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BEESWAX AS A RELEASE RETARDER FOR VERAPAMIL HYDROCHLORIDE FROM MICROSPHERES BASED ON CELLULOSE ACETATE BUTYRATE

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ABSTRACT

Verapamil hydrochloride (VPH) was encapsulated using emulsion solvent-evaporation technique. Ethyl cellulose (EC), Eudragit RS (Eud. RS) and cellulose acetate butyrate (CAB) were used as the coating polymers. The dissolution behavior of microspheres was carried out in simulated gastric fluid (SGF). The decrease in the drug/polymer (CAB) ratio led to coarser particle size without any pronounced effect on the release rate. In general, the retardation of drug release after encapsulation was smaller than required. Different amounts of beeswax were coencapsulated with verapamil HCl in the microspheres based on CAB. A significant retardation was obtained with the increase in the amount of wax used. As the mean size of microspheres increased, the release of drug decreased. Analysis of the release data revealed that the drug release kinetics was dependent on the dissolution medium and microspheres composition. DSC and X-ray analysis of the polymer, drug and drug-loaded microspheres were performed in order to characterize the physical state of the polymer and drug after encapsulation.

INTRODUCTION

Verapamil hydrochloride, an effective antiarrhythmic agent, exerts its effect through selective inhibition of slow inward transport of calcium across cell membranes. It is also used in the management of essential hypertension [1,2]. The drug has a short half-life and hence requires more frequent dosing by the oral route. For this reason a number of reports about sustained release formulations of verapamil has been developed to minimize dosage frequency [2,4].

Microspheres as a multiple-unite dosage form provide several advantages over other sustained release systems. They spread out uniformly in the gastrointestinal tract which results in a more reproducible drug absorption and minimizes side effects due to localized build up of irritating drugs against the gastrointestinal mucosa [5]. In addition, unwanted intestinal retention of the polymeric material, which may occur with nondisintegrating tablets on chronic dosing, is avoided [6]. However, It is difficult to control the highly water-soluble drugs with a large dose particularly via microencapsulation using an individual polymer. Mixtures of polymers have been used for achieving sustained release. Polycaprolactone and cellulose acetate butyrate mixtures were utilized to control the release characteristics and size of microspheres containing chlorpromazine [7]. Terbutaline sulfate sustained release microspheres were prepared with Eudragit RS, in the presence of aluminum tristearate, by an emulsion-solvent evaporation method [5]. In this study, beeswax has been utilized in controlling the release of VPH from microspheres based on CAB. It is obtained from honeycomb of the bees. White and yellow beeswaxes are GRAS-listed (Generally Recognized as Safe) and consist of mixtures of various esters of straight-chain monohydric alcohols with even number of carbon chains (C_{24}-C_{36}) esterified with straight-chain fatty acids. Beeswax also contains free acids and carbohydrates [8]. Due to wax 's chemical inertness, wax matrices have been used in sustained release preparations [9-11]. However, considering of gastric emptying time of pharmaceutics, multiple-unit formulation is more suitable for sustained release dosage forms [5]. So, incorporation of wax inside the microspheres avoids the problems arise during preparation of small pellets or granules with the wax matrix system because of the aggregation of granules in the manufacturing process.

The objective of the current study was to control the release of water-soluble drug, verapamil HCl through encapsulatrion and investigating the variables affecting both the release properties and morphology of the resultant microspheres.

EXPERIMENTAL

Materials

Verapamil hydrochloride (Sigma Chemical Co., St. Louis, USA), Ethylcellulose (100 cps, Hercules Inc., Wilmington, USA), Eudragit RS (Rohm Pharma, Darmstadt, Germany), Cellulose acetate butyrate (FMC Co, USA), Beeswax (Hamburg Bp. No 1). All the solvents and reagents were of analytical grade.

Methods

Preparation of microspheres

Microspheres were prepared by the emulsion-solvent evaporation technique. The polymer was completely dissolved in acetone (10% w/v). Verapamil HCl (VPH, 1 g) with or without beeswax (BW) was then added. The mixture was stirred and poured into a vessel containing light mineral oil (liquid paraffin, 150 ml) and span 80 (1.5 ml). After evaporation of acetone, the microspheres were separated by filtration, washed three times with *n*-hexane (50 ml) at room temperature and dried in air for 48 hours. In case of BW/CAB, BW was dispersed in a double amount of acetone used with the polymer alone. Drug-free microspheres were prepared in the same way using BW/CAB mixture at 2:8 ratio. The

following preparative variables were investigated: Polymer type (ethylcellulose; EC, Eudragit RS; Eud. RS and cellulose acetate butyrate; CAB), core:coat (VPH:CAB) ratio (2:1, 1:1 and 1:2) and BW/CAB ratio (1:9, 2:8, 3:7 and 4:6).

The dried microspheres were weighed. The yield (%) was obtained as the weight of resultant microspheres to the weight of drug and coat (polymer with or without wax) x 100.

Size distribution of microspheres

The microspheres were sized into different size fractions using the USA standard sieves (W.S. Tyler, Inc. USA) in the range of 150 µm to 1000 µm. The sieves were stacked from bottom to the top in ascending order of aperture size. Drug-incorporated microspheres (2 g) were placed on the top sieve and shaked for 10 minutes using sieve shaker (Model RX-86-1, Cole-Parmer Inst. Comp., USA). The amount of microspheres retained by each sieve was weighed and the weight percentage of microspheres in each size range was calculated.

Determination of the microspheres content

Microspheres drug content was determined by the crushing and extraction method. Twenty mg were crushed in a porcelain mortar and then quantitatively transferred into 100-ml spherical flask by aiding of simulated gastric fluid (SGF). The mixture was stirred for 24 hours, filtered, and then measured spectrophotometrically at 278 nm. The percentage of encapsulation efficiency of VPH is defined as the follows: The actual drug content/theoretical drug content x 100.

Release studies

The release properties of microspheres were evaluated using the USP apparatus II (paddle method). Simulated gastric fluid (SGF, pH 1.2) was used as the dissolution medium. An accurately weighed amount of microspheres (100 mg) was added to 500 ml of the release medium maintained at 37 ± 0.5 ° C and stirred at 100 rpm. Aliquots of 5 ml were removed and replaced with fresh medium at appropriate time intervals. The content of the withdrawn samples was quantified spectrophotometrically at 278 nm. To study the pH effect on the dissolution rate of VPH from microspheres prepared at BW/CAB as 1:9, McIlvaine buffer solutions were prepared by mixing appropriate volumes of 0.1 M citric acid and 0.2 M disodium phosphate solutions. The pH of buffer solutions was 3, 5 and 7 (±0.05 units of pH). Every experiment was repeated two times. The percent deviation was not more than ± 5%.

Scanning electron microscopy (SEM)

Scanning electron microscopy was used to characterize the microspheres. The microspheres were mounted onto metal stubs using double-sided adhesive tape, vacuum-coated with a layer of gold using a sputter coater (SPI sputter, USA). The shape, size and surface of microspheres were observed with a scanning electron microscope (Jeol JSM 5400LV SEM, 15 kV, Japan). To examine the internal morphology, the cross sections of the microspheres were obtained by cutting the dried matrix with a razor blade. The scale and the magnification for each photograph are indicated at the bottom of the figures.

