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COMMUNICATION

Dissolution Kinetics Evaluation of Controlled-Release Tablets Containing Propranolol Hydrochloride

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ABSTRACT

In the present research, controlled-release propranolol hydrochloride tablets were prepared for twice-daily administration, allowing more uniform plasmatic levels of the drug. Pharmaceutical formulations were prepared with hydrophobic Eudragit® RSPO. The physical properties of the tablets were determined. Dissolution tests were performed in capsules containing the raw material using the following dissolution media: (A) distilled water, (B) simulated gastric juice without enzymes, and (C) simulated enteric juice without enzymes. A dissolution test was also performed for simulated samples (tablets) using distilled water as the dissolution medium.

INTRODUCTION

Propranolol hydrochloride is a nonselective β-adrenergic blocking agent used in the treatment of heart diseases (1,2). It is commercially available in Brazil in conventional-release tablet formulations that are administered 2 or 4 times daily (3,4).

Controlled-release propranolol tablets can be administered twice daily, allowing uniform therapeutic plasmatic levels, thus decreasing side effects and inefficacy of treatment.

Dissolution tests results give important information about the influence of the components in solid pharmaceutical formulations, the quantity of dissolved drug, and the technique of manufacture of pharmaceutical preparations (5–9).

In this research, tablets were prepared using Eudragit® RSPO as a hydrophobic matrix; in a liquid me-

dium, it can originate channels in the tablet structure, allowing dissolution and gradative liberation of the drug (4,5,10–13).

Tablets were prepared, and many tests were performed, including the determination of physical properties and the kinetics of dissolution in different solvent media, to obtain a new controlled pharmaceutical preparation that will improve treatment efficacy, decrease side effects, and provide increased comfort to the patient.

EXPERIMENTAL

Materials, Reagents, and Equipment

Eudragit® S100 and Eudragit® RSPO were supplied by Rohm Pharma, Aerosil® by Hoechst, Avicel®PH101 by FMC—Food and Pharmaceutical Corporation, Lactose Spray Dried® by Foremost Dairos, medium-viscosity sodium carboxymethylcellulose (CMC-Na) by Mayer Laboratory, and polyvinylpirrolidone (PVP-30) by BASF Chemical Industry. All substances used in the preparation of tablets were pharmaceutical grade.

Propranolol hydrochloride (98.03% purity) was supplied by Chile Laboratories S. A. and was used as a chemical reference substance without further purification. All reagents used (sodium chloride, hydrochloric acid, sodium hydroxide, and monobasic potassium phosphate) were analytical grade.

Besides the usual laboratory equipment, Hanson Dissolution Equipment (Hanson Research Corporation, 64-700-006), with six acrylic vessels, and a Spectronic Genesys 5 ultraviolet/visible (UV/Vis) spectrophotometer with 1-cm quartz cells were used.

Methods

Preparation of Controlled Formulations

For each controlled formulation, 200 tablets were prepared. The composition of the formulations is shown in Table 1. The formulations were obtained by wet granulation according to the following procedure. Appropriate amounts of propranolol hydrochloride and Eudragit RSPO were weighed and mixed well. Tribasic calcium phosphate was added to formulations 2–7 and medium-viscosity CMC-Na was added to formulations 6 and 7. In formulation 3, 24.0 mg of Eudragit RSPO was used in the granulate preparation. The remaining Eudragit RSPO amount was added to the external layer of the granulate particle.

The mixture was moistened with a 12.5% w/v Eudragit S100 alcoholic solution for formulations 1–4 and with a 10% w/v PVP-30 aqueous solution for formulations 5–7. To obtain a homogeneous granulate, a 16-mesh sieve was used. The mixture was dried at 50°C for 2 hr. After cooling, the mixture was passed through a 17-mesh sieve to calibrate the granulate, and then the mixture was weighed. All the other components were added to each formulation and mixed well.

Preparation of the tablets was in an eccentric tablet compression machine. The granulates were analyzed for angle of repose and granulometry and according to their physical properties (average weight, hardness, friability).

