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RESEARCH PAPER

Sustained-Release Dosage Form of Nicardipine Hydrochloride: Application of Factorial Design and Effect of Surfactant on Release Kinetics

M. Özyazici, F. Sevgi, and G. Ertan

Ege University, Faculty of Pharmacy, Pharmaceutical Technology Department, 35100, Bornova, İzmir, Turkey

ABSTRACT

Microcapsules of nicardipine hydrochloride with core:wall ratios of 1:1, 2:1, and 1:2 were prepared by the coacervation-phase separation method, using ethylcellulose as the coating material. Two batches of nicardipine hydrochloride microscapsules were divided into size fraction by using standard sieves ranging from 840 μm to 476 μm. Dissolution rate studies from microcapsules were performed using the USP XXII basket method. The kinetic model according to the Rosin-Rammler-Sperling-Bennet-Weibull (RRSBW) distribution was applied for the parametric representation of the dissolution curves. Preparation and dissolution rate studies on the nicardipine hydrochloride microcapsules were performed and the influence of particle size, core:wall ratio, and the amount of nicardipine hydrochloride on the release rate was examined by 2^3 factorial design. The significance of the observed effects was tested with the F test. A surface active substance was added in the dissolution medium to understand how this substance effects the release of drug from ideal microcapsule form which is found by the findings of the 2^3 factorial design. Dissolution studies were repeated with this ideal formulation using different ratio of Tween 20.

The results of this study suggested that the solubility and bioavailability of the sustained-release dosage forms of nicardipine hydrochloride using surface active substances could be increased.

INTRODUCTION

The active substance of this investigation, nicardipine hydrochloride [2-(N-methylbenzylamino) ethylmethyl 1,4-dihydro-2,6-methyl-4-(3-nitrophenyl)pyridine 3,4,5-dicarboxylate)] is a new calcium channel-blocking agent, classified with the dihydropyridine derivatives (1,2). Several kinds of preparations have been proposed for the administration of nicardipine hydrochloride. Tablets, capsules, and coated pellets have been suggested for use as oral extended release formulations (3,4). Nowadays, this drug is widely used for the treatment of hypertension, angina pectoris, and cerebrovascular disease but its bioavailability is very limited (15–45%) (5,6). Its elimination half-life is also very short (about 1 hr) and it has some side effects such as nausea, vomiting, flushing, headache, dyspepsia, anorexia, and diarrhea, probably due to rapid absorption or gastric irritation (3,7). Therefore, some sustained-release formulations such as alginate gel beds, tablets, granules, and microspheres of nicardipine hydrochloride have been presented (8,9), but it is known that to prepare a sustained-release dosage form of a drug which can be soluble easily in acidic solution but poorly in alkaline solutions is difficult (10). The purpose of the present study was to prepare nicardipine hydrochloride microcapsules by using coacervation phase separation technique (11) and the release mechanism of nicardipine hydrochloride from microcapsules was also discussed.

Factorial designs are the designs of choice for simultaneous determination of the effects of several factors and their interactions (12). The application of factorial design to preformulation and stability studies (13,14), film coated tablets (15), tablet formulations (16), microcapsules (17,18), and tableted microcapsules (19,20) has been previously reported. Factorial designs may be useful for screening purpose or as an aid in identifying individual effects in complex systems. It offers a good degree of accuracy and the possibility of detecting interactions between factors. Factor effectiveness can be expressed with a mathematical model which explains the influence numerically (21). The objective in this work is to outline 2^3 factorial design and to study the effect of three factors; core:wall ratio, amount of nicardipine hydrochloride, and particle size on the dissolution rate of nicardipine hydrochloride from microcapsules. The ideal microcapsule formulation was found by evaluating of these findings.

The influence of surface-active agents on the dissolution rates of relatively water-insoluble drugs may involve several mechanisms. It is well known that surfactants increase the solubility and dissolution rate of poorly soluble drugs, and their effects on dissolution rate and solubility are important in determining the limits of drug availability (22–28). It was the purpose of the present study to determine the possible effects of premicellar concentrations of surfactant on the dissolution rate of ideal nicardipine hydrochloride microcapsules in order to increase bioavailability.

