A. J. Shukla and C. C. Collins, Journal of Microencapsulation, 12, 71 (1995).
13- G. M. Burke, R. W. Mendes and S. S. Jambhekar, Drug Development and Industrial Pharmacy, 12, 713 (1986).
14- S. S. Borodkin, Ion-exchange resins and sustained release. In: Encyclopedia of Pharmaceutical Technology, J. Swarbrick and J. C. Boylan (eds.), Marcel Dekker, Inc., New York (1993), pp. 203-216.
15- R. Bhaskar, R. S. R. Murthy, B. D. Miglani and K. Viswanathan, International Journal of Pharmaceutics, 28, 59 (1986).
16- M. Sriwongjanya and R. Bodmeier, European Journal of Pharmaceutics and Biopharmaceutics, 46, 321 (1998).
17- M. G. Moldenhauer and J. G. Nairn, Journal of Pharmaceutical Sciences, 79, 659 (1990).
18- M. Sriwongjanya and R. Bodmeier, International Journal of Pharmaceutics, 158, 29 (1997).
19- D. Torres, L. Boado, D. Blanco and J. L. Vila-Jato. International Journal of Pharmaceutics, 173, 171 (1998).
20- O. L. Sprockel and J. C. Price, Drug Development and Industrial Pharmacy, 16, 361 (1990).
21- Z. L. Chang, In: Analytical profiles of drugs substances. K. Florey (ed.), Academic press, Inc., New York, Vol. 27 (1988), pp. 643-674.
22- I. El-Gibaly, S. M. Safwat and M. O. Ahmed, Journal of Microencapsulation, 13, 67 (1996).
23- M. Iso, T. Shirahase, S. Hanamura, S. Urushiyama and S. Omi, Journal of Microencapsulation, 6, 165 (1989).
24- I. El-Gibaly and S. M. Safwat, Proceedings of Pharmaceutical Technology Conference, Oxford, U.K., 205 (1996).
25- A. Barkai, Y. V. Pathak and S. Benita, Drug Development and Industrial Pharmacy, 16, 2057 (1990).
26- O. L. Sprockel, W. Prapaitrakul and P. Shivanand, Journal of Pharmacy and Pharmacology, 42, 152 (1990).
27- R. K. Chang, J. C. Price and C. W. Whitworth, Drug Development and Industrial Pharmacy, 13, 1119 (1987).
28- A. Mac, D. Negi and D. Friend, Journal of Microencapsulation, 6, 361 (1989).
29- H. Huatan, J. H. Collett and D. Attwood, Journal of Microencapsulation, 12, 557 (1995).
30- I. El-Gibaly, Bulletin of Pharmaceutical Sciences, Assiut University, 21, 203 (1998).
31- O. L. Sprockel and W. Prapaitrakul, International Journal of Pharmaceutics, 48, 217 (1988).
32- W. I. Higuchi, Journal of Pharmaceutical Sciences, 57, 274 (1968).
33- R. N. Baker and H. K. Lonsdale. Controlled release: mechanisms and rates, In: Controlled Release of Biologically Active Agents, edited by A. C. Tanquary and R. E. Lacey (Plenum, New York) (1974), pp. 15-71.
34- N. A. Peppas, Pharmaceutica Acta Helveticae, 60, 110 (1985).
35- P. L. Ritger and N. A. Peppas, Journal of Controlled Release, 5, 37 (1987).
36- B. Gander, R. Gurny, E. Doelker and N. A. Peppas, Journal of Controlled Release, 5, 271 (1988).
37- F. Helfferich, Ion-Exchange; McGraw-Hill: New York (1962), pp. 261, 285.
38- P. I. Lea, Polymer Communications, 24, 45 (1983).
39- G. Ponchel, F. Touchard, D. Wouessidjewe, D. Duchêne, and N. A. Peppas, International Journal of Pharmaceutics, 38, 65 (1987).