Table 1

Composition of the Controlled-Release Tablets Containing Propranolol Hydrochloride

	Formulation						
Substance (mg/tablet)	1	2	3	4	5	6	7
Propranolol hydrochloride	80.0	80.0	80.0	80.0	80.0	80.0	80.0
Eudragit S100	7.2	8.2	5.8	8.6	—	—	—
PVP-30	—	—	—	—	7.7	8.6	8.6
Eudragit RSPO	30.0	48.0	72.0	72.0	120.0	120.0	120.0
Sodium carboxymethylcellulose	—	—	—	—	—	14.0	30.0
AvicelPH 101	10.0	25.0	25.0	40.0	—	—	—
Lactose Spray Dried®	8.0	8.0	8.0	8.0	—	—	—
Magnesium stearate	1.5	1.5	1.6	1.6	3.0	3.0	3.0
Aerosil	0.3	0.3	0.3	0.3	3.0	3.0	3.0
Tribasic calcium phosphate	—	50.0	50.0	50.0	50.0	50.0	50.0
Teoric weight	137.0	221.0	242.7	260.5	263.7	278.6	294.6

The kinetic dissolution profile of the tablets was also performed using distilled water as the dissolution medium.

In Vitro Dissolution Studies

In vitro dissolution tests were performed following the USP XXIII (14) official method with paddles (apparatus 2) at 37°C ± 0.5°C at a stirring rate of 100 rpm in two vessels. The tests were made with the raw material contained in hard gelatinous capsules in 900 ml of the following dissolution media: (A) distilled water, (B) simulated gastric juice without enzymes, and (C) simulated enteric juice without enzymes (7,14). Distilled water (A) was used as the dissolution medium for the analysis of tablets. At time intervals of 30 s from 1 to 5 min, 8 min, 10 min, and infinite time (5 min at 150 rpm), 10.0-ml aliquots were withdrawn from the dissolution vessel and filtered through cellulose acetate filters (0.22 μm). The same volume of the dissolution medium was replaced in each dissolution vessel. In the analysis of tablets, the aliquots were withdrawn at time intervals of 15, 30, 60, 90, 120, 180, 240, 300, and 360 min. The method used for quantitative determination was UV spectrophotometry at 290 nm using propranolol hydrochloride (98.03% purity) as the chemical reference substance.

RESULTS AND DISCUSSION

The calibration curve was obtained in a concentration range from 5.16 to 36.10 μg/ml of propranolol hydrochloride using the UV spectrophotometric method at 290 nm. The linear equation and the correlation coefficient r were $y = 20.637x - 0.0126$ and $r = 0.9999$, respectively.

In Table 2 and Fig. 1 are shown the results of the dissolution test performed with the raw material in hard gelatinous capsule. Studies carried out in the three dissolution media (A, B, and C) showed that more than 70% of the drug was dissolved after 1 min 30 s, and approximately 100% was dissolved after 9 min.

The kinetic dissolution equations and the lag times of the raw material are presented in Table 3. The values were characteristic of a first-order kinetic process in all three dissolution media.

Statistical analyses of the velocity constant for dissolution equations in the three dissolution media were accomplished by analysis of variance (ANOVA). Significant statistical differences were found in the three dissolution media, with calculated F (4.082) higher than F contained in tables and p lower than 0.05 (0.04012).

Table 2

UV Spectrophotometric Data Obtained in the Dissolution Test with Propranolol Hydrochloride (Raw Material) in Gelatinous Capsules Using Different Dissolution Media

	Dissolution Media Results (%)		
Time	A	B	C
30 s	33.74	11.00	25.29
1 min	56.70	53.71	62.60
1 min 30 s	71.50	76.03	79.99
2 min	81.57	83.37	83.30
2 min 30 s	88.75	86.86	83.92
3 min	94.27	86.04	85.59
3 min 30 s	—	88.83	86.45
4 min	94.82	—	86.35
5 min	97.29	—	—
5 min 30 s	100.00	—	88.50
6 min	100.00	87.36	89.29
6 min 30 s	—	95.51	88.60
7 min	98.59	—	90.37
7 min 30 s	—	—	96.51
8 min	—	94.84	97.21
8 min 30 s	—	98.74	96.88
9 min	—	—	98.32
Infinite	100.00	100.00	100.00

A, distilled water; B, simulated gastric juice without enzymes; C, simulated enteric juice without enzymes.
Infinite = 5 min at 150 rpm (when maximum values of drug dissolution were obtained).
—, not determined.