MATERIALS AND METHODS

Materials

Nicardipine hydrochloride (Yamanouchi Pharm. Co. Ltd., Japan); ethylcellulose (ethoxy number 48 and Type N-10) (Sigma, St. Louis, USA); cyclohexane (Merck, Darmstadt, Germany); Tween 20 (Atlas Chem. Industries Inc. Wilmington, DE); the other chemicals used are of analytical grade.

Methods

Factorial Design Experiments

The effect of core:wall ratio (A), amount of nicardipine hydrochloride (B), and particle size (C) were studied in separate 2^3 factorial experiments. The levels and variation intervals for the eight treatment combinations are the calculation matrix for a 2^3 factorial design, with the following combinations of factors A, B, and C at two levels: (1),a,b,ab,c,ac,bc, and abc (29).

Preparation of Nicardipine Hydrochloride Microcapsules

The microcapsules of nicardipine hydrochloride were prepared by means of a coacervation-phase separation method using ethylcellulose as the coating material (11). In a 500 ml three necked flask fitted with a stirrer, thermometer, and a reflux, 200 ml of cyclohexane was placed. 4 g of ethylcellulose as coating material was added at 50°C by continuously stirring at 500 rpm. Then, it was raised from 70°C to 80°C over a period of 75 min. The core material was then dispersed in the polymer solution by stirring at 500 rpm over 10 min. The system was cooled within 30 min by continuous stirring. Nicardipine hydrochloride microcapsules, coated with ethylcellulose, were separated by filtration and dried at room temperature.

Assay of Nicardipine Hydrochloride

Batches of 10 mg powdered microcapsules of different core:wall ratio were extracted 10 times with 10 ml simulated gastric fluid (SGF) without enzyme (USP XXII) (30). These samples were assayed spectrophotometrically at 239.4 nm.

Particle Size Distribution

Particle size distribution of the microcapsules is determined by sieve analysis. Microcapsules retained at sieves of 840–247 μm sizes are used in the dissolution experiments.

Scanning Electron Microscopic Experiments

The starting materials, nicardipine hydrochloride and its microcapsule form were evaluated by scanning electron microscopy (SEM). Particles were coated with 200 A° gold in vacuum. The SE micrographs were obtained using a JEOL-JSM-5200 Scanning Electron Microscope.

In Vitro Dissolution Rate Experiments

The USP XXII rotating basket method is used in the dissolution rate experiments. The mesh size of the basket is 40. The rotating speed used is 100 rpm. The dissolution media used are simulated gastric fluid (SGF) without enzyme. At various time intervals, 2 ml of the sample solutions were taken and replaced by an equal volume of dissolution medium (SGF pH = 1.2). The microcapsules coded in Table 1 were used in the in vitro dissolution studies.

2:1 core:wall ratio which has 840–476 μm particle size microcapsules (M4) was found as a ideal form according to the factorial design calculations and dissolution tests were repeated using this microcapsules with the changing amount of Tween 20 (Polysorbate 20) added in the medium. Code numbers and amounts of Tween 20 which were used in dissolution tests, are shown in Table 2.

Kinetic Evaluation of Dissolution Rate Results

All of the results thus obtained were evaluated kinetically by zero and first order, Hixson-Crowell, RRSBW, $Q/\sqrt{t}$, $(Bt)^a$, Higuchi and Hopfenberg slab, spherical, cylindrical (31–37). The release rate constant (k), correlation coefficients (r), and determination coefficients (r^2) were calculated by means of a computer programme (38). The results of dissolution studies obtained with adding and not adding Tween 20 were compared and evaluated kinetically and the most convenient model for the release of nicardipine hydrochloride was determined.

RESULTS AND DISCUSSION

Application of factorial design experiments to pharmaceutical problems has appeared to be extremely useful in recent years. The effects of several factors and their interactions can be determined simultaneously by factorial design experiments (39–41). The factorial design

Table 1

Properties and Codes of Formulation Used in the In Vitro Dissolution Test

Code	Core:Wall Ratio	Sieve Aperture Passed-Retained (μm)	Amount of Nicardipine Hydrochloride (mg)
M1	2:1	>840	50
M2	2:1	>840	25
M3	2:1	840–476	50
M4	2:1	840–476	25
M5	1:1	>840	50
M6	1:1	>840	25
M7	1:1	840–476	50
M8	1:1	840–476	25
M9	1:2	>840	25
M10	1:2	840–476	25

Table 2

Amounts of Tween 20 Added into the Dissolution of Ideal Microcapsule Formulation

Ratio	Amount of Added (g) a/v	Code
0.01%	0.09	P1
0.02%	0.18	P2
0.03%	0.27	P3

model was applied to the evaluation of the dissolution rate of nicardipine hydrochloride microcapsules. The effect is calculated from the change in the β (the shape parameter) and τ (time at which 63.2 percent of the active ingredient dissolved) values of the RRSBW distribution (34).

