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International Journal of Pharmaceutics 252 (2003) 99–109
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

The effect of the drug/polymer ratio on the properties of the verapamil HCl loaded microspheres

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Received 21 January 2002; received in revised form 12 November 2002; accepted 18 November 2002

Abstract

In this study, the microspheres containing verapamil hydrochloride (VRP) were prepared with Eudragit RS 100 by solvent evaporation method. In the solvent evaporation method one of the parameters which affect to the formation and properties of the microspheres is the variations of drug/polymer ratios. The aim of our study is to examine the effects of this parameter on the VRP loaded microspheres. To achieve this purpose, only drug/polymer ratio was altered while the other formulation parameters were kept constant and percentage yield value, incorporation efficiency, particle size and distribution of the microspheres were analyzed and micrographs of the microspheres were taken to determine the effects of the increase in the polymer amount of formulations. All the dispersed phase viscosities were evaluated by comparing them with the variations in particle size and distribution of the microspheres. In vitro dissolution tests were done by using dissolution media with three different pH in sequence as half-change method with flow through cell and the effect of the variation in polymer ratio on drug dissolution was evaluated according to dissolution test results. As a result of our study, it is thought that the variation in drug/polymer ratios might have an influence on the physical characteristics of the microspheres and the increasing amount of polymer might be result in decreased drug dissolve.

Keywords: Verapamil HCl; Eudragit RS 100; Microsphere; Solvent evaporation method

1. Introduction

Verapamil hydrochloride (VRP) is a phenylalkylamine derivative, calcium antagonist. Calcium antagonists are drugs which cause coronary and peripheral vasodilation by reducing calcium influx through the slow channels of vascular smooth muscle and cardiac cell membranes (McTavish and Sorkin, 1989; Wingard et al., 1991). Calcium antagonists are being used effectively in the treatment of several cardiovascular disorders, particularly angina pectoris, supraventricular tachycardies and hypertension (Wingard et al., 1991). It is established that, as a result of oral usage, 90% of VRP is absorbed and then it reaches maximum plasma concentration within 1–2 h. However, due to the extensive first pass hepatic excretion, it has such low bioavailability as 10–20% of an oral dose. VRP has nonlinear pharmacokinetic because of its saturation of presistemic metabolism leads to first pass effect which resulting in nonlinear absorption. (Eichelbaum et al., 1981; Hamann et al., 1984; Vogelgesang et al., 1984; Follath et al., 1986; Lunden, 1991).

Several conventional and controlled released dosage forms of VRP with different doses have been

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PII: S0378-5173(02)00630-0

formulated and marketed. It is clear from the investigations that there is no difference between the controlled release dosage form given once daily and conventional dosage form given several times daily with the same doses in respect to their bioavailability and antihypertensive effect (Mattila et al., 1985; McTavish and Sorkin, 1989).

In recent years, in order to reduce absorption differences in patients, in the use of multiple unit dosage form which are dispersed in gastrointestinal system more homogeneously than the single unit dosage form like tablets have become more common. Preparation of the multiple unit dosage form of drug which has nonlinear pharmacokinetic characteristics as VRP provides an advantage as regards to its decreasing inter and intra subject variability of absorption (Follonier and Doelker, 1992; Murthy et al., 1994; Soppimath et al., 2001).

Microsphere is one of the multiple unit dosage forms. Solvent evaporation method is the preparation technique that is widely preferred for the preparation of controlled release microspheres. The first stage of this method is to prepare emulsion by adding the dispersed phase consisting of the drug, polymer and appropriate dispersion agent in the organic solvent to dispersion medium which is immiscible with the dispersed phase. At the second stage, minimatrix forms are obtained by removing the solvent used at the dispersed phase from the droplets which are formed in the emulsion. In the preparation of the microspheres of the hydrophilic drugs as VRP, solvent evaporation method which is made by using W/O emulsion is preferred. The selection of the organic solvents is done according to the polarity of dispersion medium and their dielectric constants related to miscibility with dispersion medium (Bogataj et al., 1991; Thies, 1992; Benoit et al., 1996).

One of the polymers preferred in the preparation of the microspheres by solvent evaporation is also the polymethacrylates (Eudragits) that synthetic cationic and anionic polymer of dimethylaminoethylmethacrylates, methacrylic acid and methacrylic acid esters in varying ratios. Eudragit RS 100 is also one of the polymers frequently preferred to make matrix dosage form and supply controlled release. Eudragit RS 100 is a copolymer of acrylic and methacrylic acid esters containing 5% of functional quaternary ammonium groups. Because of Eudragit RS 100 contains the ammonium groups as salts, its permeability is pH independent (Eudragit Data Sheets, 2002; US Pharmacopeia 24, 2000; Kibbe, 2000).

