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Preparation and evaluation of bromocryptine mesylate-polydimethylsiloxane matrices

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The aims of the present study were to characterize the compatibility of silicone polymers with bromocryptine mesylate and excipients and to investigate the in vitro release characteristics of the drug from polydimethylsiloxane matrices. Silicon elastomers, MDX-4-4210 and A-2186, were chosen as polymer materials. Compatibility studies of polymers with drug and various liquid and solid excipients such as propylene glycol, polyethylene glycol, glycerol, sorbitan monolaurat, polysorbate 20, polysorbate 80, polyvinylpyrrolidone, citric acid, lactose, sodium chloride and low-molecular-weight gelatin were carried out. After the macroscopic examination of the excipient-polymer formulations, sorbitan monolaurat, propylene glycol, lactose, sodium chloride, citric acid and low molecular weight gelatin were chosen for investigation of the effect of these materials on drug release. Cylinder-shaped drug polymer matrices were prepared for the drug release studies. The best release profile was obtained with the formulation containing MDX-4-4210, 10% of propylene glycol and a kneading mixture of drug: low-molecular-weight gelatine in a ratio of 1 : 3.

1. Introduction

Medical grade polydimethylsiloxane polymers have been used in the development of controlled-release drug delivery systems for the administration of pharmaceuticals and veterinary drugs [1, 2]. They are lipophilic and nonporous polymers that can be used as rate controlling membranes or matrix materials in therapeutic systems. For example, polydimethysiloxanes have been utilized in the preparation of transdermal patches [3, 4], vaginal [5–7] or implanted [8] controlled drug delivery systems. Bromocryptine mesylate (BRC) was selected as a model drug. It is a semi-synthetic ergot alkaloid, which is a dopamine agonist has been used in the treatment of hyperprolactinaemic disorders, acromegaly and Parkinson's disease [9]. It is extensively subject to firstpass effect. The oral administration of BRC causes some side effects, most commonly nausea, vomiting, headache and dizziness, in about 50–70% of patients and at least 10% of them may discontinue therapy [10, 11]. Recently, it has been reported that BRC is well absorbed from the vagina and vaginally administered bromocryptine effectively reduced serum prolactin levels in normal ovulatory women and patients with hyperprolactinemia [12, 13]. Therefore, BRC may be a promising candidate drug for an intravaginal drug delivery system.

In this study, two different types of polydimethysiloxane, Silastic MDX-4-4210(S1) and silicone elastomer A-2186(S2), were used to prepare the polydimethysiloxane matrices. Silicone matrices due to their hydrophobic nature ensure a slow long-term release of the active ingredients. However, for vaginal or transdermal applications of the polydimethylsiloxane polymers, a substantial fraction of the drug dose should be released within a few days after the administration of the system. Various liquid or solid additives have been used to increase drug release from polydimethylsiloxane matrices [14–16].

The objectives of the present study were to characterize the compatibility of silicone polymers with BRC and excipients and to investigate the *in vitro* release characteristics of BRC from polydimethylsiloxane matrices to evaluate the availability of BRC from such preparations in the form of an intravaginal device.

2. Investigations, results and discussion

The octanol/pH = 5 buffer partition coefficient of BRC at 37 °C was 7.58 (±4.39) (mean ± confidence interval). The polymer/pH = 5 buffer partition coefficient values of BRC (k) was determined as 29.5 (±15.6) and 14.1 (±6.9) for polymers S1 and S2, respectively. The solubility (C_s) of BRC was 0.742 (±0.390) μg/ml and 0.354 (±0.173) μg/ml in polymer S1 and polymer S2, respectively.

2.1. Compatibility studies of polymers with drug and excipients

Polydimethysiloxanes are hydrophobic in nature. Therefore, liquid or solid additives have been used to improve the release rate of the drug from a silicone matrix, [14, 15].

Various excipients were added to silicone matrices and the mixtures of polymers with drug and excipients were subjected to macroscopic examination. Results were obtained by the evaluation of curing and the morphological appearance of the materials were used to assess the results. The macroscopic characterization of the polymer-drug excipient mixtures is shown in Table 1. Fully cured samples were accepted whereas partly cured or sticky samples failed the test.