To verify in which pair of dissolution media the difference was, they were organized by pairs following the Student's t distribution. The results indicated that a significant statistical difference was only observed in the pair formed by distilled water (A) and simulated enteric juice without enzymes (C), with p lower than 0.05 (0,01309) and t calculated (2.841) higher than t contained in tables.

The data obtained in the physical analysis of both granulates and tablets are presented in Table 4. The repose angle values of the granulates were always below 30° and thus were in accordance with the specifications to originate adequate flux during compression of the tablets.

The kinetic results are showed in Fig. 2 and Table 5. Tribasic calcium phosphate was added to formulations 2–7 to raise the hardness values of the tablets, thus delaying the release, and consequently the dissolution time, of the drug. The best results were obtained with formulations 2, 4, and 5.

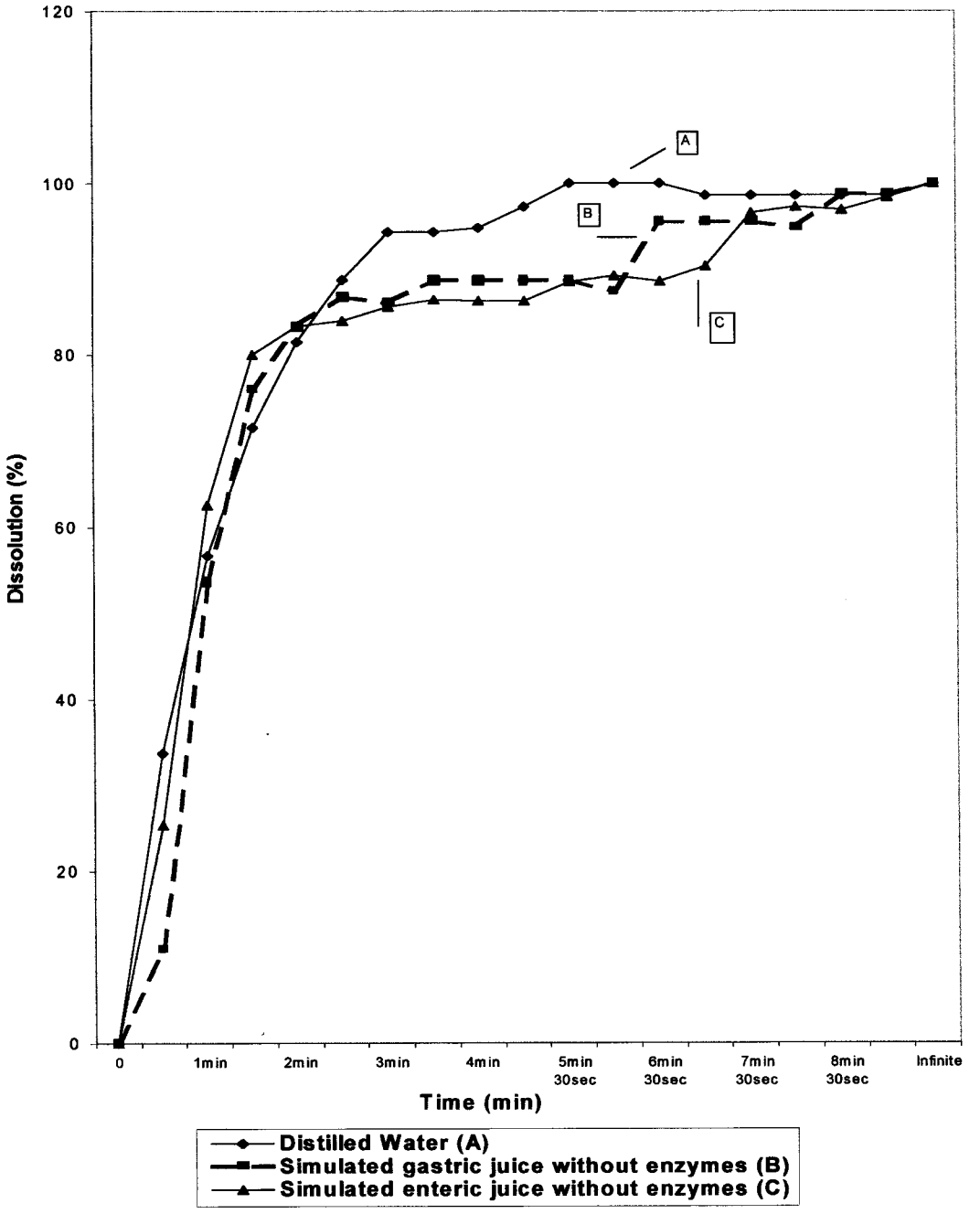

Figure 1. Dissolution average of propranolol in (A) distilled water, (B) simulated gastric juice without enzymes, and (C) simulated enteric juice without enzymes (analytical method: UV spectrophotometry).

Table 3

Lag Time Values and Kinetic Equations of Propranolol Hydrochloride (Raw Material) Obtained by Dissolution Tests

	Dissolution Media					
	A		B		C	
Sample	LT (min)	Kinetic Equation	LT (min)	Kinetic Equation	LT (min)	Kinetic Equation
1	2.63	$\ln w = -1.531k + 8.083$	1.96	$\ln w = -0.751k + 6.076$	2.84	$\ln w = -0.992k + 7.420$
2	2.81	$w = -40.485k + 213.568$	2.93	$\ln w = -1.927k + 10.245$	1.79	$\ln w = -0.693k + 5.842$
3	2.91	$\ln w = -1.757k + 9.724$	1.74	$\ln w = -0.948k + 6.255$	0.29	$\ln w = -0.374k + 4.713$
4	3.19	$\ln w = -3.049k + 14.337$	1.45	$\ln w = -0.787k + 5.749$	0	$\ln w = -0.277k + 4.213$
5	3.01	$\ln w = -0.739k + 6.826$	1.23	$\ln w = -0.715k + 5.487$	0	$\ln w = -0.305k + 3.993$
6	4.41	$\ln w = -0.817k + 8.205$	0	$\ln w = -0.258k + 4.295$	0	$\ln w = -0.433k + 4.635$

A, distilled water; B, simulated gastric juice without enzymes; C, simulated enteric juice without enzymes.