Tables 3 and 4 show the effect of A, B, C, and the AC interactions on the β and τ values and also their significance at the 99.9 per cent probability levels (13,42,43).

Factor B (amount of nicardipine hydrochloride) equal to 50 mg and at factor C (particle size) equal to 840–476 μm, an increase in core:wall ratio from 2:1 to 1:1 results in an increase in the τ from 167.137 to 252.931. In the 2^3 experiment described above, triplicate results from the analysis were obtained for each combinations of factors fitting a linear equation to a 2^3 factorial design gave a predictor equation which was a first-order polynomial, having the form (29):

Table 3

Results and Analysis of Variance for a 2^3 Factorial Experiment (Run in Triplicate). The Effect of Core:Wall Ratio, Amount of Nicardipine Hydrochloride, and Particle Size of Microcapsules on the β Values

Source of variation	β values Exp. 1	Exp. 2	Exp. 3	d.f.	Sum of Square	Mean Square	F
(1)	1.414	1.647	1.343				
a	0.738	0.695	0.785	1	0.037683	0.037683	5.02
b	0.831	0.860	0.866	1	0.018537	0.018537	2.47
ab	1.031	1.118	1.002	1	0.049413	0.049413	6.58
c	0.781	0.868	0.802	1	0.450729	0.450729	60.06*
ac	1.277	1.068	1.123	1	0.712425	0.712425	94.94*
bc	0.983	1.060	0.944	1	0.259376	0.259376	34.56*
abc	1.413	1.622	1.478	1	0.214893	0.214893	26.64*
Residual				16	0.120069	0.007504	
Total				23	1.863126		

Significance level based on 1 d.f.; *$p < 0.01$.

Table 4

Results and Analysis of Variance for a 2^3 Factorial Experiment (Run in Triplicate). The Effect of Core:Wall Ratio, Amount of Nicardipine Hydrochloride and Particle Size of Microcapsules on the τ Values

Source of Variation	β values Exp. 1	Exp. 2	Exp. 3	d.f.	Sum of square	Mean square	F
(1)	91.233	92.015	91.672				
a	166.752	174.005	168.383	1	30193.89	30193.89	1363.50*
b	122.594	128.301	126.179	1	6102.02	6102.02	275.56*
ab	168.943	175.348	169.274	1	13518.68	13518.68	610.48*
c	126.268	128.944	125.250	1	168.13	168.13	7.59
ac	197.765	205.129	200.742	1	502.74	502.74	22.70*
bc	170.129	164.403	166.880	1	1197.49	1197.49	54.08*
abc	251.962	264.134	242.697	1	725.29	725.29	32.75*
Residual				16	354.31	22.14	
Total				23	52762.55		

Significance level based on 1 d.f.; *$p < 0.01$.

$$y = b_o + b_1x_1 + b_2x_2 + b_3x_3 + b_{12}x_1x_2 + b_{13}x_1x_3 + b_{23}x_2x_3\, b_{123}x_{123} \quad (1)$$

where y: level of given response (dependent variable);
b: regression coefficients for first-order polynomial;
x: level of independent variable.

On the shape parameter (β);
core:wall ratio is non effective, $p > 0.01$;
amount of nicardipine hydrochloride (mg) is non effective, $p > 0.01$;
particle size of microcapsules (μm) is effective, $p > 0.01$;
core:wall ratio, amount of nicardipine hydrochloride (mg), particle size of microcapsules (μm) are effective, $p < 0.01$.

On the time at which 63.2 percent of the active ingredient dissolved (τ);
core:wall ratio is effective, $p < 0.01$;
amount of nicardipine hydrochloride (mg) is effective, $p < 0.01$;
particle size of microcapsules (μm) is non effective, $p > 0.01$;
core:wall ratio, amount of nicardipine hydrochloride (mg), particle size of microcapsules (μm) are effective, $p < 0.01$.