Thermal analysis (DSC)

To evaluate the internal structure modifications after drug incorporation, differential scanning calorimeter analysis was performed on pure substances, drug-free microspheres and drug-loaded microspheres. The instrument (DSC-50 Shimadzu, Japan) was calibrated with an indium standard. An empty pan, sealed in the same way as the sample, was used as a reference. Three -five mg samples were sealed into aluminum pans. The run was performed at 10°C/min between 0 and 200°C. Thermal analysis data were obtained using TA 50I PC system with Shimadzu software programs.

For more investigations, solid dispersion (co-precipitate) of the drug and CAB after dissolving in acetone was obtained through evaporation (CAB:VPH ratios were 0.5:1, 1:1, 2:1, 4:1 and 8:1). In addition, different ratios of BW/VPH (9:1, 4:1, 1.5:1, 0.67:1, and 0.25:1) were prepared by the addition of drug to BW melt and thoroughly mixing.

Powder X-ray diffractometry (XRD)

An X-ray powder diffractometer (model FW 1700 Series, Philips, Netherlands) was used to determine the physical nature of verapamil hydrochloride in the microspheres. The diffractometer was equipped with continuous higher voltage generator (4 K VA model: PW 1730/10), vertical Gonimeter (model; PW 1050) and automatic control unit (model PW 1710/00). The operation conditions were as the following: X-ray, Ni filtered Cu-kα radiation; voltage 40 kv; current 30 mA; scanning speed 10 mm/sec. Samples of VPH, CAB, free-drug microcapsules and loaded-drug microspheres were examined for comparison.

RESULTS AND DISCUSSION

An emulsion-solvent evaporation method for preparing microspheres is generally known to be simple, reproducible and economical [12,13]. It comprises dispersing drug-polymer solution into an immiscible vehicle to form an emulsion. As the solvent evaporated, the droplet becomes gradually concentrated and the nucleation takes place. Drug-loaded microspheres are thus produced [14].

The adopted method produced discrete and free-flowing

microspheres. When the microspheres were examined under the scanning electron microscope, they appeared spherical with a continuous surface (Fig. 1). Drug-free microspheres had a smooth surface (Fig. 1a). While drug-loaded microspheres and based on CAB alone displayed a rough surface (Fig. 1b) which could be attributed to the deposition of drug crystals on the surface of microspheres after solvent evaporation. Mathiowitz et al. [15] have reported that the external surface of the microspheres appeared smooth for drug loading up to 16.5% and above that level, some crystals appeared on the surface. Microspheres based on BW/CAB had shiny appearance with smooth surface (Figs. 1c, 1d and 1e). They became less spherical with an increase in BW/CAB ratio (Fig 1e). Fig. 2 shows the cross-sectional view of drug-loaded microspheres based on CAB or BW/CAB (3:7 and 4:6). The microspheres based on BW/CAB revealed a low porous internal structure with a dense external structure. It was postulated that the hollow core is formed as the soft microspheres harden first on the outside of the microspheres due to the removal of solvent. As the amount of drug in the core to coat is increased, the characteristics of the hollow core changed to a spongy center [16,17]. BW/CAB microspheres prepared at 4:6 ratio (Fig. 2c) exhibited a less external dense structure with more porous internal structure. It is worthy to remind that the increase in BW/CAB ratio led to a decrease in the amount of CAB responsible for the coacervate droplets and hence the external membrane.

Table 1 displays the characteristics of VPH-loaded microspheres prepared using CAB alone or BW/CAB. The yield of all prepared microspheres was determined by dividing the weight of obtained product by theoretical yield and multiplying the whole by 100. In all prepared microspheres, acceptable yield was achieved between 60.5 and 92.02 (% w/w). For microspheres based on CAB and prepared at different core:coat ratios, the yield increased with an increase core/coat ratio. Drug content determinations in various particle size fractions were performed. The drug loading efficiency Table 1 increased with an increase in core/coat ratio. This finding may be attributed to the increase in the amount of acetone used as a solvent in case of higher amount of polymer (concentration of polymer in acetone kept constant). Since the evaporation of acetone and hence solidification of the microspheres extended the time during which the emulsion droplets remained in a fluid state, a large proportion of drug and/or polymer could be extracted by the external phase. The same reason can explain the low drug content in case of microspheres based on BW/CAB wherein, the amount of acetone was two-fold as in the case of microspheres prepared using CAB alone

Fig. 3 illustrates the size distribution of CAB-microspheres prepared using different ratios of VPH and CAB. The mean size of microspheres decreased as the core/coat ratio decreased due to the reduced viscosity of the internal phase. Fig. 4 displays the size distribution of VPH- microspheres based on BW/CAB. Varying the ratio of BW/CAB but keeping the ratio of coating materials and drug constant brought the size distribution within the narrow range. These results indicated that the use of mixtures of two polymers to control microsphere size is feasible [7]. As the amount of BW increased, the size of the microspheres increased. This was as a result of a decrease in concentration of CAB and increase in the coencapsulated BW leading to an increase in the viscosity of the internal phase. Consequently, larger droplets of emulsion were produced and thus an increase in particle size after evaporation of organic solvent [18,19].

The release studies were performed in simulated gastric fluid since it is the first medium meets the orally administered dosage forms. At the same time, it represents the challenge for a basic drug, VPH, due to its high solubility in low pH [20]. Various polymers were used as coating material for encapsulation of VPH at 1:1 core:coat ratio. The release patterns of VPH from the microspheres prepared using various types of polymers prevailed that ethylcellulose and Eudragit RS could not regulate the drug release (Fig. 5). As could be seen, nearly all amount of drug was released in the first 30 minutes. Therefore; cellulose acetate butyrate was selected in this study because it gave the lowest release rate. In trial for more retardation of the drug, the effect of drug/polymer ratio on the drug release rate was explored. Figure 6 shows the release of VPH from CAB-microspheres prepared at different drug:polymer ratios. As the drug/polymer ratio decreased from 2:1 through 1:1 to 1:2 the drug release rate decreased. It is considered that a lower drug/polymer ratio resulted in a longer diffusion path, so that drug release is retarded. The same result was also displayed in other studies [5,21].

The aforementioned results emphasize that there is a need for modifying the drug release using other substance. Beeswax represents a biocompatible material, non-immunogenic and due to its physical properties and behavior in the intestinal lumen proved to be suitable to prepare gastro-resistant microspheres [22]. Beeswax has been utilized in the preparation of microspheres loaded with valporoic acid [22] valporoic acid & vitamin E [23] and fluorouracil & ftorafur [24]. Hence, beeswax was coencapsulated with VPH using CAB as a microsphere membrane. Fig. 7 depicts the release of drug from microspheres prepared with a mixture of BW/CAB at different ratios but keeping the core:coat at ratio 1:1. Coencapsulation of BW significantly decreases the rate of drug release. This can be explained as the following: the internal phase during emulsification was consisted of

CAB, BW and VPH. With the time, evaporation of acetone forms a compact matrix in which the drug was embedded. SGF faced difficulties in penetrating this

Table (1) Characteristics of verapamil microspheres based on CAB or BW/CAB mixture.