The initial compatibility studies of drug and additives showed that silicone elastomer that was blended with solid materials such as lactose, sodium chloride, citric acid and LMWG had the desired physical and handling properties. However, most of the preparations containing liquid additives were physically unacceptable. It has been reported that polyethylene glycols and glycerol can be used in silicone matrices to enhance drug release [15, 16], but in our case these additives gave undesirable properties to the silicone matrices. Matrices containing only a small proportion of propylene glycol (1–10%) can be acceptable. When we compared some parameters such as handling time, homogeneity, and miscibility of the drug/excipients and polymer, removing air and placing into moulds for the two polymers, it was seen that the handling of Silastic MDX-4-4210(S1) was easier than Silicone elastomer A-2186(S2). Therefore, only polymer S1 was used to prepare formulations for *in vitro* drug release studies.

Table 1: Macroscopic characterization of silicone elastomer containing drug or excipients

Polymer	Material	%	Characterization
S1-S2	–	–	fully-cured
S1-S2	Bromocryptine	1	fully-cured
S1-S2	Arlacel 20	–	fully-cured, slightly sticky
S1-S2	Propylene glycol	1, 5, 10	fully-cured
S1-S2	Propylene glycol	15, 50	fully-cured, sticky
S1-S2	PEG 200,400,600	5	fully-cured, sticky
S1-S2	PEG 200,400,600	10, 15	partly-cured, sticky
S1-S2	Glycerol	5, 10	partly-cured, sticky
S1-S2	Polysorbate 20	10	fully-cured, sticky
S1-S2	Polysorbate 80	10	fully-cured, sticky
S1-S2	Polyvinylpyrrolidone	10	partly-cured, sticky
S1-S2	Citric acid	10	fully-cured
S1-S2	Lactose	10	fully-cured
S1-S2	Sodium chloride	10	fully-cured
S1-S2	LMWG	10	fully-cured

2.2. In vitro release studies

The *in vitro* release profile of BRC from cylinder-shaped silicone matrices with and without liquid additives such as Arlacel 20 and propylene glycol is shown in Fig. 1. It has been reported that the addition of 30% propylene glycol as a co-solvent increased the release of coumarin from silicon matrices [3]. In our case, the release of BRC from cylinder-shaped matrices was very low (Fig. 1). Addition of propylene glycol or Arlacel 20 slightly increased the release rate. About 7% and 16% of drug was released over 10 days with the addition of propylene glycol and Arlacel 20, respectively. Although Arlacel 20, increased the release rate much more compared with propylene glycol, the physical properties of formulations containing propylene glycol were more desirable. Therefore, propylene glycol was used for further formulations due to its ease of preparation. The release of BRC was still low even with the addition of propylene glycol or Arlacel 20 to the formulations and therefore, different materials should be tested to increase the release rate of BRC. For this purpose various solid materials were used.

Water-soluble solid materials such as sodium chloride, lactose and citric acid can lead to the formulation of pores and crack in the polymer matrix to enhance the release of drugs [14, 17]. Sodium chloride also effects the mechanical and osmotic properties of the matrix. Citric acid has been used to enhance the vaginal absorption of insulin [18]. It has been reported that the release rate of bovine serum albumin-sodium chloride granules was related to the granule size [15], so, citric acid was kneaded first to increase the particle size. The release profiles of BRC from matrices containing solid materials are shown in Fig. 2. The release of drug from silicone matrices containing lactose, sodium chloride and citric acid was low even after 10–11 days. Another material was necessary to increase the release rate. Low-molecular-weight gelatin (LMWG) has been used to enhance the solubility and dissolution rate of poorly water-soluble drugs [19, 20]. In our experiments, we examined the effect of LMWG on the release rate of BRC from silicone matrices. Fig. 3 shows the release of BRC from silicone matrices containing kneaded BRC-LMWG mixtures in weight ratios of 1 : 2, 1 : 3 and 1 : 4. Incorporation of BRC into LMWG significantly enhanced the release rate of the drug vs. that with drug alone. The amount of drug released increased with increasing LMWG content. On the other hand, there was no significant difference between the release rate of formulations with weight ratios of 1 : 3 and 1 : 4. LMWG may improve the hydrophilicity of the drug by surrounding the drug particles as a film layer. On the other hand the particle size of the kneaded mixtures was larger than that of the drug alone, which can be useful for increasing the porosity of the silicone matrices.