LT = lag time; w = dissolved raw material (%); k = dissociation constant.

The amount of Eudragit RSPO added to formulations can modulate the drug release velocity (15). The best drug release profiles were observed in formulations 2 and 4, which presented maximum release time after 6 h.

In formulations 5, 6, and 7, 10% PVP-30 w/v was added to the granulate in order to facilitate the compression. In formulations 6 and 7, medium-viscosity CMC-Na was added to the external layer of the granulate. The aim was to promote a delay in drug release due to the formation of a gel layer around the tablet surface. This objective was not reached, probably due to the fact that the type and the amount of CMC-Na was inadequate to promote tablet wetting, which would control the dissolution process.

Tablets prepared with such hydrophobic substances as Eudragit RSPO released the drug gradually. In this manner, formulation 2, which contains 48.0 mg of Eudragit RSPO, was delayed 40 times faster compared to propranolol as the raw material. Similarly, in formulations 1, 4, and 5, the release was delayed by 26, 33, and 26 times the drug liberation, respectively (Table 5, Fig. 2).

Table 4

Data Obtained in the Analysis of Granulates and Controlled-Release Tablets Containing Propranolol Hydrochloride with Eudragit RSPO, Eudragit S100 (Formulations 1–4) and PVP-30 (Formulations 5–7)

	Formulation						
Determination	1	2	3	4	5	6	7
Angle of repose (°)	19.44	19.69	21.80	30.46	27.8	26.8	27.8
Granulometry (%)							
30-mesh sieve	58.16	0.00	31.96	44.25	57.44	61.80	71.97
40-mesh sieve	10.28	39.14	11.63	3.93	16.23	12.94	10.18
50-mesh sieve	3.89	8.02	6.66	2.55	11.64	10.44	5.63
60-mesh sieve	1.68	3.73	2.84	1.39	4.10	4.28	2.04
70-mesh sieve	2.08	4.94	2.79	1.85	3.85	4.18	1.94
120-mesh sieve	6.95	16.01	7.26	9.60	4.65	6.37	3.88
>120-mesh sieve	6.24	28.16	25.60	36.44	2.10	6.26	4.37
Average weight of tablet (mg)	129.94	255.75	262.98	275.76	263.50	279.70	292.10
Hardness (kgf)	5.04	6.75	3.93	5.38	9.50	7.00	6.30
Friability (%)	0.66	0.46	0.58	0.39	0.20	0.17	0.15

