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Original article

EFFECTS OF STIRRING RATE AND DRUG: POLYMER RATIO ON THE CHARACTERISTICS OF LEVOBUNOLOL HCL LOADED POLY (ε-CAPROLACTONE) MICROPARTICLES

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Abstract

In this study, the effects of stirring rates (8000, 9500, 13500 rpm) and drug:polymer ratios (1:25, 4:25, 6:25) on the pharmaceutical characteristics of Levobunolol HCl-loaded poly (ε-caprolactone) microparticles in order to optimize formulations for ocular delivery were examined.

Microparticles were prepared using multiple emulsion (W/O/W) solvent evaporation technique. Microparticles were characterized in terms of surface morphology, drug loading efficiency, production yield, particle size and size distribution, drug release, zeta potential and residual solvent. The physical state of microparticles was also determined by scanning electron microscopy (SEM).

Spherical, smoother particles were obtained with a drug:polymer ratio of 6:25 at 8000 rpm. Drug:polymer ratio played greater role on drug loading efficiency than stirring rate. An increase in the stirring rate from 8000 to 9500 rpm resulted a decrease in particle size at all drug:polymer ratios. The fasted drug release and the highest drug-loading efficiency obtained from formulation of A10 prepared with 1:25 drug:polymer ratio at the stirring rate of 8000 rpm. Drug release was mainly fitted to the Higuchi model.

The findings showed that both stirring rates and drug:polymer ratios had an effect on the pharmaceutical properties of microparticles.

Key words: *Stirring rate, Drug:polymer ratio, Levobunolol HCl, Poly (ε-caprolactone), Microparticles*

Karıştırma Hızı ve Etkin Madde:Polimer Oranının Levobunolol HCl Yüklenmiş Poli (ε-kaprolakton) Mikropartiküllerinin Karakteristikleri Üzerindeki Etkileri

Bu çalışmada, oküler salım amacıyla formülasyonları optimize etmek için Levobunolol HCl yüklenmiş Poli (ε-kaprolakton) mikropartiküllerinin karakteristikleri üzerinde karıştırma hızlarının (8000, 9500, 13500 rpm) ve etkin madde:polimer oranlarının (1:25, 4:25, 6:25) etkileri incelenmiştir.

Mikropartiküller çoklu emülsiyon (S/Y/S) çözücü buharlaştırılması tekniği kullanılarak hazırlandı. Mikropartiküller, yüzey morfolojisi, etkin madde yükleme etkinliği, ürün verimi, partikül büyüklüğü ve dağılımı, zeta potansiyeli ve artık çözücü açısından tanımlanmıştır. Mikropartiküllerin fiziksel durumu da taramalı elektron mikroskopisiyle (SEM) tayin edilmiştir.

Küresel ve daha düzgün yüzeyli partiküller 8000 rpm de, 6:25 etkin madde:polimer oranı ile elde edilmiştir. Etkin madde yükleme etkinliği üzerinde etkin madde:polimer oranı karıştırma hızından daha fazla etkili olmuştur. Karıştırma hızının 8000 den 9500 rpm'e çıkarılması tüm etkin madde:polimer oranları için partikül büyüklüğünde azalma ile sonuçlamıştır. En fazla yükleme etkinliği ve en hızlı etkin madde salımı 8000 rpm karıştırma hızında ve 1:25 etkin madde:polimer oranında hazırlanan A10 formülasyonu ile elde edilmiştir. Etkin madde salımı başlıca Higuchi modeline uyum göstermiştir.

Bulgular hem karıştırma hızlarının hem de etkin madde:polimer oranlarının mikropartiküllerin farmasötik özelliklerin üzerinde etkisinin olduğunu göstermiştir.

Anahtar kelimeler: *Karıştırma hızı, Etkin madde:polimer oranı, Levobunolol HCl, Poli (ε-kaprolakton), Mikropartiküller*

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INTRODUCTION

Levobunolol-HCl (L-HCl) is a nonselective beta-blocker commonly used in the topical treatment of increased intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension (1). Beta-blockers applied topically to the eye are often associated with systemic toxicity and heart-related side effects caused by transconjunctival absorption and transnasal absorption after drainage via the nasolacrimal duct (2,3).