The kinetic analysis of release data, as evaluated by a computer program (DISSOL) [21] is shown in Table 2. On evaluating the results according to the values of the determination coefficient (r^2) and the sum of the weighted

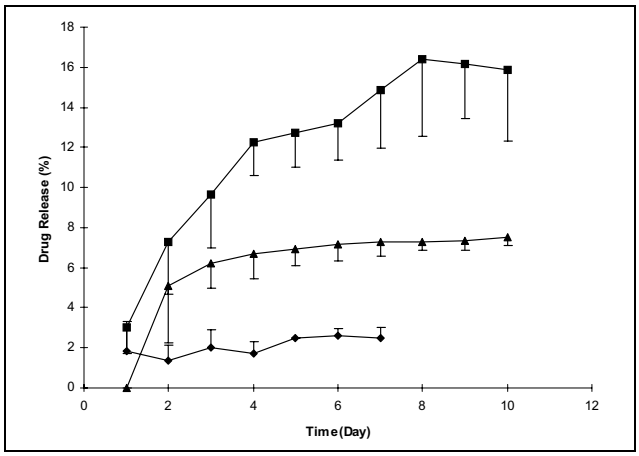

Fig. 1: Cumulative release of BRC from cylinder-shaped formulations containing liquid excipients. ◆: BRC alone, ■: Arlacel 20, ▲: propylene glycol. Each point represents the mean ± confidence interval (n = 3)

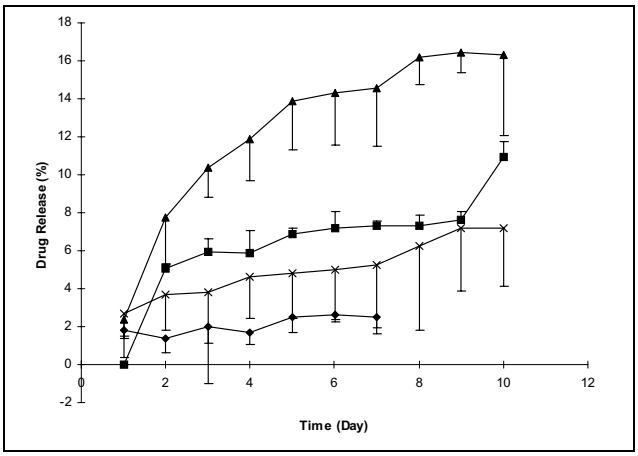

Fig. 2: Cumulative release of BRC from cylinder-shaped formulations containing solid excipients. ◆: BRC alone, ■: Lactose, ▲: NaCl, ×: citric acid. Each point represents the mean ± confidence interval (n = 3)

Table 2: Kinetic assessment of release data[a]

Code	Kinetic parameters								
	Zero order			First order			$Q - \sqrt{t}$		
	k_0^b	r^2	SWSD	k_1^c	r^2	SWSD	k^d	r^2	SWSD
CS1	8.79×10^{-4}	0.651	0.00134	7.48×10^{-5}	0.652	0.00134	1.26×10^{-7}	0.598	0.933×10^{-4}
CS2	3.33×10^{-3}	0.861	0.0239	6.24×10^{-4}	0.872	0.0226	3.45×10^{-6}	0.940	0.00127
CS3	1.36×10^{-3}	0.525	0.0119	2.36×10^{-4}	0.532	0.0120	8.62×10^{-7}	0.656	0.00168
CS4	2.41×10^{-3}	0.786	0.00265	4.24×10^{-4}	0.786	0.00252	9.01×10^{-7}	0.839	0.00282
CS5	3.41×10^{-3}	0.829	0.0258	6.37×10^{-4}	0.845	0.0247	3.62×10^{-6}	0.922	0.00174
CS6	1.21×10^{-3}	0.962	0.00565	2.12×10^{-4}	0.961	0.00551	5.78×10^{-7}	0.938	0.149×10^{-3}
CS7	0.0113	0.954	0.0595	2.87×10^{-3}	0.944	0.0240	2.63×10^{-5}	0.957	0.0270
CS8	0.0231	0.983	0.0564	0.0731	0.575	1.48×10^{-4}	1.06×10^{-4}	0.988	0.241
CS9	0.0232	0.948	0.0639	0.0117	0.987	0.430	9.14×10^{-5}	0.984	0.189