In this study, firstly, VRP loaded controlled release microspheres were prepared by solvent evaporation method with the preparation of W/O emulsion and then the effects of the variations of drug/polymer ratio on the preparation of microspheres and their characteristics were determined and evaluated by incorporation efficiency, yield value, particle size and distribution, dispersed phase viscosity, surface characteristics of microspheres, and dissolution tests.

2. Materials and methods

2.1. Materials

VRP (Knoll), Eudragit RS 100 (Röhm Pharma GmbH, Germany), sucrose stearate (Crodesta F160, Croda GmbH, Germany).

2.2. Preparation of microspheres

Microspheres were prepared by solvent evaporation method (Goto et al., 1986a,b; Kawata et al., 1986; Yüksel and Baykara, 1997). It was thought that acetone could be used as common solvent of VRP and polymer. But, because of the solubility of VRP in methanol is higher than in acetone, if acetone is used alone higher amount of solvent will be needed to prepare dispersed phase. In order to prevent the usage of more solvent, a mixture of acetone and methanol was used. VRP and Eudragit RS 100 were dissolved completely in the acetone–methanol mixture by stirring at 500 rpm with magnetic stirrer. Sucrose stearate was added to this mixture and was stirred at the same rate with magnetic stirrer for a few minutes and then it was kept in the ultrasonic bath until dispersed completely. This mixture was cooled to 10 °C in an ice bath while it was stirred by magnetic stirrer at 500 rpm. As can be seen from the previous studies, when a solvent with a dielectric constant about 10 or above is used, nonpolar liquid paraffin is preferred as dispersing medium (Goto et al., 1986a; Bogataj et al., 1991; Thies, 1992; Kim et al., 1994; Bhardwaj et al., 1995). Therefore,

Table 1
Formulations prepared with different drug/polymer ratio

	Formulation				
	F1	F2	F3	F4	F5
VRP (g)	1.50	1.50	1.50	1.50	1.50
Eudragit RS 100 (g)	3.00	4.50	6.00	7.50	9.00
Sucrose stearate (g)[a]	0.450	0.675	0.900	1.13	1.35
Methanol (ml)	3.50	3.50	3.50	3.50	3.50
Acetone (ml)	11.5	19.0	26.5	34.0	41.5
Liquid paraffin (ml)	200	200	200	200	200
Drug/polymer	1/2	1/3	1/4	1/5	1/6
Polymer/solvent	1/5	1/5	1/5	1/5	1/5
Sucrose stearate (%)	3	3	3	3	3

[a] Amounts of sucrose stearate were calculated from dispersed phase volume (w/v %).

we preferred the liquid paraffin as dispersing medium appropriate to methanol and acetone. Mixture mentioned before was poured into the liquid paraffin previously cooled to 10 °C with 1 ml/min rate while it was stirred by a stirrer fitted to 400 rpm (Model RZR-2000; Heidolph Electro, Kelheim, Germany) for 1 h at this temperature in an ice bath. Emulsion constituted was heated to 35 °C gradually (1 °C/min) and stirred at this temperature for 4 h. During this time acetone and methanol were completely removed by evaporation. The solidified microspheres were filtered, washed six times with 50 ml of *n*-hexane, dried under vacuum at a room temperature for 12 h and stored in desiccator containing $CaCl_2$.

In our study, in order to investigate the effect of the increasing amount of the polymer on microsphere formation, the drug/polymer ratio was altered while the polymer/solvent ratio, the percentage amount of dispersing agent and mixing rate were kept constant (Table 1).

2.3. Percentage yield value of microspheres

The percentage yield values which calculated from the ratio of filtered and dried microsphere amount (A) of each formulation to total solid material amount in the dispersed phase (B) (the percentage yield value $= (A/B) \times 100$) are given in Table 2.

2.4. Incorporation efficiency of microspheres

Microspheres containing approximately 10 mg VRP were accurately weighed and dissolved in methanol used as a common solvent of drug and polymer, and then drug concentration was determined spectrophotometrically ($n = 5$) (Shimadzu UV-1202 Visible) at 279 nm. Incorporation efficiency was calculated as in the following equation

$$\text{Incorporation efficiency} = \left(\frac{b}{a}\right) \times 100$$

Table 2
Percentage yield values and incorporation efficiencies of formulations

Formulation	Percentage yield value	b[a] ± S.E.	a[b]	$[(b/a) \times 100]$[c] ± S.E.
F1	86.3	27.4 ± 1.49	30.3	90.5 ± 4.92
F2	99.6	18.0 ± 0.654	22.5	80.2 ± 2.90
F3	99.6	14.7 ± 0.179	17.9	82.2 ± 0.976
F4	98.5	12.9 ± 0.164	14.8	87.0 ± 1.09
F5	94.1	10.6 ± 0.295	12.7	83.3 ± 2.33

[a] Mean drug entrapped ($n = 5$).
[b] Theoretical drug content.
[c] Mean incorporation efficiency ($n = 5$).