Poly (ε-caprolactone) (PCL) is a biocompatible, biodegradeble polymer used to encapsulate ophthalmic drugs. The hydrophobicity, in vitro stability and low cost of PCL have led to investigation into its potential as an ocular colloidal carrier of β-blocking agents and indomethacin (4,5).

In this study, microparticles loaded with L-HCl were prepared to increase the drug's residence time in the eye, thereby reducing wastage and minimizing side effects. The multiple emulsion water-in-oil-in-water (W/O/W) solvent evaporation technique was used to encapsulate the hydrophilic L-HCl. Other hydrophilic drugs such as bovine serum albumin (5), propranolol HCl (6) and nifedipine (7) have been encapsulated in PCL using the W/O/W technique. Although conceptually simple, there are numerous variables involved in the technique that affect microparticle characteristics, including loading efficiency, morphology, particle size, zeta potential and release behaviour (8).

Several studies have attempted to examine the effects of process parameters such as drug:polymer ratios and stirring rates on the properties of particular dosage forms. Quintanar-Guerrero et al. (9) reported that nanoparticle size and polydispersity were influenced by polymer concentrations and stirring rates. Jelvehgari et al. (10) showed that drug:polymer ratio, stirring rate and the volume of the dispersed phase influenced the particle size and drug-release behaviour of benzoil peroxide-loaded microsponges. Luan et al. (11) also looked at how factors such as external phase volume, homogenization speed, stirring time affected drug loading efficiency and initial release of peptide containinig poly (lactide-co-glycolide) microparticles.

The present study was designed to examine the effects of two process parameters (drug:polymer ratio and stirring rate) on the drug loading efficiency, production yield, surface properties, particle size, drug release characteristics and zeta potential of levobunolol HCl-loaded microparticles.

EXPERIMENTAL

Materials

L-HCl was provided by Abdi İbrahim (Turkey); PCL (M.w. 80000) was supplied by the Aldrich Chemical Company, Inc. (Milwaukee, USA); Polyvinyl alcohol (PVA) (Mowiol 4-88, M.w. 31000) was provided by Hoechst (Frankfurt/Main, Germany); and dialysis tubes (diameter 23mm, M.w. Cutoff: 12400) and appropriate closures were provided by Sigma (Steinheim, Germany). All other chemicals were purchased as analytical grade.

Microparticle preparation

L-HCl-loaded microparticles were prepared using the multiple emulsion (W/O/W) solvent evaporation technique (6, 12). The drug was dissolved in 1 mL of distilled water and emulsified into a polymer (PCL) solution in 10 mL of dichloromethane using an Ultraturrax (Kilca Labortechnick T25 basic) at 8000, 9500, or 13500 rpm. The resulting primary emulsion was poured into 100 mL of 0.5% (w/v) aqueous solution of stabilizer (PVA) at pH 12 and homogenized using an Ultraturrax at 8000, 9500, or 13500 rpm for 3 min. The solvent was

evaporated from the W/O/W emulsion by stirring for 3 hours at 1500 rpm using a three-bladed propeller (Stir-pak® Cole Parmer Inst. Co.) at 25°C. Microparticles were collected by centrifugation at 30000 rpm for 10 min (Beckman Optima XL 100K) and washed twice with water before freeze-drying (Christ® Gamma 2-16, LSC). Details of the formulations are shown in Table 1.

Table 1. Microparticle Formulations*.

Code	Stirring Rate (rpm)	Amount of Drug (mg)	Amount of Polymer (mg)	Drug:polymer Ratio
A10	8000	10	250	1:25
A40	8000	40	250	4:25
A60	8000	60	250	6:25
B10	9500	10	250	1:25
B40	9500	40	250	4:25
B60	9500	60	250	6:25
C10	13500	10	250	1:25
C40	13500	40	250	4:25
C60	13500	60	250	6:25

* Internal phase volume =1 mL
External phase volume = 200 mL
PVA % (w/v) = 0.5
pH of external phase =12