BW/CAB ratio	Core/coat ratio	Fraction size (μm)	Yield (%)	Drug loading (%)		Encapsulation efficiency (%)
				Theoretical	Actual	
-	2:1	315-400	92.02	66.67	65.30	97.95
-	1:1	315-400	79.83	50.00	43.11	85.92
-	1:2	315-400	60.50	33.33	13.18	39.54
1:9	1:1	630-800	70.00	50.00	36.33	85.92
2:8	1:1	630-800	80.00	50.00	34.13	68.27
3:7	1:1	630-800	73.8	50.00	23.19	46.38
		800-1000			22.75	45.49
		>1000			19.63	39.25
4:6	1:1	630-800	85.40	50.00	25.83	51.64
		800-1000			27.07	54.14
		>1000			28.19	56.18

matrix due to the increase in its hydrophobicity. Increase in the ratio of BW/CAB, decreased the verapamil release indicating a more decrease in the porosity of diffusion barrier and higher hydrophobicity inside the microspheres (Fig. 7). The complete absence of the burst effect reveals that the small VPH crystals on the surface of BW/CAB microspheres appeared in SEM were completely coated with the polymer and beeswax. The results suggest that BW might be softening by the heat generated during emulsification and hence it shared CAB in formation of the VPH-embedded matrix. In addition it acted as an internal sealing material for the microsphere membrane. Maximum retardation occurred for BW/CAB ratio 3:7. Increase in BW/CAB above that ratio (4:6) gave release rate higher than that of 3:7 ratio. A decrease in CAB concentration led to formation of both porous matrix and a thin film around the drug matrix (Fig 2c). Consequently, an increase in SGF penetration was achieved. At the same time, increase in the amount of BW resulted in high viscosity of the internal phase leading to formation of imperfect microspheres as shown in SEM (Fig. 1e); less spherical microspheres were produced. Since, high amount of BW increased the viscosity of the internal phase, difference in velocity between the coacervated droplets (CAB) and the particles (VPH and BW) was created. This difference in velocity appears to play a major part in the coating process. This phenomenon explains the prevention of coacervated droplets from being completely aggregated around the drug and wax particles [25].

Fig. 8 depicts the effect of particle size on verapamil release from microspheres based on BW/CAB (3:7), the release rate was inversely related to microspheres size. The results can be explained on the basis of the increase in both surface area and diffusion path length.

VPH by its physico-chemical properties as a weak base can experience problems in its release from controlled-release dosage forms in the small intestine. The drug solubility declines from 0.165 g/ml at pH 5 to 0.025 and 0.010 g/ml at pH 6.0 and 7.0 respectively [26]. Therefore, the effect of pH of the dissolution medium on drug release was investigated. Fig. 9 shows the release of drug from BW/CAB microspheres (1:9) at different pH values. The release rate in SGF (pH 1.2) was the highest as a result of high solubility of drug at low pH [20]. As the pH of release medium increased, the drug release decreased. However, this decrease in drug release was inconsistent with the drug solubility at different pH values, which could be attributed to the more erosion of the BW with the increase in the pH. This might avoid the problems of drug release in the small intestine where precipitation of poorly soluble free base occurs within the microspheres. The precipitated drug is no longer

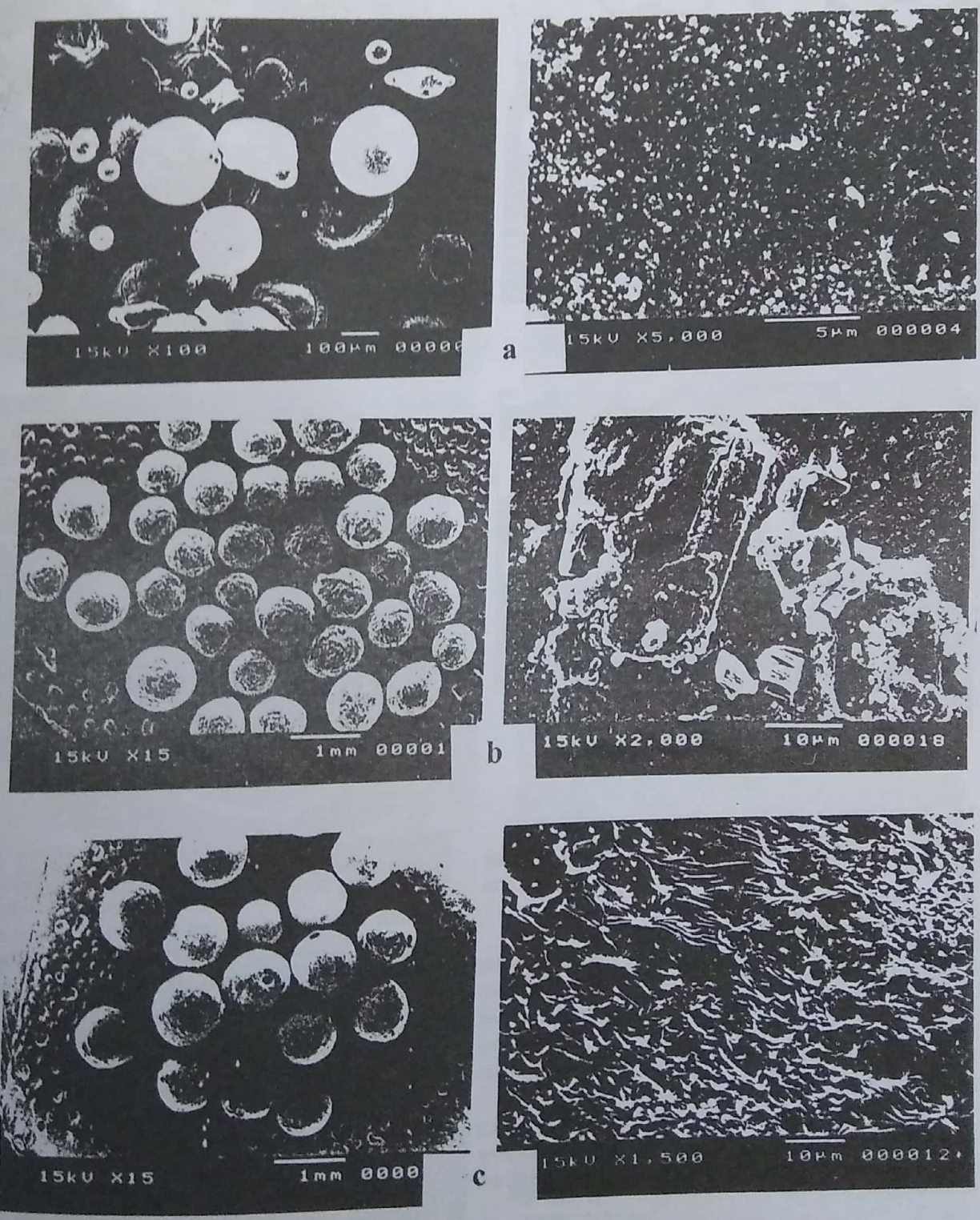

Fig. 1.SEM of (a) VPH-free microspheres; (b) VPH-loaded microspheres based on CAB and VPH-loaded microspheres based on BW/CAB at (c) 1:9; (d) 3:7; (e) 4:6 ratios. Photo on the right side is the high magnification of the left one.