The significance of the observed effects is tested with the F test. Based on the mean squares in Table 3 and 4 (1 d.f; $F = 8.53$) A, B, C, and AC interactions have significance ($p < 0.01$). The fitted first-order polynomial model obtained as a result of the 2^3 factorial design is:

$$y_1 = 1.072 + 0.039x_1 + 0.027x_2 + 0.045x_3 + 0.137x_1x_2 + 0.172x_1x_3 + 0.103x_2x_3 - 0.094x_1x_2x_3;$$

$$y_2 = 163.291 + 35.496x_1 + 15.945x_2 + 23.733x_3 - 21.174x_1x_2 + 4.577x_1x_3 + 7.063x_2x_3 + 5.497x_1x_2x_3 \quad (2)$$

The responses measured on the resulting dissolution rate nicardipine hydrochloride microcapsules were y_1, β value; y_2, τ value. The three independent formulation variables selected for this particular study were: x_1, core:wall ratio; x_2, amount of nicardipine hydrochloride (mg); particle size of microcapsules (μm). Factorial design could be an important screening tool for microcapsule preformulation work and shows clearly the interaction between factors that a "one factor at a time" model can not reveal. In our experiments factor effectiveness was found to be in the following orders:

For the shape parameter (β): particle sizes of microcapsules (μm) > core:wall ratio > amount of nicardipine hydrochloride (mg).

For the time at which 63.2 per cent of the active ingredient dissolved (τ): core:wall ratio > amount of nicardipine hydrochloride (mg) > particle sizes of microcapsules (μm). Code M4 is found as ideal microcapsule formulation according to the results of the factorial design experiments.

In this investigation ethylcellulose is taken as the wall material and the coacervation phase separation method is employed. The reason ethylcellulose is selected as the wall material as follows: it is used in microcapsule, tablet, and suspension formulations, it's the most used wall material in microcapsule formulations, and it has no side-effects (44–49).

The effect of size distribution of the microcapsules on the pattern of release of the particle size of the microcapsules are known (11,50–52). Therefore particle sizes of the prepared microcapsules are determined by sieve analysis a mechanical shaker. The yield of prepared microcapsules were shown Table 5. Since particle size is one of the important factors in effecting the release profiles of the active substance, three different microcapsule particle sizes: > 840 μm, 840–476 μm, and 476–247 μm are separated and two different microcapsule particle sizes (> 840 μm, 840–476 μm) are used for the release rate experiments, because 476–247 μm particle size has a low yield.

When the microcapsules were investigated for their coating, it was seen under the scanning electron micros-

Table 5

Yield of Nicardipine Hydrochloride from Microcapsule and Microcapsule Particle Size Distribution

Core:Wall Ratio	Yield %	Particle Size % >840 (μm)	Distribution of 840–476 (μm)	Microcapsules 476–247 (μm)
2:1	94.41	39.27	58.95	1.76
1:1	95.87	17.99	75.62	6.38
1:2	77.50	20.00	74.83	5.16

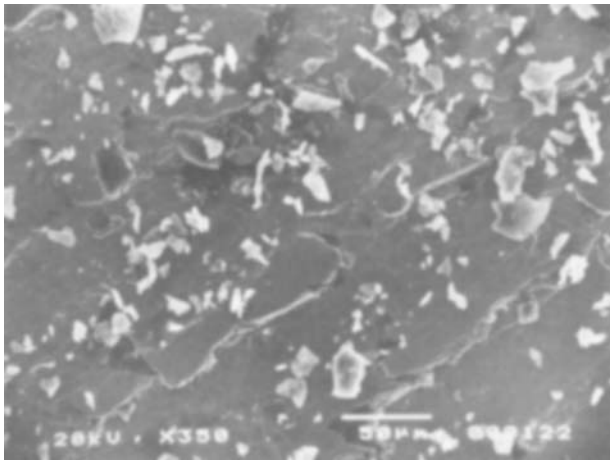

Figure 1. Scanning electron photomicrograph of nicardipine hydrochloride (x 350).

copy (SEM) that the microcapsules formed aggregates during the drying and isolation steps. Nicardipine hydrochloride and its microcapsules photographs from SEM are shown in Figures 1 and 2.