Drug loading efficiency and production yields

The amount of L-HCl in the microparticles was calculated by measuring the mass of non-entrapped drug recovered from the supernatant following ultracentrifugation using UV spectrophotometry at 314 nm (Shimadzu UV visible 1202). Analytical validation of spectrophotometric results was performed in water (supernatant) according to ICH Guideline Q2R1 (13,14). Validation consisted of measuring linearity and range, accuracy, precision, limit of detection (LOD) and limit of quantification (LOQ). Reproducibility results were estimated using two different concentrations of L-HCl 5 times on the same day to determine relative standard deviation (RSD%) for showing the precision of the method. Accuracy describes the closeness of mean test results by the method to nominal concentration of the analyt. Calibration curves for L-HCl samples in water were drawn by plotting L-HCl absorbance *vs* concentration, which yielded a correlation coefficient (r) of 0.999, showing good linearity, over a concentration range of 1.5-96 μgmL^{-1}. The limit of detection (LOD) and the limit of quantification (LOQ) were calculated in water using the following equations: LOD= 3 s/m; LOQ= 10 s/m, where s is the standard deviation of response and m is the slope of the calibration curve. LOD and LOQ were found to be 0.091μgmL^{-1} and LOQ of 0.276 μgmL^{-1}, respectively. Reproducibility was found as 1.27 %. Mean recovery was found as 100.5%, with RSD value of 0.36 %, showing good accuracy. Solution stability was checked by comparing standard solutions of L-HCl in water aged at +4°C and 25°C in the dark against a freshly prepared sample, with results showing the working reference solutions to be stable for up to 7 days.

The mass of drug in microparticles, drug entrapment efficiency (%) and production yield (%) were calculated using the equations below (6, 15,16). Results are given in Table 2.

$$\text{Mass of drug in microparticles} = \text{Mass of drug used in formulation} - \text{Drug mass at supernatant}$$

$$\text{Drug loading efficiency (\%)} = \frac{\text{Mass of drug in microparticles}}{\text{Mass of drug used in formulation}} \text{ X } 100$$

$$\text{Production yield (\%)} = \frac{\text{Mass of microparticles recovered}}{\text{Mass of polymeric material, drug and excipient used in formulation}} \text{ X } 100$$

Surface morphology

Microparticle surface morphology was recorded by SEM (JSM-840A, JEOL, Japan). Microparticles were mounted onto metal stubs using double-sided adhesive tape, vacuum-coated with a thin layer (200 Å) of gold and examined at 20 kV.

Particle size and size distribution

Mean particle size and size distribution were recorded by laser diffractometry using a Mastersizer Hydro 2000S (Malvern Instruments, UK) (Table 2). Prior to measurement, samples were dispersed in 5 ml aqueous solution and ultrasonicated for 30 s. Analysis were carried out in triplicate. Mean particle size was represented as the volume mean microparticle diameter (*D* (0.5)).

Zeta potential

Zeta potential was measured by laser Doppler anemometry (Zetasizer NanoZS, Malvern, UK) in a pH 7.4 phosphate buffer. Mean values and standard deviations for each sample were calculated from three measurements.

In vitro release studies

In vitro release of microparticles was examined using a dialysis tube as described by Miyazaki et al. (17). PCL microparticles containing 0.25 mg L-HCl were suspended in 100 µL of pH 7.4 isotonic phosphate buffer in the dialysis tube, hermetically sealed and dropped into 10 mL of pH 7.4 isotonic phosphate buffer at 35°C (ocular surface temperature). The total volume of the receptor buffer solution was removed at predetermined time intervals (15, 30, 60, 120, 180, 240, 360 min) and replaced with 10 mL of fresh buffer medium. All tests were performed in triplicate. Drug concentrations in the buffer were measured using UV spectrophotometry (Shimadzu, UV visible 1202) at 314.5 nm. Analytic validation at the pH 7.4 buffer showed linearity (r = 0.999) over a concentration range of 1.5-96 µgmL^{-1}, 100.13% accuracy (0.53% RSD), Reproducibility was found as RSD value of 0.60, and LOD and LOQ values was found as 0.0372 µgmL^{-1} and 0.1127 µgmL^{-1}, respectively. The results showed that the working reference solutions remained stable for up to 7 days.

Linear regression analysis of in vitro release data was carried out, and mathematical models (zero-order, first-order, Higuchi) were fitted to individual release data using SPSS 15.0 for Windows (18) (Table 3).