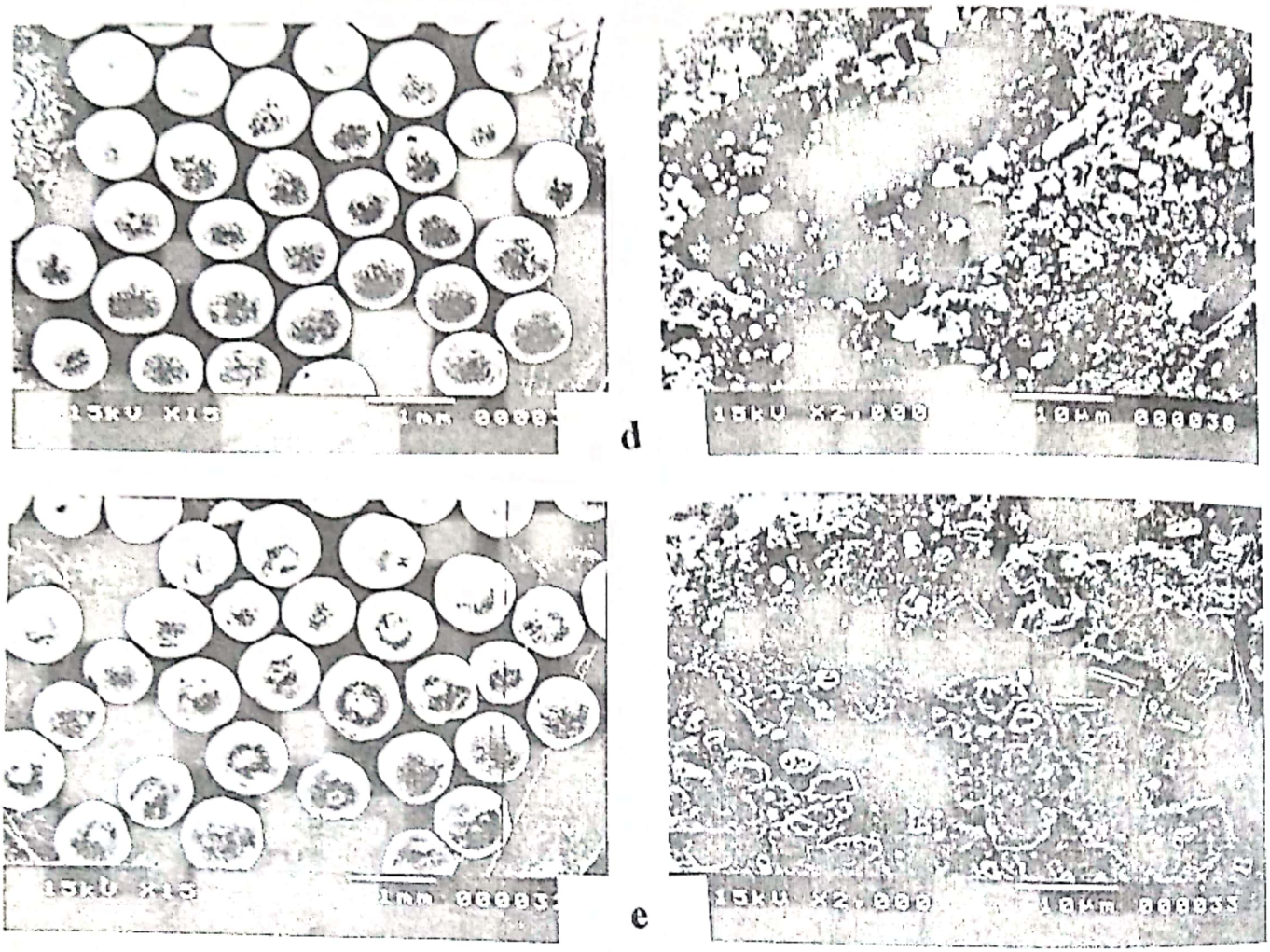

Fig. 1. (Continue)

capable of diffusion through such a diffusion membrane but remains as residual contents inside the dosage form and is not pharmaceutically available [27,28].

For better understanding the drug release mechanism, the release data were tested assuming common kinetic models (zero-order, first-order, Higuchi square-root model). Release rate constants and correlation of determinations are displayed in Table 2. A comparative evaluation of r^2 values showed that the best-fit kinetic model was diffusion one for drug release [29].

To clarify the effect of pH on the mechanism of drug release, verapamil release data were analyzed according to the simple power equation of drug release from polymer devices [30] as follows:

$$M_t/M_\infty = Kt^n$$

Where M_t/M_∞ denotes the drug fraction released at time t, K is a constant incorporating structural and geometric characteristic of controlled release device.

The value of kinetic exponent (n) defines the mechanism of release [31]. This equation was applied to the release from matrices of several geometries (slabs, cylinders, spheres, and discs). Table 2 comprises the value of kinetic exponent n and correlation of determination (r^2). The values of (n) for drug release in SGF were in the range 0.376-0.574, thus the release process is diffusion-controlled considering the shape of microspheres are spherical. Fickian diffusion was expected to be a predominant release mechanism in SGF because of high solubility of verapamil and gastro-resistance properties of the microsphere components. Thus, an approximately linear relationship between fractional release and the square root of time could be obtained (Table 2). Increase in pH of dissolution medium (at pH 3 and 5), combination of diffusion and slow erosion were contributed in the release of drug (n=0.572 and 0.668 respectively). At pH 7 (n=1.032), the slow erosion of the microspheres was the predominant facilitating an