Table 3
Particle size and distribution data of microspheres determined by laser diffraction method

Formulation	*D*(0.5)	Span	Mode	*D*(4.3)	*D*(3.2)
F1	657.39	1.15	1139.73	713.32	486.34
F2	513.96	0.97	487.20	553.96	420.29
F3	450.63	1.38	519.60	444.94	251.26
F4	336.04	1.51	437.14	357.54	223.84
F5	420.88	0.98	453.27	422.58	329.31

D(0.5), volume median diameter; Span, simple measurement of the width of distribution; Mode, the most common value of frequency distribution, i.e. highest point of the frequency curve; *D*(4.3), volume mean diameter; *D*(3.2), the surface area of mean diameter (Rawle, 1993).

where, *a* is the theoretical drug content and *b* is the drug entrapped.

2.5. Determination of particle size and distribution of microspheres

Particle size and distribution were determined by laser diffraction granulometry (X-Long pad Malvern Inst.) with a small sample dispersion unit (50–80 ml). In this study, filtered and degaussed purified water was used as a carrier fluid. About 0.3–0.5 mg of microspheres were dispersed in purified water in the sample unit and were circulated 2000 times per minute. Results of the measures are given in Table 3.

2.6. Determination of the dispersed phase and dispersing medium viscosity

Viscosities of liquid paraffin as dispersing medium and different dispersed phase of formulations were determined with rotation viscosimetry (Brookfield Model DV-II) by using RV1 spindle for liquid paraffin, RV3 spindle for dispersed phases at the rate of 50 rpm and at 10 and 25 °C. Determined viscosities are given in Table 4.

2.7. Scanning electron micrography (SEM)

The shape and surface characteristics of microspheres were observed by a SEM (Jeol JSM-6400) (Fig. 1). Microspheres were dusted onto double sided carbon dust which was placed onto sample carrier in the shape of a cylinder with 5 mm of height and 10 mm of diameter and were coated with Au–Pd mixture under vacuum (100 mTorr) with sputter coater (Hummer VII) to thickness of 50 nm. The samples were imaged using a 5–15 kV electron beam.

Table 4
Viscosities of dispersion medium and dispersed phase of the formulations at the different temperatures

Temperature (°C)	Viscosity (mPa s)					
	Liquid paraffin	F1	F2	F3	F4	F5
10	28.0	20.0	18.0	18.0	14.0	18.0
25	38.8	14.0	16.0	16.0	10.0	16.0

2.8. In vitro dissolution studies

To determine the drug dissolution from microspheres, flow through cell method (US Pharmacopeia 24) (Desaga) was used. As dissolution media, simulated gastric fluid (pH 1.2), phosphate buffer (pH 6.8), and simulated intestinal fluid (pH 7.5) were used. Polysorbate 80 (0.02%, w/v) was added to each dissolution media to improve the wetting of the microspheres. These dissolution media with different pH were used in sequence for 2 h (pH 1.2), 3 h (pH 6.8) and 4 h (pH 7.5) for half-change method (Ammar and Khalil, 1997). Flow rate of dissolution fluid was adjusted to 8 ml/min in order to maintain sink condition. The amount of drug dissolved in test solutions was assayed spectrophotometrically (Shimadzu UV-1202 Visible) at 278 nm. The amounts of drug dissolved were plotted versus time as percent dissolved drug (Figs. 2–3).

Arithmetic means of dissolved drug and their standard errors, and the results of ANOVA were calculated by using SPSS 9.0 for windows (SPSS Chicago, IL). With the analysis of repeated measurements (univariate ANOVA), whether there was significant time × group interaction between the different formulations or not were determined. If there were differences between the formulations, Duncan's Multiple Range Test with MSTAT C program was applied to determine whence the differences arose (Tables 5 and 6). The mathematical models, first-order ($\text{diss}(\%) = 100(1 - e^{-kt})$), Higuchi ($\text{diss}(\%) = kt^{0.5}$), and Weibull ($\text{diss}(\%) = 100(1 - e^{-(t/T_d)\beta})$) equations were fitted to individual dissolution data with linear