It is known that the amount of the active substance changes depending on the microcapsule's particle size and core:wall ratio. The prepared and formulated microcapsules are used in the dissolution rate experiments (Table 6). The microcapsule of ethylcellulose neither disintegrated nor changed their surface during the source of the dissolution experiments. This is an evidence that a diffusion controlled process is responsible for the release of nicardipine hydrochloride. Since there was no loss of the wall integrity during the dissolution experiments and it remained intact after an exposure to the dissolution medium, release of drug was presumably by diffusion (53). Also the linear portion seen Figure 3 may be indicative of drug release through diffusion (36). Diffusion is a physical process where the wall does not dissolve in the medium but penetrates the dissolution fluid. It could also be expected that these microcapsules behave like plastic matrices (54).

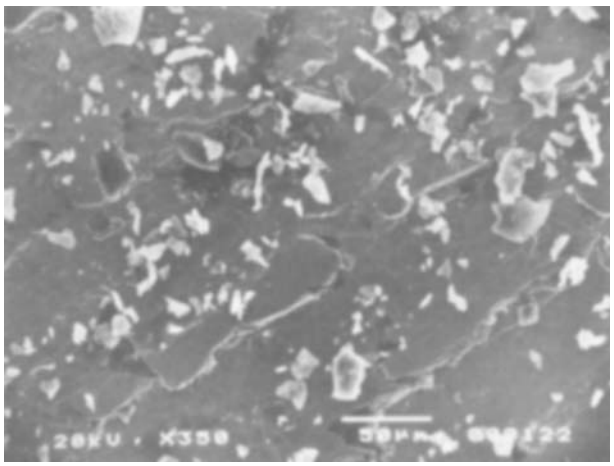

Figure 2. Scanning electron photomicrograph of nicardipine hydrochloride microcapsules (x 35).

Table 6

Formulations Used in the In Vitro Dissolution Tests

Code	Core:Wall Ratio	Microcapsule Particle Size (μm)
M2	2:1	>840
M4	2:1	840–476
M6	1:1	>840
M8	1:1	840–476
M9	1:2	>840
M10	1:2	840–476
G	Hard gelatin capsules (containing 20 mg nicardipine hydrochloride)	
L	Conventional tablet	

The effect of media pH, microcapsule particle size, and the core:wall ratio on the dissolution kinetics is studied and evaluated kinetically by first and zero order, Hixson-Crowell, Higuchi, RRSBW, $Q/\sqrt{t}$, $(Bt)^a$, and Hopfenberg release kinetics. The dissolution and the in vitro release of the drug are not always easy to correlate and no one model is able to adequately describe the release situation. Because of this reason, the dissolution data were examined by the above release kinetics. The release rate constants (k), correlation coefficients (r), and determination coefficients (r^2) are calculated by means of a computer program (38). The best fitting equation with the highest determination coefficient is the RRSBW distribution (34). Graphically RRSBW distribution gave a straight line with a slope of $\beta = 1.03$ and time $t = 201.3$ min when the active ingredient was dissolved 63.2% (Figure 4). Since the most retardant effect was obtained for microcapsules with 2:1 core:wall ratio and particle size 840–476 μm (coded as M4), the RRSBW distribution plot of the microcapsules are given for this ratio.

The effects of core:wall ratios and microcapsules particle size on drug release profiles are shown in Figure 3; as the concentration of the polymer in the system