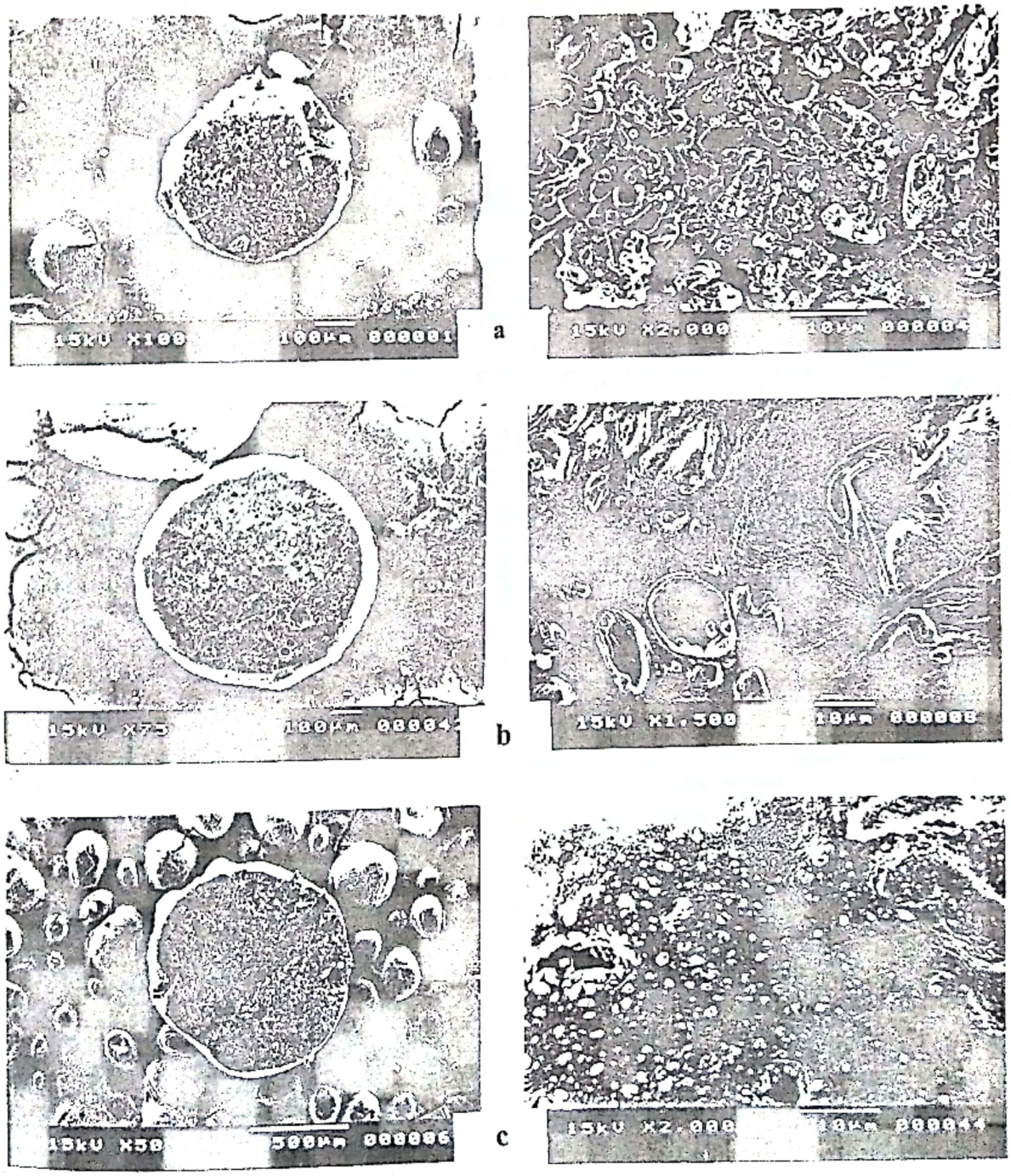

Fig. 2. SEM of cross-sectional view of (a) VPH-loaded microspheres based on CAB and VPH-loaded microspheres based on BW/CAB at (b) 3:7; (c) 4:6 ratios. Photo on the right side is the high magnification of the left one.

Table 2 Kinetic parameters of verapamil release from microspheres based on BW/CAB at different ratios

pH	BW: CAB ratio	Particle size fraction of microspheres (μm)	Zero-order		First-order		Higuchi diffusion model		Simple power equation	
			K_o (%/h)	r^2	$K_1 \times 10^{-2}$ (h^{-1})	r^2	K_H (%/$\sqrt{h}$)	r^2	n	r^2
1.2	1:9	630-800	5.803	0.898	9.743	0.948	20.421	0.983	0.447	0.993
3	1:9	630-800	3.964	0.898	5.156	0.927	13.964	0.983	0.572	0.981
5	1:9	630-800	3.455	0.930	4.209	0.950	12.005	0.993	0.668	0.989
7	1:9	630-800	3.759	0.978	4.443	0.990	12.737	0.993	1.032	0.975
1.2	2:8	630-800	5.318	0.802	7.752	0.936	18.738	0.979	0.574	0.981
1.2	3:7	630-800	1.635	0.991	1.805	0.993	5.468	0.980	0.444	0.954
1.2	4:6	630-800	3.479	0.931	4.469	0.951	12.051	0.988	0.464	0.992
1.2	4:6	800-1000	2.306	0.958	2.676	0.957	7.850	0.979	0.412	0.964
1.2	4:6	>1000	1.626	0.954	1.811	0.962	5.582	0.994	0.376	0.992

Legend: r^2 = correlation of determination, K= dissolution rate constant, n= Kinetic exponent

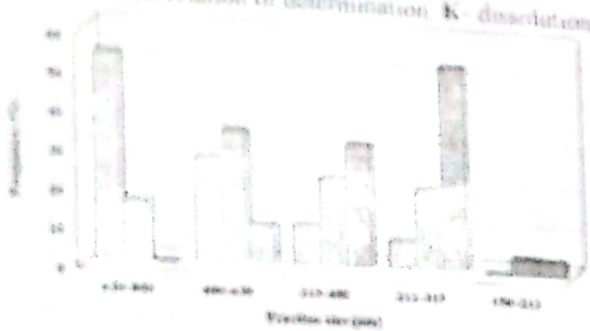

Fig. 3. Particle size distribution of verapamil microspheres based on CAB at different core coat ratios: 2:1, 1:1, 1:2

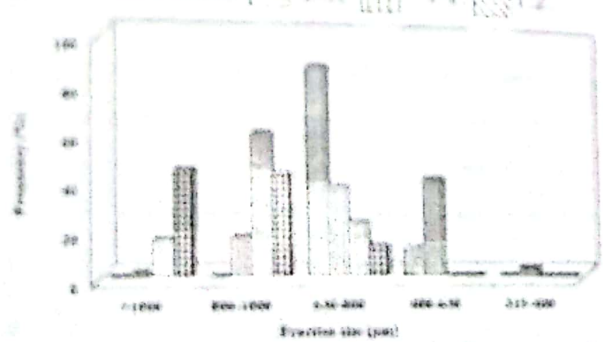

Fig. 4. Particle size distribution of verapamil microspheres based on BW/CAB at different ratios: 1:9, 2:8, 3:7, 4:6

approach toward zero-order release. It was reported that the release of drug from wax matrices has been a matter of controversy since wax systems tend to be crude and more heterogeneous than polymeric system [15]. Some have suggested that the mechanism of release from wax matrices involves the leaching of drug by the eluting system [16,17]. Others have reported that release from wax matrices is diffusion controlled and is best described by Higuchi's model [18,19].