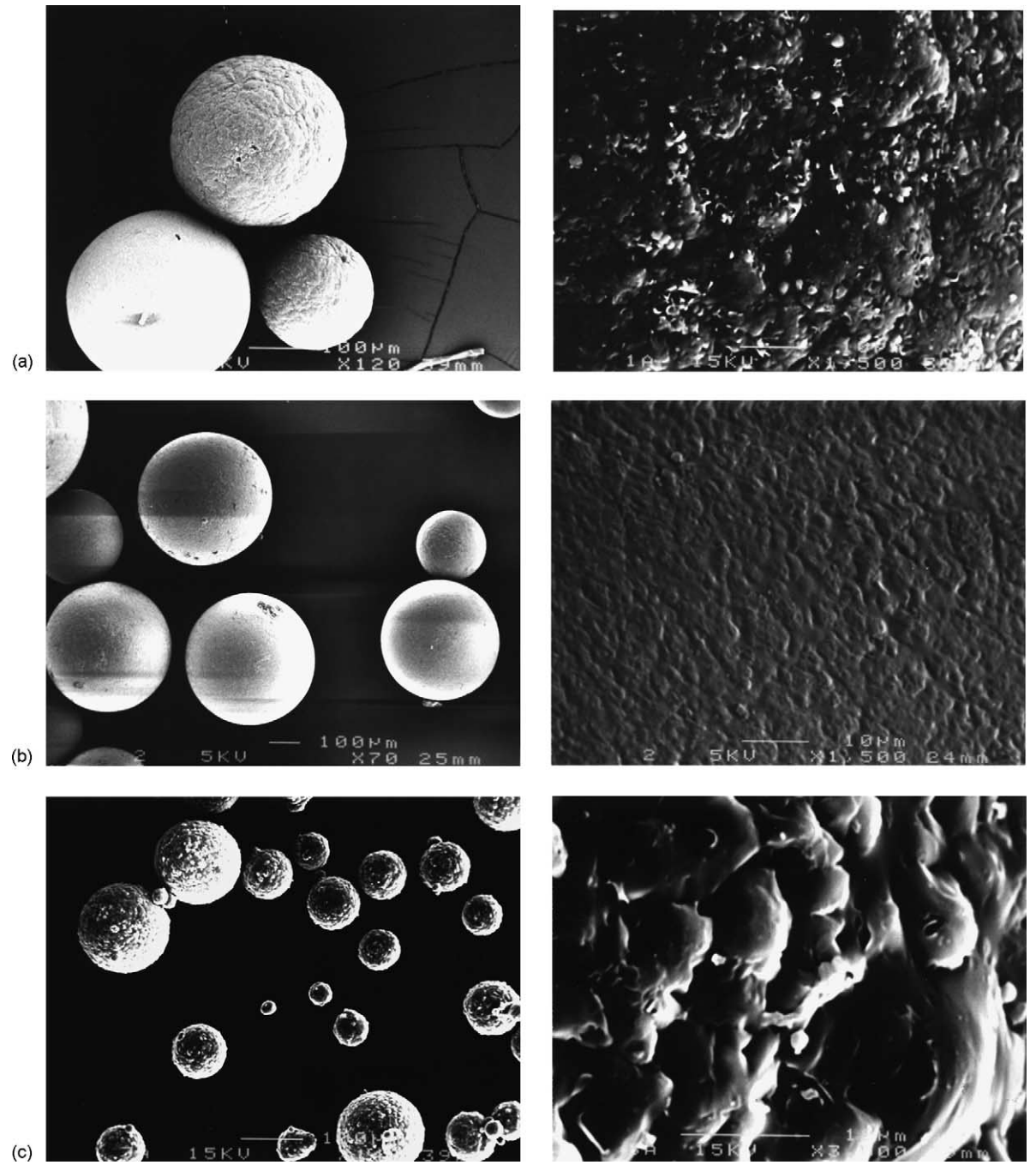

Fig. 1. Scanning electron micrographs of microspheres and their surfaces prepared from the formulations given in Table 1 (a) F1, (b) F2, (c) F3, (d) F4, (e) F5.