Residual solvent

The presence of residual dichloromethane at stirring rates both 8000 rpm and 13500 rpm was determined by gas chromatography equipped with flame ionisation detector (Agilent 6890N Network GC system) using an HP Innowax capillary column (60.0 m x 0.25 mm x 0.25 μm) and helium (1.0 μL) as the carrier gas. The temperatures were selected as follows: injector temperature 60 ºC for 30 min and detector temperature 250 ºC. Each microparticle batch was analysed in triplicate.

RESULTS AND DISCUSSION

Surface morphology

Figures 1a-e show the surface morphology of L-HC1 loaded microparticles fabricated at different stirring rates and drug:polymer ratios. It can be seen in Figures 1a-c, an increase in the stirring rate from 8000 (A10) to 9500 (B10) and 13500 (C10) rpm resulted in pitted and collapsed microparticles at the lowest drug:polymer ratio (1:25). The poor surface characteristics and irregular shapes were attributed to an increase in the speed of drug dissolution and the rate of crystallization of PCL polymer from the organic solvent caused by the increased stirring rate (19). By increasing the drug:polymer ratio from 1:25 (C10) to 6:25 (C60) at 13500 rpm, it was possible to obtain spherical, smooth and homogeneously distributed particles with no evidence of collapse; however, as the SEM image of C60 (Figure 1d) shows, cocoon-like formations adhered to the microparticle surfaces were attributed to polymer residues present on the microparticle surfaces. Spherical, smoother and homogeneously distributed particles with no evidence of collapse were also obtained with a drug:polymer ratio of 6:25 at 8000 rpm (A60) (Figure 1e), with no residual formations on the microparticle surfaces.

Drug loading efficiency and production yield

The effects of drug:polymer ratio and stirring rate on drug-loading efficiency and production yield are shown in Table 2. As the drug:polymer ratio increased from 1:25 to 6:25, drug-loading efficiency decreased from 30.6% (A10) to 16.5% (A60) at a stirring rate of 8000 rpm and from 18.6% (B10) to 13.8% (B60) at 9500 rpm. These results appeared to indicate that the drug:polymer ratio played a greater role on loading efficiency than the stirring rate, and that as the amount of drug in the formulation increased, there was an increase in the amount of drug migrating to the external aqueous phase, but the amount of polymer was insufficient to encapsulate the increased amount of drug into microparticles, resulting in a decrease in loading efficiency. In contrast, at a stirring rate of 13500 rpm, drug-loading efficiency increased with an increase in drug:polymer ratio, from 10.6% at 1:25 (C10) to 20.3% at 6:25 (C60) (Table 2). This difference in loading efficiency was possible as a result of a decrease in the amount of the drug migrating to the external phase because of rapid polymer precipitation caused by rapid evaporation of the organic solvent at the higher stirring rate. Huatan et al. (19) also reported an increase in entrapment efficiency with an increase in the protein-to-polymer ratio in their entrapment of hydrophilic protein, bovine serum albumin (BSA), into ternary blend based on PCL microspheres.