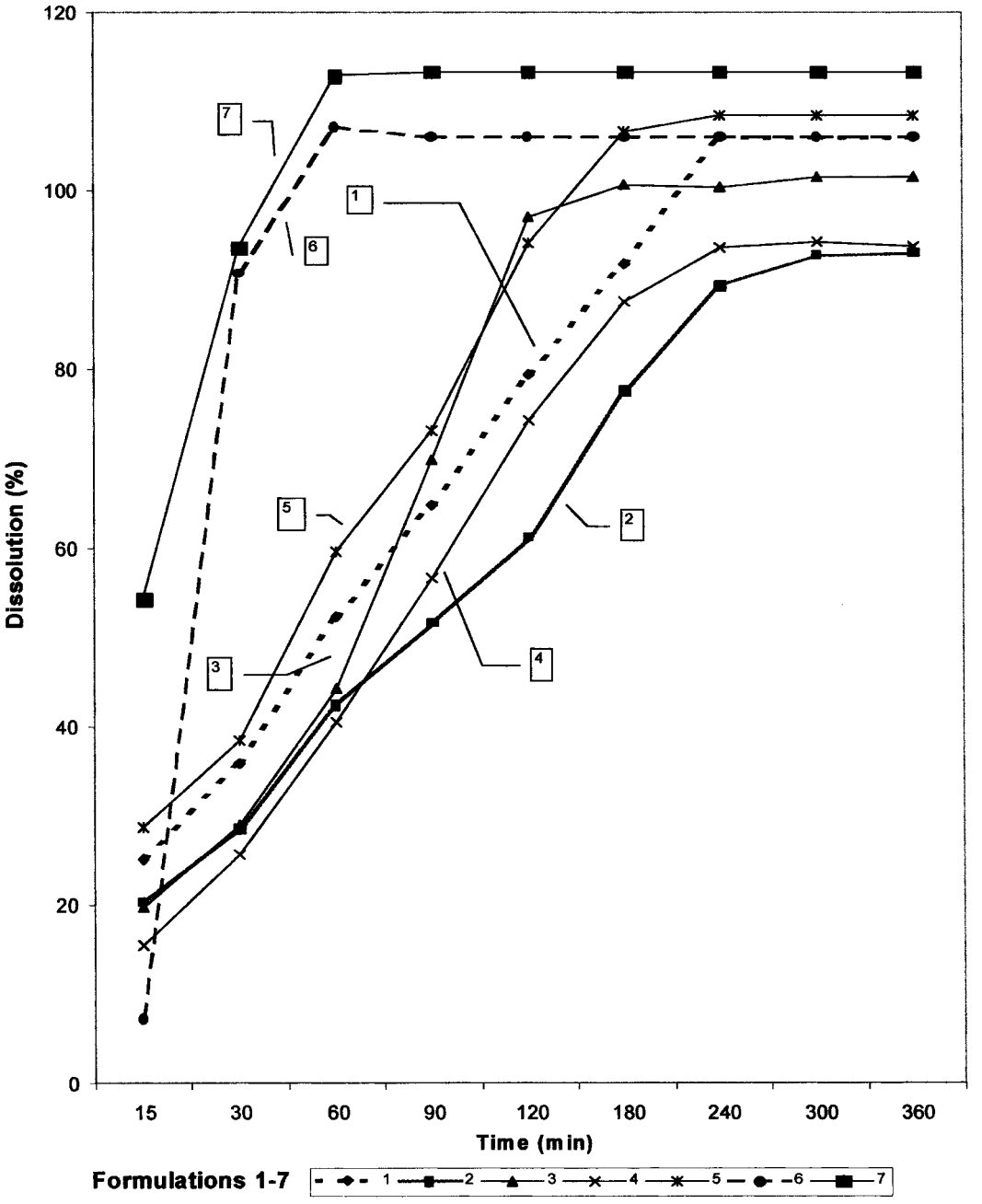

Figure 2. Influence of Eudragit RSPO, Eudragit S100 (formulations 1–4), and PVP-30 (formulations 5–7) on the dissolution profiles of propranolol hydrochloride contained in tablets using water as the dissolution medium.