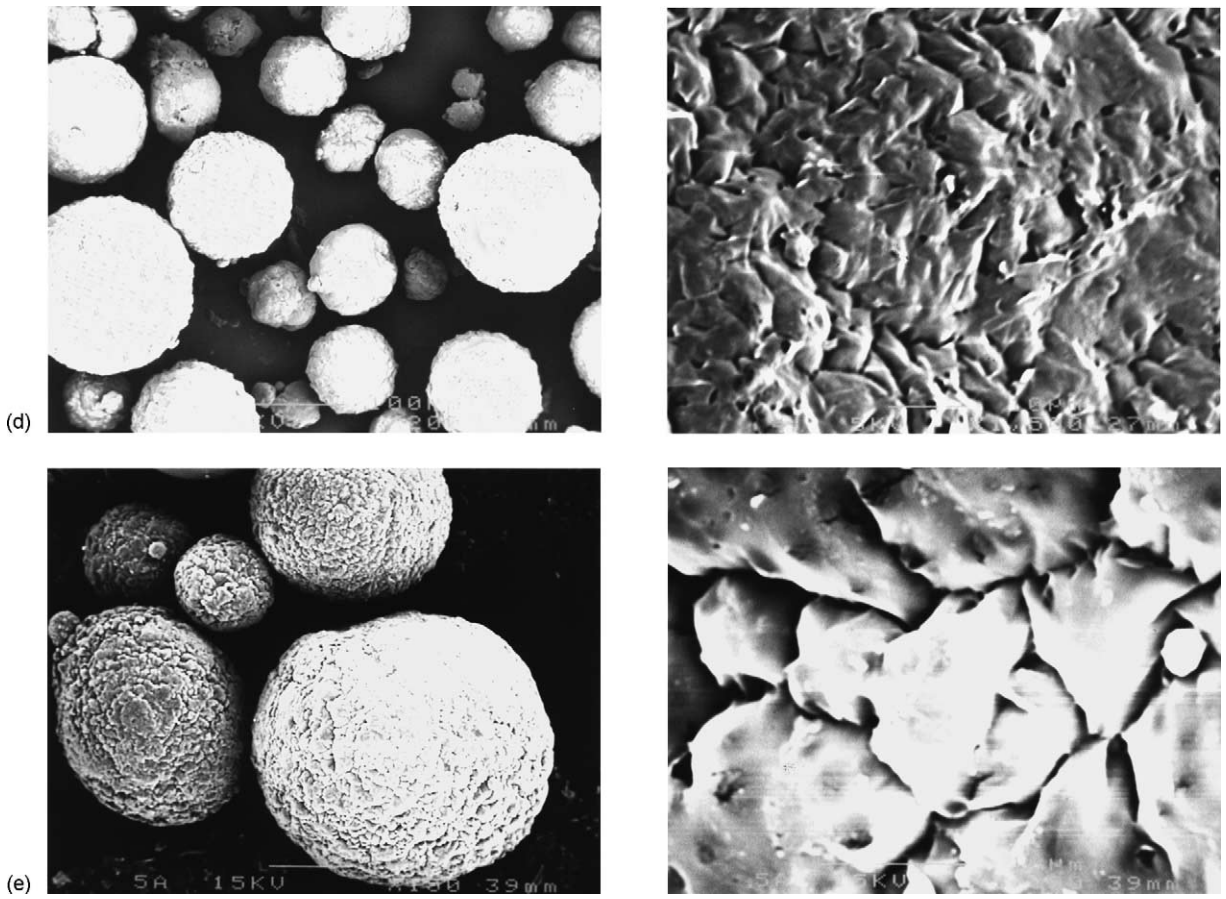

Fig. 1. (*Continued*).

Table 5
The amount of cumulative percent dissolved VRP with half-change method ($n = 3$)

Time (min)	Diss (%) ± S.E.				
	F1	F2	F3	F4	F5
15	42.0 ± 0.897a	31.7 ± 2.41b	30.2 ± 3.60b	25.2 ± 0.639c	22.3 ± 1.15c
30	70.8 ± 4.38a	57.5 ± 6.15b	56.1 ± 5.37b	47.5 ± 0.291c	35.0 ± 1.50d
60	92.4 ± 2.19a	81.9 ± 4.90b	83.4 ± 4.88b	66.2 ± 0.208c	52.8 ± 2.40d
120	99.7 ± 0.333a	93.5 ± 2.68b	96.2 ± 3.35ab	80.5 ± 0.291c	67.4 ± 3.76d
180	99.7 ± 0.333a	94.9 ± 2.45b	96.9 ± 3.10ab	81.9 ± 0.231c	69.7 ± 3.78d
240	99.8 ± 0.167a	95.7 ± 2.49a	96.9 ± 3.07a	82.6 ± 0.233b	70.8 ± 3.81c
300	100 ± 0a	96.1 ± 2.23a	97.0 ± 3.00a	83.3 ± 0.289b	72.0 ± 3.93c
360	100 ± 0a	96.1 ± 2.23a	97.0 ± 3.00a	83.4 ± 0.346b	72.2 ± 3.93c
420	100 ± 0a	96.1 ± 2.23a	97.0 ± 3.00a	83.6 ± 0.346b	72.2 ± 3.93c
480	100 ± 0a	96.1 ± 2.23a	97.0 ± 3.00a	83.7 ± 0.384b	72.4 ± 3.90c
540	100 ± 0a	96.7 ± 2.31a	97.0 ± 3.00a	83.7 ± 0.384b	72.4 ± 3.90c

Letters (a–d) show the difference of dissolved amount between the formulations at the same time point. Different letters means that $P < 0.001$, same letters means that $P > 0.001$.