In order to establish the physical state of the drug in the microspheres, DSC and X-ray analysis were performed. DSC analysis of polymer, drug, drug-free microspheres and drug-loaded microspheres are shown in Fig. 10. Verapamil HCl has a sharp peak appeared at 142° C (Fig. 10a). No peak was observed for drug-free microspheres under the experimental conditions (Fig. 10b). The presence of VPH in the microspheres resulted in lowering and broadening of the melting peak from 142° C to 136° C in case of microspheres based on CAB alone (Fig. 10c) or lower ratios of BW/CAB (1:9 and 2:8) (Figs. 10d and 10e). Microspheres based on high ratios of BW/CAB (3:7 and 4:6) showed no peaks (Figs 10f and 10g). These results displayed that the drug is partly or completely amorphous or solid solution in the microspheres. It seemed that DSC thermograms

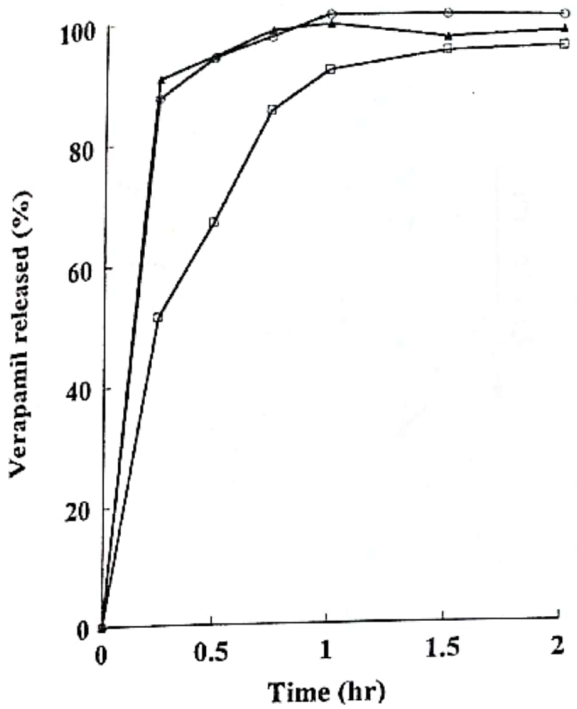

Fig. 5. The release profiles of verapamil, in SGF, from microspheres (315-400 µm) prepared using different polymers at 1:1 core: coat ratio. ○ EC; ▲ Eud. RS; □ CAB.

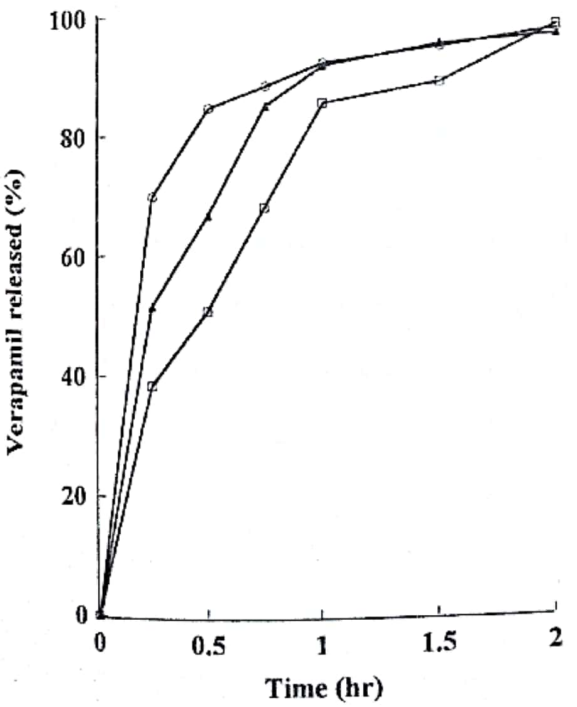

Fig. 6. The release profiles of verapamil, in SGF, from microspheres based on CAB (315-400 µm) at different core : coat ratios ○ 2:1; ▲ 1:1; □ 1:2.

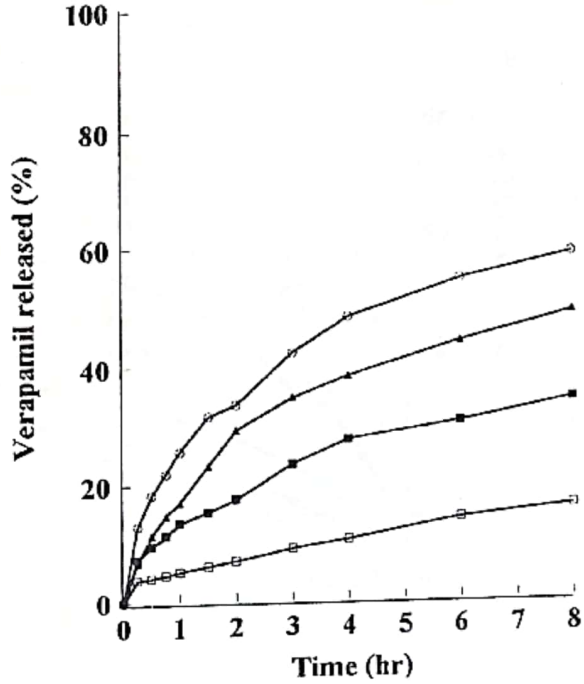

Fig. 7. The release profiles of verapamil, in SGF, from microspheres (630-800 µm) based on BW/CAB at different ratios. ○ 1:9; ▲ 2:8; □ 3:7; ■ 4:6.

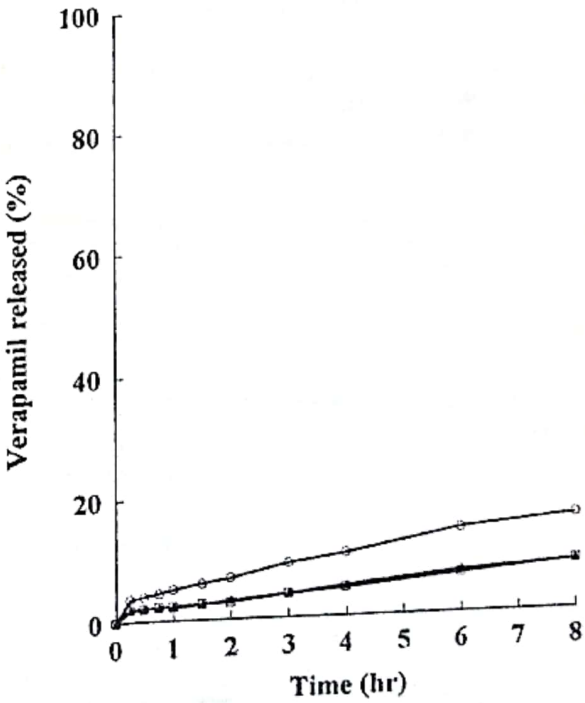

Fig. 8. Effect of particle size on the release profiles of verapamil, in SGF, from microspheres based on BW/CAB (3:7) at 1:1 core : coat ratio. ○ 630:800 µm; ▲ 800-1000 µm; □ >1000 µm.

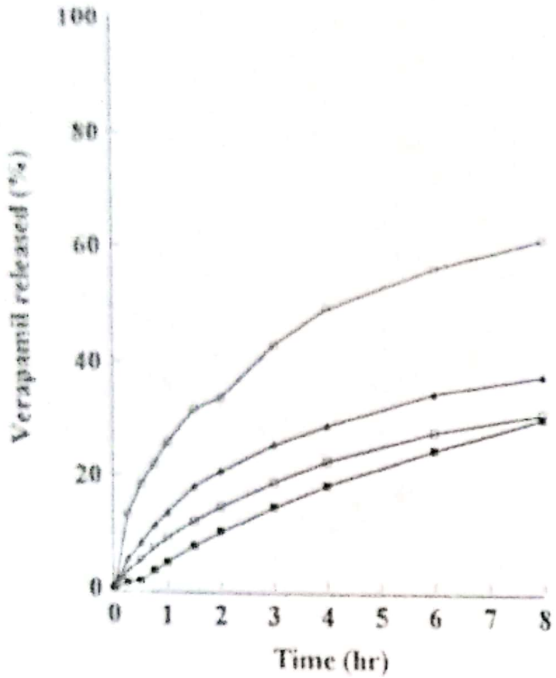

Fig. 9. Effect of pH on the release profiles of verapamil, in SGF, from microspheres (630-800 μm) based on BW/CAB (1:9) at 1:1 core : coat ratio. ○ pH 1.2; ▲ pH 3; □ pH 5; ■ pH 7.