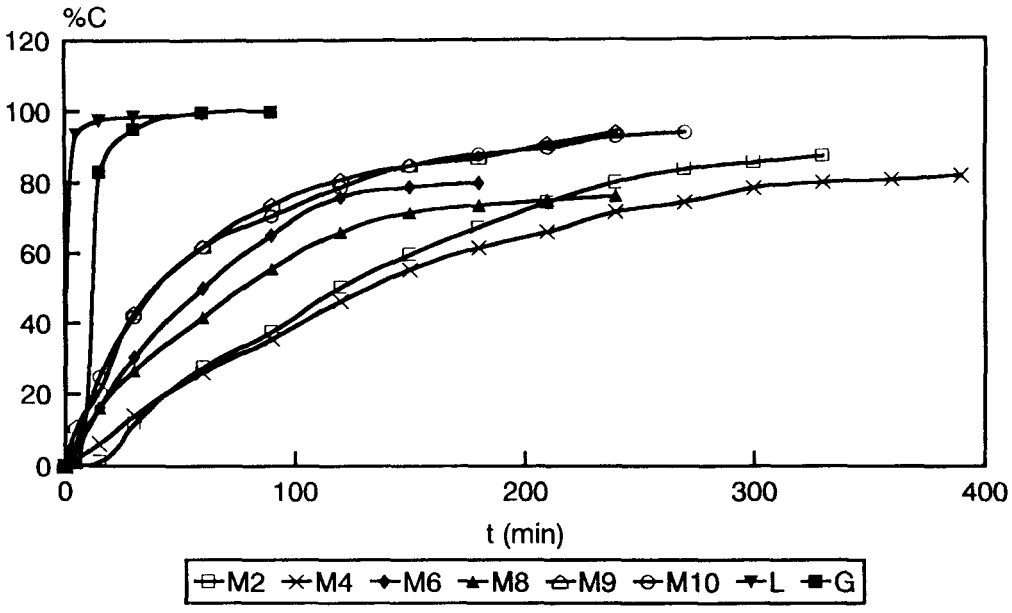

Figure 3. Release of nicardipine hydrochloride from microcapsules, hard gelatin capsule, and conventional tablet.

decreased, the release rate of nicardipine hydrochloride increased. This shows that the release rate is controlled by the wall thickness. As the wall thickness increased the release rate of nicardipine hydrochloride was slower and liberation of the active ingredient was incomplete. This finding is in accordance with the results found in previous study (55).

The dissolution data for hard gelatin capsules contained drug and conventional tablet were also determined. The time at which 50% of the active ingredient

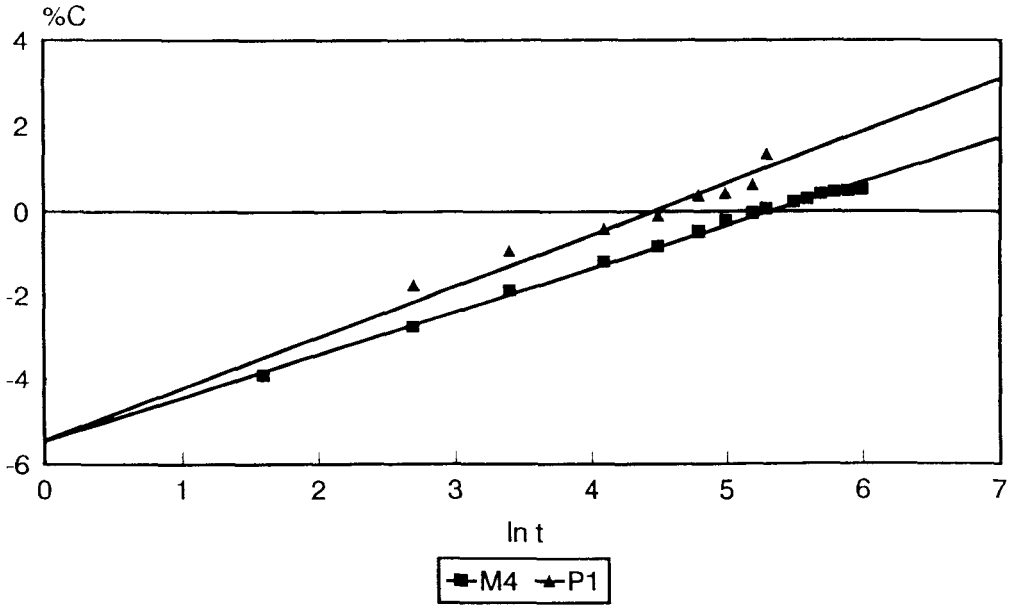

Figure 4. RRSBW distribution plots of the nicardipine hydrochloride microcapsule (r^2 = 0.996) and adding 0.01% Tween 20 (r^2 = 0.965).

(t_{50}) to be dissolved were found to be 18.9 and 19.9 min, respectively. A comparison of this value with microcapsules showed prolongation of release of nicardipine hydrochloride by microencapsulation (M4) to 149.5 min (Figure 3). Therefore, it appears that the ethylcellulose microcapsules could be used to prepare a sustained-release preparation of nicardipine hydrochloride and that the release of the core material is a function of both the core:wall ratio and the microcapsule size.