Table 5

Dissolution Test Results for Controlled-Release Tablets Containing Propranolol Hydrochloride Prepared with Eudragit RSPO, Eudragit S100 (Formulations 1–4) and PVP-30 (Formulations 5–7) Using UV Spectrophotometry

Time (min)	Formulation Dissolution (%)						
	1	2	3	4	5	6	7
15	25.12	20.22	19.68	15.44	28.64	7.30	54.26
30	35.83	28.50	28.88	25.65	38.46	90.64	93.64
60	52.26	42.33	44.16	40.41	59.60	107.24	112.99
90	64.80	51.44	69.80	56.65	73.16	106.70	113.34
120	79.43	61.10	97.02	74.22	94.12	—	—
180	91.87	77.57	100.63	87.58	106.72	—	—
240	106.0	89.34	100.37	93.56	108.53	—	—
300	—	92.69	101.56	94.28	—	—	—
360	—	93.03	—	93.73	—	—	—

CONCLUSIONS

The free solubilization of propranolol hydrochloride was a dominant factor in drug pharmacokinetics in all studied dissolution media. The use of a 12.5% w/v Eudragit S100 alcoholic solution as the granulating agent led to a mixture with difficult granulation compared to those obtained using a 10% w/v PVP-30 alcoholic solution.

The increase in the amount of the hydrophobic matrix Eudragit RSPO in the formulations did not delay or control the velocity of liberation of propranolol hydrochloride contained in tablets.

Neither swelling nor formation of a protective film membrane around the tablets were observed during the dissolution test in water in the formulations made with medium-viscosity CMC-Na, probably due to the high solubility of propranolol hydrochloride in that solvent. Consequently, CMC-Na was not a suitable component for the preparation of propranolol controlled-release tablets.

The formulations prepared with Eudragit RSPO matrix could be coated with acrylic polymers to delay drug liberation, thus leading to adequate controlled-release propranolol hydrochloride tablets.

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REFERENCES

1. W. H. Martindale, *The Extra Pharmacopeia*, 30th ed., Pharmaceutical Press, London, 1993, p. 1783.
2. A. Korolkovas, *Essentials of Medicinal Chemistry*, 2nd ed., New York, Wiley-Interscience, 1988, p. 435.
3. A. Korolkovas, *Dicionário Terapẽutico Guanabara*, 2nd ed., Guanabara Koogan, Rio de Janeiro, 1995, pp. 8, l0.
4. K. Mitchell, J. L. Ford, D. J. Armstrong, P. N. C. Elliot, C. Rostron, and J. E. Hogan, Int. J. Pharm, 66, 233 (1990).
5. G. Singh, S. N. Sharma, and U. V. Banakar, Acta Pharm. Jugosl., 42, 225 (1992).
6. P. B. Bottini, J. G. Devane, and O. I. Corrigan, Drug Dev. Ind. Pharm., l0, 1757 (1984).
7. S. K. Das and B. K. Gupta, Drug Dev. Ind. Pharm., 14, 537 (1992).
8. B. Lang, Pharm. Pharmacol., 26, 661 (1971).
9. H. A. Lieberman, L. Lachman, and J. B. Schartz, *Pharmaceutical Dosage Forms: Tablets*, 2nd ed., Vol. 2, Marcel Dekker, New York, 1990, pp. 332, 549.
10. Röhm Pharma, *Eudragit RL/RS PO* [catalogue], GMBH Weiterstadt, Standards Sheet, Info RL/RS-7b/e, August 1991.
11. S. Ganga, P. N. Singh, and J. Singh, Drug Dev. Ind. Pharm., 18, 2049 (1992).
12. S. Ganga and J. Singh, Pharmazie, 46, 816 (1991).
13. D. Khattar, A. Ahuja, and R. K. Khar, Pharmazie, 45, 356 (1990).
14. U.S. Pharmacopeial Convention, *United States Pharmacopeia*, 23rd ed., Author, Rockville, MD, 1995, p. 1327.
l5. H. Al-Hamoud, M. Efentakis, and N. H. Choulis, Int. J. Pharm., 68, R1 (1991).