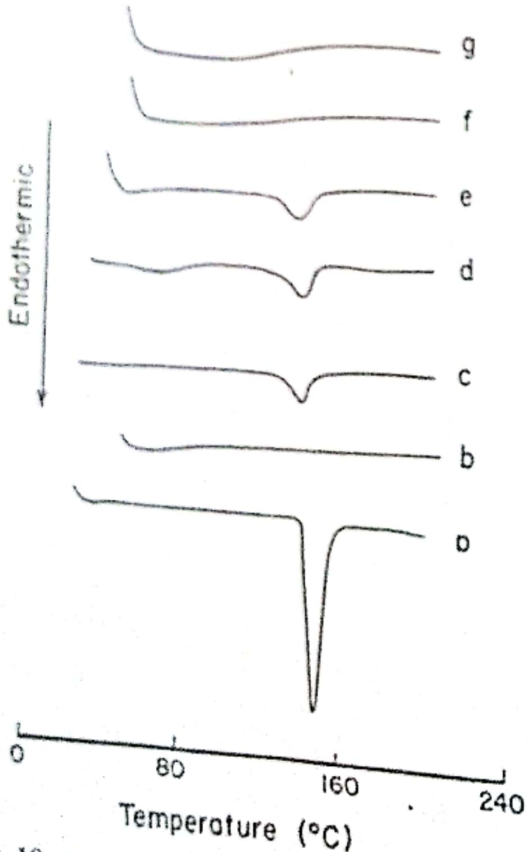

Fig. 10. DSC thermograms of (a) VPH; (b) VPH-free microspheres; (c) VPH-loaded microspheres based on CAB alone and VPH-loaded microspheres based on BW/CAB at (d) 1:9; (e) 2:8; (f) 3:7; (g) 4:6 ratios.

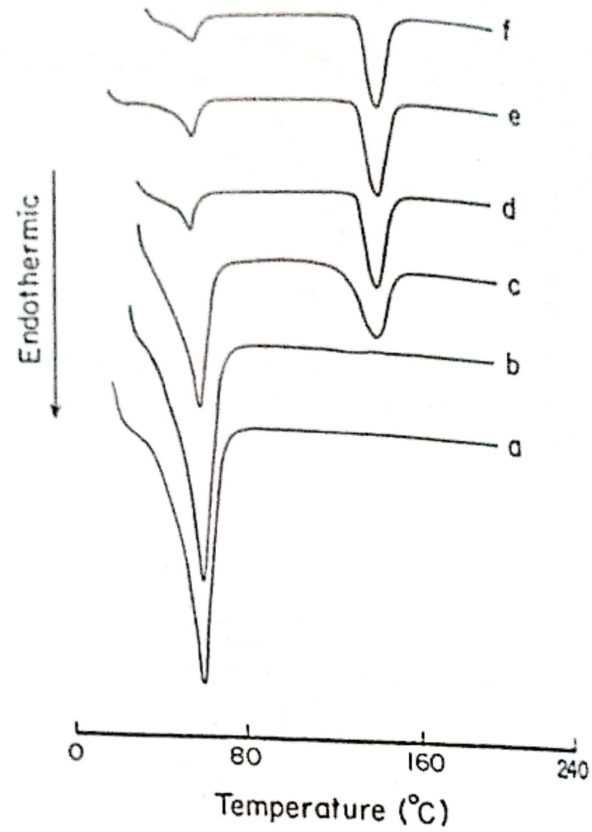

Fig. 11. DSC thermograms of (a) BW and BW/VPH solid dispersion at different weight ratios. (b) 9:1; (c) 4:1; (d) 1.5:1; (e) 0.67:1; (f) 0.25:1.

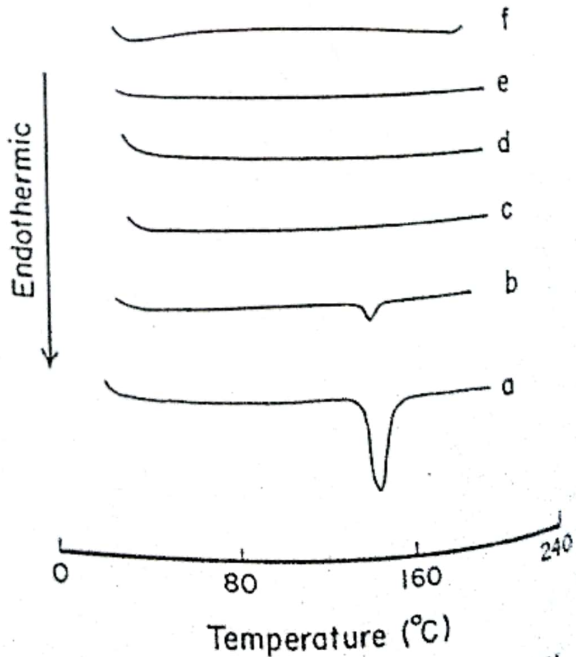

Fig. 12. DSC thermograms of CAB/VPH coprecipitate at different weight ratios (a) 0.5:1; (b) 1:1; (c) 2:1; (d) 4:1; (e) 8:1 and (f) CAB alone.