A surfactant may decrease the interfacial energy barrier between the drug and the dissolution medium, allowing the drug to be "wet" more completely and thereby effectively increase the available surface area of the solid. Additionally, concentrations of surfactant above the critical micelle concentration (C.M.C.) may markedly increase the apparent solubility of the drug in the medium by means of micellar solubilization. It would thereby effect an increase in the dissolution rate, which is a function of diffusional parameters, and the hydrodynamics of the system (56,57). While the influence of micellar solubilization on dissolution has been studied rather extensively, the effect of low concentrations (below the C.M.C.) of surface-active agents on the dissolution of drugs from powders and other solid dosage forms has been given limited attention (58). Nicardipine hydrochloride is a poorly soluble drug in the alkaline medium, and it is absorbed in the stomach and the duodenum (2,3,59). No study on solubilization of nicardipine hydrochloride microcapsule in aqueous solutions of surfactants has yet been reported. The dissolution procedure was repeated with ideal microcapsules number M4 by adding increasing amounts of Tween 20 in Table 2. The dissolution profiles obtained by adding Tween 20 are shown in Figure 5.

In addition, it is reported that amount of the active drug solubility could increase both solid dispersion (10) and a one special design method (60). In our experiment, solubility has increased by the addition of Tween 20. This effect of Tween 20 is in parallel with the results of dissolution in the literature (61). Amount of the active drug from M4 microcapsules has found 82% and after Tween 20 was added in the medium, this ratio was raised 98%. Therefore, solubility ratio has increased 16% in the gastric medium (Figure 5).

The effect of Tween 20 on dissolution kinetic was studied and the highest determination was observed by the RRSBW distribution (Figure 4). According to the concentrations of Tween 20 0.01–0.02–0.03% added to the dissolution medium, these t_{50} values were observed

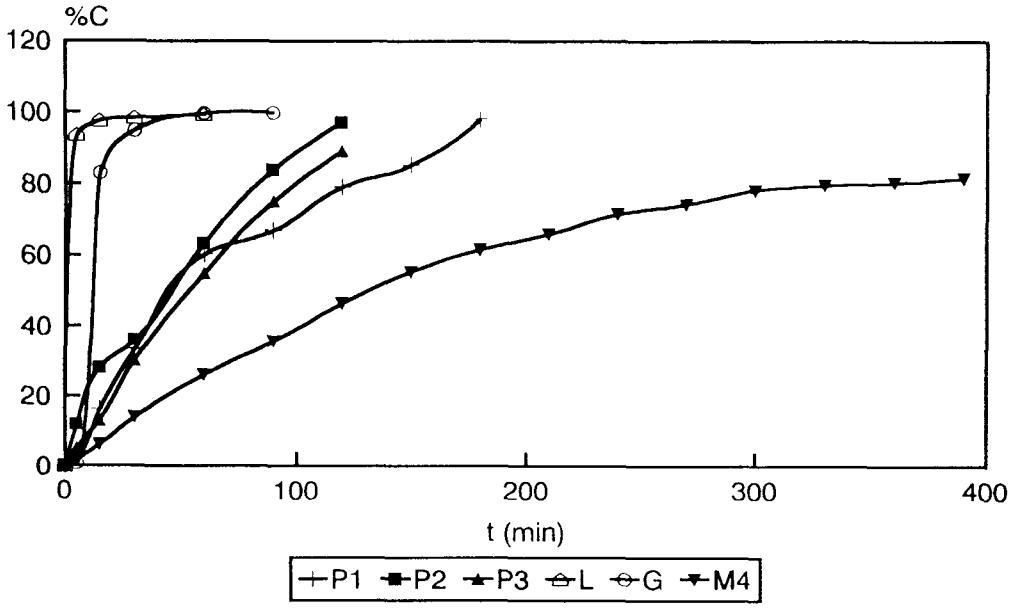

Figure 5. Release of nicardipine hydrochloride from microcapsules with Tween 20.

respectively; 46.4–25.3-37.8min. Also; it is observed that the t_{50} value is 149.5 min without adding any Tween 20 to the dissolution medium.

In conclusion a faster dissolution profile was obtained with surfactants. A relationship was found between the surface tension of the medium and the dissolution rate of nicardipine hydrochloride. It is thought that mainly wetting and the micelle solubilization of surfactants play an important role for nicardipine hydrochloride dissolution. As a result, although Tween 20 was added to the medium, the sustained-release action of the drug embedded by the microcapsules continued, and almost all of the drug was released. Moreover, the release time reduced in accordence with the staying time of the drug in the gastric medium (3.5 hr).

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