[a] Summary of output obtained from the program DISSOL; [b]k_0 is the zero order release rate constant(mg/h); k_1 is the first order release rate constant(h^{-1}); k is the rate constant obtained from the slope of the linear regression of cumulative amount released per unit area versus square of time ($mg \cdot cm^{-2}\ h^{-1/2}$); r^2 is the coefficient of determination, SWSD is the sum of weighted squared deviations

squared deviations (SWSD), the kinetics of the most of the formulations fitted $Q\ \sqrt{t}$ kinetics i.e., matrix kinetics. The solubility of BRC in the silicone polymer was 0.742 mg/ml. The solubility of BRC was less than the total amount of BRC in the matrix. Therefore, a heterogeneous matrix was formed. There are spaces and channels in heterogeneous matrices as called porosity and tortuosity. The drug diffuses via these capillary channels. Eq. (1) can be used for the calculation of the porosity and tortuosity of the matrix formulations [22].

$$M_t = Q = \left[\varepsilon \cdot \frac{D}{\tau}(2 \cdot C_0 - \varepsilon \cdot C_s) \cdot C_s \cdot t\right]^{1/2} \quad (1)$$

Where Q = amount of drug released after time t per unit exposed area, D = diffusivity of the drug in the permeating fluid, τ = tortuosity factor of the capillary system ($\cong$ 3), C_0: total amount of drug present in the matrix per unit volume (mg/ml), C_s: solubility of the drug in the permeating fluid (mg/ml).

When C_s is neglected in sink conditions, Eq. (2) is obtained.

$$Q = \left[\varepsilon \cdot \frac{D}{\tau}(2 \cdot C_0 \cdot C_s) \cdot t\right]^{1/2} \quad (2)$$

The slope of this equation includes the parameters ε, τ, C_0 and C_s. A parameter A can be calculated from the slope of $Q\ \sqrt{t}$ kinetics and the other parameters such as C_0 and C_s. This parameter includes all porosity; tortuosity and diffusion coefficient and it can be used to represent the porosity and tortuosity of the matrix. Table 3 shows the calculated A parameters of the formulations. The lowest A values was obtained for formulation CS1. The addition of the various excipients increased the value of A i.e., the porosity and tortuosity of the matrix.

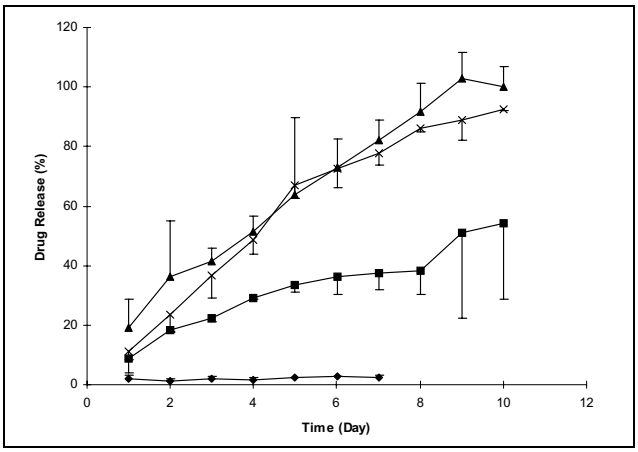

Fig. 3: Cumulative release of BRC from cylinder-shaped formulations containing LMWG. ◆: BRC alone, ■: 1 : 2 (drug-LMWG), ▲: 1 : 3, ×: 1 : 4. Each point represents the mean ± confidence interval (n = 3)