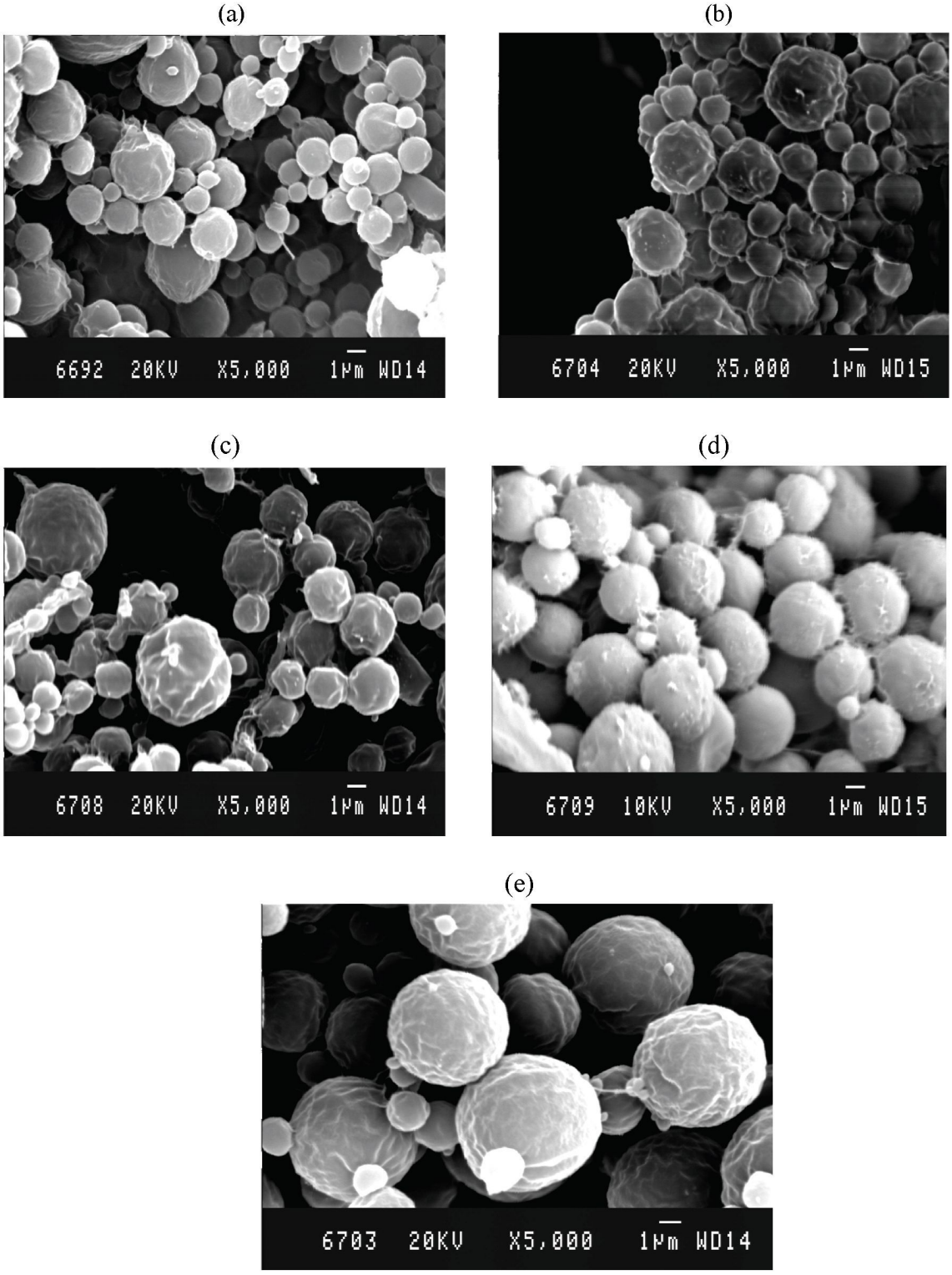

Figure 1. Micrographs of microparticles prepared at different stirring rates and drug:polymer ratios (a) 8000 rpm, 1:25 ratio (A10) (b) 9500 rpm, 1:25 ratio (B10) (c) 13500 rpm, 1:25 ratio (C10) (d) 13500 rpm, 6:25 ratio (C60) (e) 8000 rpm, 6:25 ratio (A60).

Table 2. Microparticle properties as a function of stirring rate and drug: polymer ratio.

Code	Production Yield (%)	Drug Loading Efficiency (%)	*D* (0.5) ± SD[a] (μm)	Span[b] ± SD[a]	Zeta Potential (mV) ± SD[a]
A10	55.8	30.6	7.88 ± 0.0930	5.92 ± 0.454	- 19.8 ± 3.15
A40	26.2	22.6	5.66 ± 0.467	9.59 ± 2.35	- 11.6 ± 0.611
A60	31.9	16.5	8.13 ±0.240	7.13 ± 0.250	- 21.2 ± 0.404
B10	72.0	18.6	2.88 ±0.107	9.39 ± 4.42	- 6.39 ±1.39
B40	50.7	19.2	3.37 ± 0.0318	12.8 ± 0.455	- 21.9 ±2.35
B60	58.3	13.8	4.22 ± 0.0401	2.46 ± 0.120	- 5.88 ±1.06
C10	56.8	10.6	4.58 ± 0.707	17.9 ± 16.2	- 10.2 ±0.115
C40	58.5	21.8	4.19 ± 0.183	13.4 ± 9.01	- 11.7 ± 1.10
C60	49.5	20.3	8.19 ± 0.190	5.48 ± 0.852	- 5.89 ± 0.952

[a]Standard Deviation , *n=3*
[b]Span = *D* (0.9)- *D* (0.1) / *D* (0.5), where *D* (0.9), *D* (0.1) and *D* (0.5) are, respectively, the sizes in diameters at 90%, 10% and 50% of the undersized particle distribution curve.