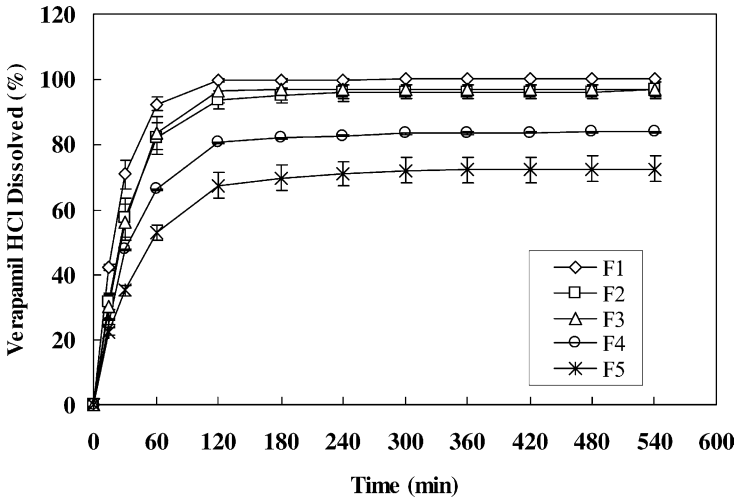

Fig. 2. Dissolution profiles of VRP microspheres prepared with different drug/polymer ratios ($n = 3$) (half-change method: at pH 1.2 for the first 120 min, pH 6.8 from 120 to 300 min, and pH 7.5 from 300 to 540 min by flow through cell method).

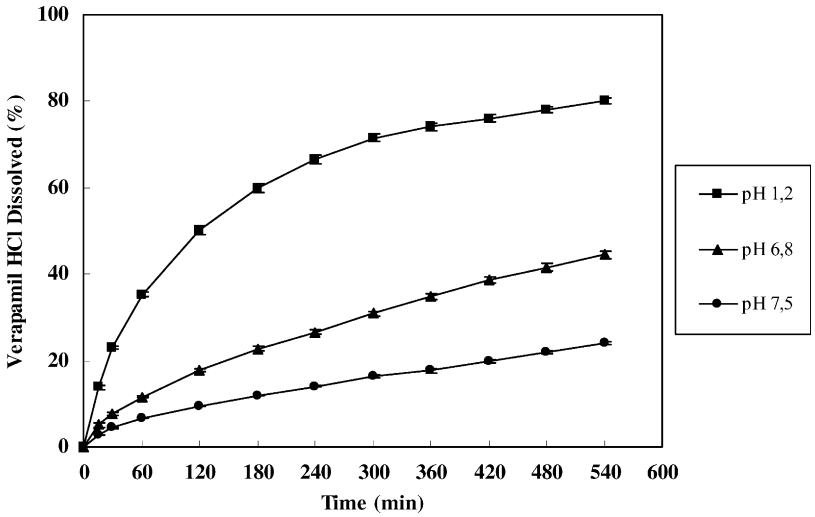

Fig. 3. Dissolution profiles of F5 formulation at the various dissolution medium with different pH by flow through cell method ($n = 3$).

regression by SPSS 9.0 for Windows (Tables 7 and 8) (Higuchi, 1963; Gibaldi and Feldman, 1967; Langenbucher, 1972).

3. Results and discussion

The incorporation efficiencies of VRP into the microspheres were greater than 80%. Incorporation efficiency data were compared by Duncan's Multiple Range Tests, and they were found to be significantly different ($P < 0.001$) depending on the variation of drug/polymer ratio for the formulations investigated (Table 2). The highest incorporation efficiency of F1 formulation can be explained through the fact that the amount of drug in per unit polymer is greater than that in other formulations. Fairly high yield values were obtained from formulations (86.3–99.6%) (Table 2).

Table 6
The amount of cumulative percent dissolved VRP from F5 formulation with various dissolution medium with different pH ($n = 3$)

Time (min)	Diss (%) ± S.E.		
	pH 1.2	pH 6.8	pH 7.5
15	13.8 ± 0.551b	5.08 ± 0.497c	2.73 ± 0.0971d
30	23.0 ± 0.462b	7.61 ± 0.254c	4.42 ± 0.133d
60	35.3 ± 0.500b	11.6 ± 0.203c	6.67 ± 0.0872d
120	50.1 ± 1.04b	17.7 ± 0.273c	9.43 ± 0.0491d
180	59.9 ± 1.01b	22.8 ± 0.437c	11.9 ± 0.0667d
240	66.4 ± 1.04b	26.6 ± 0.470c	14.1 ± 0.153d
300	71.6 ± 0.869a	30.9 ± 0.536b	16.4 ± 0.233c
360	74.1 ± 0.809a	34.9 ± 0.684c	17.6 ± 0.449d
420	76.1 ± 0.780a	38.7 ± 0.742c	19.8 ± 0.393d
480	78.0 ± 0.722a	41.6 ± 0.788c	21.9 ± 0.393d
540	80.0 ± 0.727a	44.5 ± 0.833c	24.0 ± 0.404d

Letters (a–d) show the difference of dissolved amount between the formulations at the same time point. Different letters means that $P < 0.001$, same letters means that $P > 0.001$.