Table 3: The values of parameter A calculated according to the $Q\ \sqrt{t}$ kinetics

Code	Parameter A
CS1	2.54×10^{-7}
CS2	6.96×10^{-6}
CS3	1.74×10^{-6}
CS4	1.82×10^{-6}
CS5	7.32×10^{-6}
CS6	1.17×10^{-6}
CS7	5.32×10^{-5}
CS8	2.14×10^{-4}

Table 4: Codes and contents of the cylinder-shaped formulations

Code	Additive	%	Ratio (drug : additive)
CS1	–	–	–
CS2	Arlacel 20	10	–
CS3	Propylene glycol	10	–
CS4	Lactose	10	–
CS5	Sodium chloride	10	–
CS6	Propylene glycol Citric acid	10	1 : 2
CS7	Propylene glycol LMWG	10	1 : 2
CS8	Propylene glycol LMWG	10	1 : 3
CS9	Propylene glycol LMWG	10	1 : 4

In conclusion, the best release profile of BRC was obtained with the formulation containing silicone polymer MDX-4-4210, 10% of propylene glycol and a kneading mixture of drug: low-molecular-weight gelatine in a ratio of 1 : 3. This formulation can be used to prepare an intravaginal device containing BRC for further studies.

3. Experimental

3.1. Materials

Bromocryptine mesylate (BRC) was donated by Novartis Co.Turkey. Silastic MDX4-4210(S1) and Silicone elastomer A-2186 (S2) were kindly provided by Dow Corning, U.S.A. and Factor II. Inc., U.S.A., respectively.

Low-molecular-weight gelatine (MW ≅ 5000) was donated by Nitta Gelatine Co., Ltd, Osaka, Japan. Spray-dried lactose was purchased from DMV Inc., The Netherlands. The other materials were of analytical grade. Plastic tubes made of polvinylchloride with an external diameter of 6 mm, an internal diameter of 4.7 mm. and a length of 35 mm were used to mould of the cylinder-shaped formulations.

3.2. Determination of octanol/buffer partition coefficient of BRC

First the stability of BRC was studied. For this purpose, a BRC solution of known concentration of in pH = 5 buffer (citric acid/phosphate) was stored at 37 °C and 50 °C for 10 days. At appropriate intervals, samples were withdrawn and a spectrum was recorded. The assay of BRC was carried out spectrophotometrically at 310 nm. The results were compared with the initial data. No significant change of the spectrum and absorbance values of BRC was seen for either both storage condition.
To determine the octanol/buffer partition coefficient of BRC, a saturated solution of BRC in pH = 5 buffer (citric acid/phosphate) was shaken with octanol in a water bath at 37 °C for up to six days. The concentrations of BRC were determined spectrophotometrically at 310 nm. All experiments were done in triplicate.

3.3. Determination of polymer/buffer partition coefficient of BRC and solubility of BRC in polymers

The solubility of a drug in a polymer is one of the important factors affecting the release rate of the drug from matrix type dosage forms. The solubility of BRC in two different silicone polymers was determined. For this purpose, the cured polymers (one part of the curing agent with 10 parts of the base elastomer) were devided into cubes. The diameters and the weight of the cubic pieces were measured. These polymer pieces were placed into BRC solution in pH = 5 buffer at 37 °C in a water-bath with shaking. At appropriate intervals, the BRC concentration in the buffer solution was determined spectrophotometrically at 310 nm. After the equilibration of the system, the partition coefficient (k) and the solubility of BRC in polymer (C_s) were calculated using Eqs. (3) and (4) [23].

$$k = \frac{V_1(C_1 - C_2)}{V_2 \cdot C_2} \quad (3)$$

$$C_s = k \cdot C_a \quad (4)$$

Where k = polymer/buffer partition coefficient, V_1 = volume of the BRC solution (ml) V_2 = volume of the polymer (ml), C_1= the first concentration of the BRC solution (μg/ml), C_2 = the last concentration of the BRC solution (μg/ml), C_s = solubility of BRC in polymer (μg/ml), C_a = solubility of BRC in pH = 5.0 buffer (μg/ml).
Experiments were done in triplicate.