When the drug:polymer ratio remained constant at 1:25, increasing the stirring rate led to a decrease in drug-loading efficiency from 30.6% at 8000 rpm (A10) to 18.6% at 9500 (B10) and 10.6% at 13500 rpm (C10). However, at drug:polymer ratios of 4:25 and 6:25, increasing the stirring rate did not significantly affect drug-loading efficiency (Table 2). In their studies, Elbahri and Taverdet (20) and Luan et al. (11) reported that stirring speed did not have a significant effect on drug-loading efficiency.

An increase in the drug:polymer ratio from 1:25 to 6:25 also resulted in a decreased in production yields from 55.8% (A10) to 31.9% (A60) at 8000 rpm, from 72% (B10) to 58.3% at 9500 rpm (B60) and from 56.8% (C10) to 49.5% (C60) at 13500 rpm. However, production yields were not significantly affected by stirring rates (Table 2). This finding contrasts with that of Jelvehgari et al (10), who reported a decrease in production yield with an increase in stirring rate because of an increase in the amount of polymer adhering to the paddle and container due to increased diffusion turbulence and frothing within the external phase.

Particle size and size distribution

The effects of drug:polymer ratio and stirring rate on particle size are shown in Table 2. An increase in the stirring rate from 8000 rpm to 9500 rpm resulted in a decrease in mean particle size from 7.88 μm (A10) to 2.88 μm (B10) at a drug:polymer ratio of 1:25, from 5.66 μm (A40) to 3.37 μm (B40) at 4:25 and from 8.13 μm (A60) to 4.22 μm (B60) at 6:25; however, at a stirring rate of 13500, an increase in drug:polymer ratio was found to have no significant effect on particle size. Other authors have reported mean particle size to decrease with increases in stirring rates (9, 10, 21, 22).

An increase in the drug:polymer ratio from 1:25 to 6:25 resulted in an increase in the mean particle size at all stirring rates. This is in line with Chiao and Price (23), who found that increasing the drug:polymer ratio from 0.5:1 to 1:1 led to an increase in the size of propranolol HCl microspheres, which they attributed to a higher internal-phase viscosity resulting from the increased drug:polymer ratio.

The effects of drug:polymer ratio and stirring rate on microparticle polydispersity as represented by Span value is shown in Table 2. The effects of drug:polymer ratio and stirring

rate on polydispersity were inconsistent. An increase in drug:polymer ratio from 1:25 to 6:25 resulted in an increase in polydispersity from 5.92 to 7.13 at 8000 rpm, but a decrease in polydispersity from 9.39 to 2.46 at 9500 rpm and from 17.9 to 5.48 at 13500 rpm.

Zeta potential

The effects of drug:polymer ratio and stirring rate on microparticle zeta potentials are shown in Table 2. Measurements ranged from - 5.88 to - 21.2 mV. These negative charges can be explained by the presence of PCL and PVA, both of which have strong negative charges (24, 25). It has been suggested that full electrostatic stabilization requires a zeta potential of > 30 mV, whereas potentials between 5 mV and 15 mV result in limited flocculation, and those between – 5 mV and + 3 mV yield maximum flocculation (26). Accordingly, the zeta potentials in the present study were in the range of limited electrostatic stabilization potential. At the higher stirring rates (9500 and 13500 rpm), zeta potential values obtained as - 5.88 mV (B60) and - 5.89 mV (C60), respectively. Zeta potentials of microparticles were also influenced by the highest drug:polymer ratio (6:25). As the SEM micrograph of C60 shows, in this formulation, microparticles tended to aggregate with polymeric extensions between them (Figure 1d).

In vitro release studies

In vitro release profiles are shown in Figures 2-4. Of all the formulations tested, A10 (1:25 drug:polymer ratio at a stirring rate of 8000 rpm) had the fastest drug release as well as the highest drug-loading efficiency (30.6 %) (Figure 2, Table 2). The rapid release was probably due to the adsorption of most of the drug on or close to the microparticle surfaces (6).