The data describing the particle sizes of the microspheres are given in Table 3. When the particle sizes were examined, it is seen that the particle size decreases with the increasing polymer amount. As some researchers pointed out, particle sizes were also observed to be proportional with dispersed phase viscosities (Pongpaibul and Whitworth, 1986; Malamataris and Avgerinos, 1990; Chiao and Price, 1994; Kim et al., 1994). When the viscosities of dispersed phases at the 10 °C were considered, it was determined that while the viscosities decreased from 20 to 14 mPa s for F1 to F4, the particle sizes also decreased. The bigger difference between dispersed phase and dispersing medium viscosities the lower mean particle sizes (Tables 3 and 4). When the dispersed phase with higher viscosity was poured into the dispersion medium, bigger droplets were formed and mean particle sizes (volume median diameter) increased. In the same way, the surface area of mean diameter and volume mean diameter were also varied like volume median diameter (Table 3). The span value of F4 formulation which has the smallest volume median diameter was the highest

Table 7
Parameters of the mathematical models and descriptive statistics of regression for the dissolution data of formulation F1 to F5 with half-change method

Model	Statistics	F1	F2	F3	F4	F5
First-order	r^2	0.948	0.575	0.657	0.666	0.622
	k	4.067×10^{-2}	6.399×10^{-3}	1.972×10^{-2}	3.258×10^{-3}	2.365×10^{-3}
	S.E.	0.003	0.001	0.004	0	0
	RMS	0.1160	1.065	0.6140	0.1510	9.659×10^{-2}
Higuchi	r^2	0.981	0.701	0.899	0.773	0.790
	k	12.189	3.528	7.741	3.479	3.114
	S.E.	0.5420	0.3950	0.6490	0.3390	0.2280
	RMS	28.15	299.7	149.6	183.0	132.6
Weibull	r^2	0.957	0.795	0.853	0.862	0.846
	T_d	25.41	38.49	38.89	86.26	175.8
	β	1.074	0.5860	0.9410	0.4830	0.4570
	S.E.	0.080	0.053	0.123	0.036	0.037
	RMS	5.583×10^{-3}	2.305×10^{-2}	2.335×10^{-2}	9.512×10^{-3}	9.718×10^{-3}

r^2, determination coefficient; RMS, residual mean square; S.E., standard error of model parameters; k, dissolution rate constant; β, shape parameter; T_d, time at which 63.2 of the material dissolved.

Table 8
Parameters of the mathematical models and descriptive statistics of regression for the dissolution data of F5 formulation at the different pH values

Model	Statistics	pH 1.2	pH 6.8	pH 7.5
First-order	r^2	0.935	0.986	0.977
	k	2.902×10^{-3}	1.046×10^{-3}	4.663×10^{-4}
	S.E.	0	0	0
	RMS	2.050×10^{-2}	5.493×10^{-4}	1.780×10^{-4}
Higuchi	r^2	0.963	0.990	0.990
	k	3.570	1.978	1.025
	S.E.	0.1200	0.0330	0.0180
	RMS	27.72	2.129	0.617
Weibull	r^2	0.992	0.993	0.996
	T_d	8.530	1239	4872
	β	0.450	0.688	0.618
	S.E.	0.007	0.011	0.007
	RMS	4.160×10^{-4}	9.268×10^{-4}	4.090×10^{-4}

r^2, determination coefficient; RMS, residual mean square; S.E., standard error of model parameters; k, dissolution rate constant; β, shape parameter; T_d, time at which 63.2 of the material dissolved.

as can be shown in Table 3. The higher span value of F4 formulation means a broad particle size distribution resulting from the biggest difference between the viscosities of its dispersed phase and dispersing medium compared with the other formulations.

It is seen from Fig. 1 that surfaces of all microspheres are rough and there are several cracks on the surfaces. It is observed that in spite of using the constant polymer/solvent ratio, the depth of cracks on the surface of microspheres become greater while the polymer amount of formulation was increased. This can be attributed to the increasing volume of dispersed phase against to the constant volume of dispersing medium, i.e. liquid paraffin (Table 1) resulting from the extended diffusion of organic solvent to the dispersing medium. Drug crystals were observed on the surface of microspheres of F1 formulation which have the least polymer amount (drug/polymer: 1/2) (Fig. 1a). It can be seen from the micrographs that (Fig. 1d) there are some amorphous granules together with microspheres of F4 formulation with the least dispersed phase viscosity. It is thought that the surface characteristics of microspheres can depend both on the polymer characteristics and on the amount of polymer in the formulations.