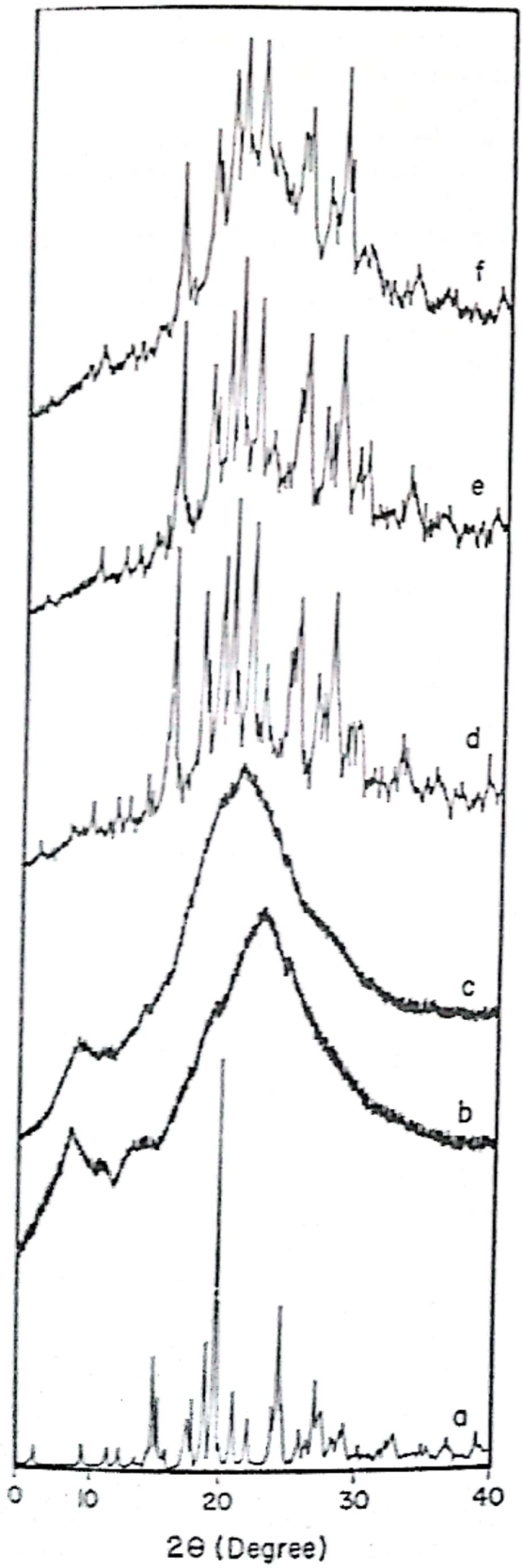

Fig. 13. XRD patterns of (a) VPH; (b) CAB; (c) VPH-free microspheres; (d) VPH-loaded microspheres based on CAB alone and VPH-loaded microspheres based on BW/CAB at (e) 1:9; (f) 4:6 ratios.

pattern was dependent on the drug content. The shift to lower melting point was exhibited in case of microspheres with higher drug content (CAB or BW/CAB ratios 1:9 and 2:8; the drug contents were 43.11, 36.33 and 34.13 respectively). In contrast, microspheres with lower drug content (BW/CAB ratios 3:7 and 4:6; drug contents were 23.19 and 25.83 respectively), drug peak disappeared completely. Mathiowitz et al. [37] reported that when the melting point of some dyes and polymer was monitored before and after encapsulation, the results proved that the dye forms a solution inside the polymer at loading lower than 23%.

In order to investigate the role of BW and CAB on drug thermal behavior, different weight ratios of BW/drug (9:1, 4:1, 1.5:1, 0.67:1, and 0.25:1) were prepared by the addition of drug to BW melt and thoroughly mixing. Coprecipitate of the drug and CAB after dissolving in acetone was also prepared in different ratios as the follows: polymer/drug; 0.5:1, 1:1, 2:1, 4:1 and 8:1. Fig. 11 shows the DSC of drug and BW/drug solid dispersion. Beeswax displayed a melting peak at 60° C, which is the melting point of BW (Fig. 11a). Solid dispersion of BW/drug in different ratios (Figs. 11c, 11d, 11e and 11f) exhibited two peaks: The first one at 60 °C which is due to melting of BW, the second one at about 142° C which is due to melting of VPH. There was neither change nor disappearance of the melting point of the drug indicating the absence of interaction between BW and drug. In case of BW/VPH at 9:1 ratio (Fig. 11b). However, of the disappearance of melting peak of the drug displayed that the drug might dissolve in BW melt as solid solution. Fig 12 shows DSC for CAB/VPH coprecipitate and CAB alone. VPH endothermic peak was weaken at low CAB amount (Figs 12a and 12b) and completely disappeared at high CAB ratios (Figs. 12c, 12d and 12e). No peak was exhibited for CAB under the experiment conditions (Fig. 12f). CAB might inhibit the association of the drug molecule to form the crystal nucleus, hence prevents the crystal growth, as well as, the interaction between drug and CAB could be the inhibitory and/or retardatory factor in the crystallization. This inhibitory effect was associated with the proportion of CAB. The results suggest a complete dissolution of VPH crystals in the CAB-microspheres, i.e., the presence of VPH in an amorphous state, dissolved or molecularly dispersed in microspheres. So, in view of these results, it was concluded that the intermolecular interactions of drug-CAB were maintained during solvent evaporation process. The absence of BW endothermic peaks in DSC analysis of microspheres (Fig. 10) indicated that BW was in amorphous form, i.e., It was in dissolved form during the microspheres preparation. Therefore, the homogenous droplets in emulsion solidified in

microspheres forms possessing uniform, smooth and nonporous surfaces. This could help in the retardation of the drug release in case of using CAB/BW in preparing the microspheres.

However, the absence of the thermal events at low loadings, does not always indicate the presence of the drug in amorphous state[37], In order to verify this point X-ray diffraction was employed.

The XRD patterns of microspheres prepared using CAB alone or BW/CAB at 1:9 and 4:6 ratios were examined and compared with those of pure drug, polymer and drug-free microspheres (prepared using BW/CAB ratio 2:8). The diffraction spectra of VPH (Fig. 13a) showed that the drug was highly crystalline in nature as indicated by numerous distinctive peaks in the X-ray diffractogram. No peaks were noticed for CAB (Fig. 13b) or VPH-free microspheres (Fig. 13c).

The spectra of VPH microspheres (Figs. 13d, 13e and 13f) possessed all the characteristic diffraction lines of crystalline VPH. This revealed that the drug was kept in crystalline state in the microspheres.

In conclusions, this study was undertaken to investigate the feasibility of encapsulation of verapamil HCl and to evaluate the dissolution characteristics of microspheres obtained. It was found that the conventional method of encapsulation with different types of polymers gave undesirable results. The coencapsulation of beeswax with verapamil HCl was found to be promising in controlling the release of water-soluble drug, VPH. Characterization of the drug inside the microspheres revealed the presence of the drug in crystalline dispersed state. Such information may aid in the prediction of drug stability in the formulation and its release pattern.

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استخدام شمع النحل لإبطاء انطلاق عقار الفراباميل هيدروكلوريد من الحبيبات الدقيقة المحضرة باستخدام بيوتيرات خلات السليلوز

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تم تحضير الحبيبات الدقيقة لعقار الفراباميل هيدروكلوريد بطريقة تبخير الوسط المنتشر للمستحلب و قد استخدم إيثيل السليلوز و يودراجيت ر س و بيوتيرات خلات السليلوز كمواد مغلفة .

و بدراسة الصفات الإنطلاقية للحبيبات في المحاليل المشابهة للوسط المعدي وجد أن انطلاق العقار كان سريعاً وعند زيادة نسبة مادة الغلاف إلي العقار أدت إلي حبيبات أصغر حجماً بدون تأثير واضح علي انطلاق العقار.

و لذا تم تحضير الحبيبات الدقيقة للعقار مع شمع النحل باستخدام بيوتيرات خلات السليلوز كمادة مغلفة و قد اثبتت التجارب أن شمع النحل أدي إلي إبطاء ظاهر في انطلاق العقار كما أن زيادة نسبته قد قللت من معدل الانطلاق و قد تم أيضاً دراسة ميكانيكية انطلاق الدواء كما تم تحليل العقار قبل و بعد الحوصلة الدقيقة باستخدام طريقة انكسار أشعة أكس و طريقة تقدير السعر الحراري التفاوتي .