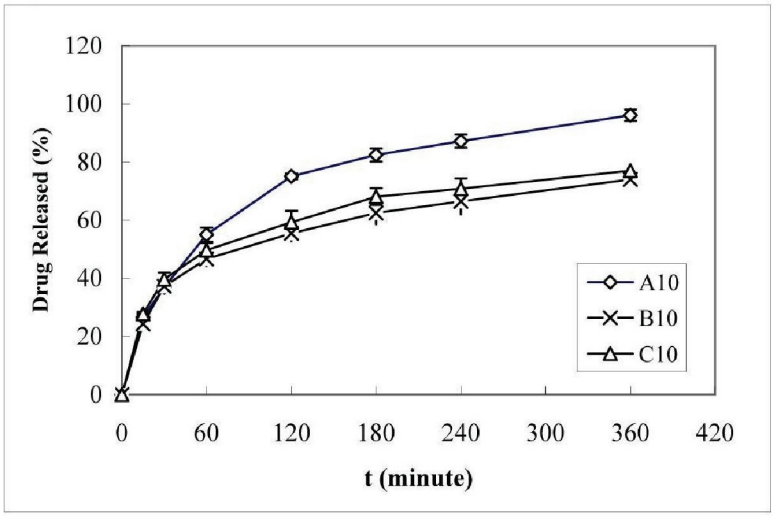

Figure 2. Drug release profiles of microparticles at 1:25 drug:polymer ratio with three different stirring rates (n=3).

As Figure 3 shows, at 4:25 drug:polymer ratio, the drug-release profiles for microparticles formulated with stirring rates of 8000 rpm (A40) and 9500 rpm (B40) were similar and significantly higher than microparticles formulated at 13500 rpm (C40). The reason for the difference in release behaviors (between A40 and C40, B40 and C40) is unclear; however, since there were no significant differences in particle size or drug-loading efficiency among formulations A40, B40 and C40 (Table 2), the difference in release behaviors can not be related to either particle size or drug-loading efficiency. At 13500 rpm, drug-release profiles of formulations with 4:25 (C40) and 6:25 (C60) drug:polymer ratios were slower than that of the

1:25 formulation (C10). In this case, the slower drug release could be explained by the tight polymer layer formed by the quicker evaporation of the solvent at the higher stirring rate. For each of the three stirring rates tested, the 6:25 drug: polymer ratio resulted in the slowest release profiles, all of which were similar (Figure 4).

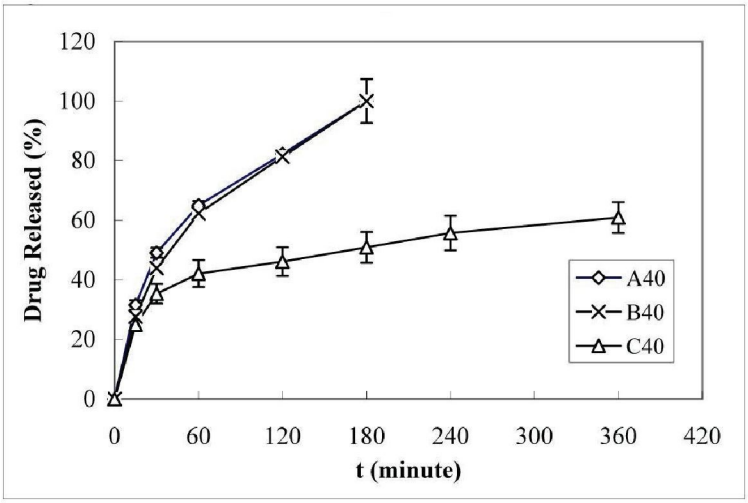

Figure 3. Drug release profiles of microparticles at 4:25 drug:polymer ratio with three different stirring rates (n=3).

This finding is contrast to other studies (27, 28), which suggested that longer diffusion paths were responsible for the slower drug-release profiles found to be associated with lower drug:polymer ratios. Release profiles of A60, B60 and C60 suggest that the high stirring rate had no effect on drug release at the highest drug: polymer ratio. In comparison to the other formulations tested, microparticles C60 (Figure 1 d) and A60 (Figure 1 e) were observed to have smoother, more spherical surfaces composed of a tight polymer layer, and these surface characteristics appear to be responsible for the slower release profiles of these microparticles.