It is determined from the in vitro dissolution studies made with half-change method that while the amount of polymer in the formulation increased, the drug release decreased. The results of univariate ANOVA showed that the cumulative percent amounts of dissolved drug were significantly different at each time point for different formulations so time × group interactions were found to be significant in all formulations ($P < 0.001$) (Tables 5 and 6). Differences of percent amount of dissolved drug for different formulations were determined by using Duncan's Multiple Range Tests. Differences between the formulations were defined by letters (a–d) with the mean dissolved drug at each time point for all formulations (Tables 5 and 6). Same letters were used for $P > 0.001$ and different letters were used for $P < 0.001$. Percents dissolved were not significantly different during first 1 h for F2 and F3 (Table 5). Compared to all the other formulations, percent amount of dissolved drug was higher and significantly different ($P < 0.001$) for F1 formulation which have the least polymer amount and the drug crystals on the surface as can be seen from micrographs (Figs. 1a and 2). This situation is due to the fact that scarcity of polymer augmented release of the drug and also the thin polymer wall of microspheres as diffusion path led the drug to be easily released in the dissolution medium. The percent amount of dissolved drugs of F1, F2 and F3 were not significantly different after the forth hours. But it is found that, percent amount of dissolved drug for F5 formulation

which has the highest polymer amount were less than the other formulations (Fig. 2 and Table 5). Differences between F5 and the other formulations were also significant ($P < 0.001$) in all time point (Fig. 2 and Table 5). All these results show that drug dissolution rate could be decreased with increased polymer amount as also being forwarded by some researchers (Pongpaibul et al., 1984; Malamataris and Avgerinos, 1990; Kim et al., 1994). It can be seen from the deeper cracks on the surface of microspheres (Fig. 1e) that as the polymer amount increases the matrix wall of microspheres becomes thicker. The formation of a thicker matrix wall lead to slower dissolution rate of drug caused by longer diffusion path.

According to the dissolution tests conducted by half-change method, F5 formulation gave the lowest dissolution rate. Since VRP has weak basic properties, its solubility varies in parts of gastrointestinal tract with different pH values. We also performed dissolution tests separately in three dissolution media with different pH values (1.2, 6.8 and 7.5) for 8 h by flow through cell to see if the dissolution profiles were identical at these pH values (Fig. 3). As seen from Table 6 and Fig. 3, in pH 1.2 dissolution medium drug dissolution is faster than in the other dissolution media with different pH and the lowest dissolution data were determined with pH 7.5 as expected from a weak basic drug (Kramer and Blume, 1994; Goracinova et al., 1995). Time × group interactions were significant for all medium with different pH for F5 formulation ($P < 0.001$) (Table 6), i.e. that percent amounts of dissolved drug are significantly different and the dissolution profiles are not parallel ($P < 0.001$). These results show a pH dependent release behaviour although a pH independent permeability of polymer, Eudragit RS 100, was used in the formulation.

Mathematical models have been used extensively for the parametric representation of dissolution data (Yüksel et al., 2000). After fitting these models to the dissolution data of formulations which tested with half-change method the selection was based on the comparison of higher determination coefficient and smaller residual mean square (Table 8). Generally, the determination coefficients were low for all mathematical models when applied for half-change method. Because the dissolution profiles showed steeper slope at pH 1.2 and then reached plateaus at pH 6.8 and 7.5 based on the solubility of drug as seen in Fig. 2. However, higher determination coefficients and lower residual mean square data were obtained from Weibull distribution with its parameters describing the types of dissolution profiles and dissolution time. The shape parameter, β, characterizes the profile as either exponential ($\beta = 1$), s-shaped with upward curvature followed by a turning point ($\beta > 1$), or as one with steeper initial slope than consistent with the exponential ($\beta < 1$) (Langenbucher, 1972). All β values were less than 1 except F1 formulation which also fitted to first-order model (Table 7). As can be seen from Tables 7 and 8, determination coefficients of F5 formulations data obtained from single dissolution medium were higher than the half-change method. The time parameter, T_d, represents the time interval necessary to dissolve 63.2% of the drug substance (Langenbucher, 1972). The time parameter is the highest for F5 formulation. While the polymer amounts increased in the formulations the time parameters became bigger (Table 7). The time necessary to dissolve 63.2% of drug substance from F5 microspheres at the pH 7.5 was the highest and at the pH 1.2 was the lowest (Table 8). That also shows that the dissolution of VRP from Eudragit RS 100 microspheres is pH dependent.

In conclusion, VRP loaded microspheres were successfully prepared by solvent evaporation method using Eudragit RS 100. It is established that the drug dissolution profile could be slowed down by increasing polymer amount in the formulations and the particle size, surface characteristics of microspheres, and dissolution rate of VRP could be modified through the variation of drug/polymer ratio.

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