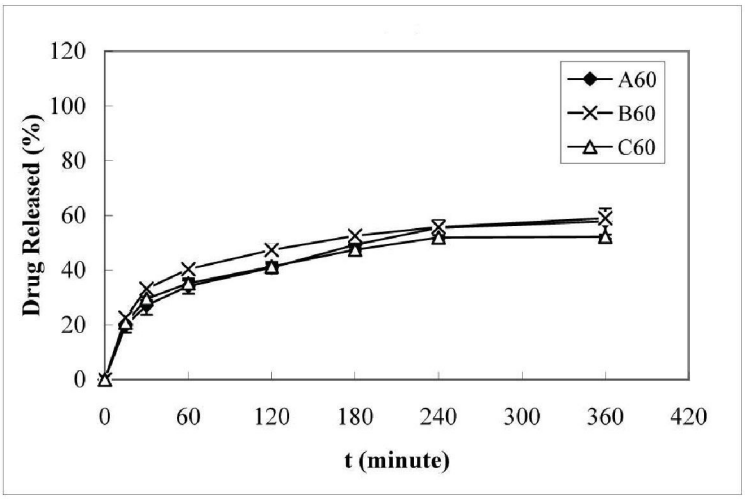

Figure 4. Drug release profiles of microparticles at 6:25 drug:polymer ratio with three different stirring rates (n=3).

Microparticle release mechanisms were assessed by comparing their respective determination coefficients (r^2) (Table 3). Drug release was shown to follow a Higuchi model, with the release mechanism apparently controlled by a rapid diffusion-release process, rather than polymer degradation.

Table 3. Parameters of mathematical models and descriptive statistics of regression for drug-release data*.

Model	Statistics	A10	A40	A60	B10	B40	B60	C10	C40	C60
Zero order	r^2	0.774	0.717	0.740	0.692	0.724	0.658	0.674	0.605	0.650
	k_0	-0.235	-0.211	0.136	-0.160	-0.197	-0.125	-0.0173	-0.124	-0.114
	SE	0.027	0.028	0.017	0.023	0.029	0.021	0.026	0.023	0.018
	RMS	247	269	100	174	271	139	222	173	107
First order	r^2	0.614	0.582	0.806	0.808	0.745	0.768	0.791	0.677	0.739
	k_1	-0.120	-0.015	-0.002	0.003	-0.004	-0.002	0.004	-0.002	-0.002
	SE	0.002	0.003	0.001	0.001	0.001	0.001	0.001	0.001	0.001
	RMS	1.41	2.52	0.018	0.035	0.079	0.022	0.056	0.038	0.017
Higuchi	r^2	0.950	0.914	0.910	0.898	0.894	0.878	0.839	0.805	0.870
	k	5.19	4.74	3.01	3.62	4.42	2.91	3.84	2.89	2.62
	SE	0.254	0.309	0.201	0.261	0.359	2.25	3.36	0.327	0.215
	RMS	54.9	81.5	34.5	58.1	104	49.9	109	85.4	39.5

* r^2, determination coefficient; RMS, residual mean square; SE, standard error of model parameters; k, dissolution rate constant.

Residual solvent

No residual dichloromethane was detected in the L-HCl-loaded microparticles. Of all the organic solvents, dichloromethane has the highest water-solubility and the lowest heat of evaporation. The rate of solvent diffusion in the aqueous phase and its removal from the water/air interface by evaporation are related to the water solubility of the solvent (8). The further evaporation of dichloromethane during microparticles lyophilization ensured that no residual amounts of solvent remained.

CONCLUSION

The findings of the present study showed that both drug: polymer ratio and stirring rate had an effect on the pharmaceutical properties of L-HC1-loaded PCL microparticles. At a constant drug:polymer ratio of 1:25, an increase in stirring rate caused a change in microparticle surface characteristics from relatively smooth and regular in shape (Figure 1a) to dimpled and irregular (Figures 1b,c). An increase in stirring rate from 8000 to 9500 rpm also resulted in a decrease in particle size for all drug: polymer ratios tested. For all stirring rates tested, microparticles formulated with the highest drug:polymer ratios had the slowest release characteristics. Whereas in vitro release of L-HCl from microparticles was closely correlated with drug:polymer ratios, there was no correlation between in-vitro release characteristics and stirring rates. Drug release from L-HCl microparticles was shown to be governed by diffusion.

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