3.4. Compatibility studies of polymers with drug and excipients.

One part of the curing agent with 10 parts by weight of the base elastomer was used. Drug or excipients (1, 5, 10, 20, 50%) were blended with silicone elastomer before the addition of the curing agent and kept at room temperature. Propylene glycol, polyethylene glycol (PEG) 200, 400, 600, 1000, glycerol, sorbitan monolaurat (Arlacel 20), polysorbate 20, polysorbate 80, polyvinypyrrolidone (PVP), citric acid, spray-dried lactose, sodium chloride and low-molecular-weight gelatine (LMWG) were used as excipients. The miscibility of additives and silicone polymers and the morphological appearance and curability of the polymers were evaluated, and compared with the control which was prepared without additives.

3.5. Preparation of the formulations

Cylinder-shaped drug-polymer matrices were prepared to characterize drug release. Formulations were prepared by blending 10 parts of elastomer base with one part of curing agent. Drug/excipients or kneaded mixtures were mixed with polymer to homogeneity. The mixtures were moulded in the plastic tubes. After deaerating under vacuum at 1.65×10^{-3} pa for 15 min, they were allowed to cure at room temperature. The cured formulations, 4.7 mm in diameter and 35 mm in length, were obtained by removing the plastic tube. The excipients with the exception of citric acid and LMWG, were simply mixed with the drug before it was added to the elastomer base, but LMWG was kneaded with the drug in various ratios of 1 : 2, 1 : 3 and 1 : 4 (drug: LMWG). The drug-LMWG kneaded mixtures were prepared with the method published elsewhere [24]. Briefly, the required amounts of drug and polymer were weighed and placed in a mortar, and then the mixtures were kneaded with 1.5 times their amount of water for 1 h. The kneaded mixtures were dried under vacuum at room temperature for 48 h and then screened through a 25-mesh sieve. Drug was also kneaded with the citric acid in a ratio of 1 : 2. Each formulation contained 6 mg of drug.
After macroscopic examination of the excipient-polymer formulations, some excipients such as propylene glycol, spray-dried lactose, sodium chloride, citric acid and LMWG were chosen for pore formation..
The contents of the formulations are shown in Table 4.

3.6. In vitro release studies

Release experiments were performed under sink conditions in an Erlenmeyer flask containing 100 ml of phosphate-citrate buffer pH = 5 at 37 °C. The flasks were shaken at 37 °C in a water bath. The samples were withdrawn at appropriate time intervals and assayed spectrophotometrically at 310 nm. The buffer solution was replaced with fresh solution each day. The experiments lasted for 6–12 days.

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References

1 Hsieh, D. S. T; Mann, K; Chien, Y. W: Drug Dev. Ind. Pharm. **11**, 1391 (1985)
2 Hoth, M.; Merkle, H. P.: Drug Dev. Ind. Pharm. **17**, 985 (1991)
3 Ritschel, W. A; Nayak, P. M.: Arzneim.-Forschung/Drug Res. **37**, 302 (1987)
4 Pfister, W. R.; Fraleigh, R. M.; Walters, P. A.: Proceed. Intern. Symp. Control. Rel. Bioact. Mater. **17**, 277 (1990)
5 Mishell, D. R.; Lumkin, M. E.: Fertil. Steril. **21**, 99 (1970)
6 Burton, F. G.; Skiens, W. E.; Gordon, N. R.; Veal, J. T.; Kalkwarf, D. R.; Duncan, G. W.: Contraception **17**, 221 (1978)
7 Olsson, S. E.; Odlind, V.: Contraception **42**, 563 (1990)
8 Ermini, M; Carpino, F.; Russo, M,; Benagiano, G: Acta Endocr. **73**, 360 (1973)
9 Parkes, D.: New Eng. J. Med. **301,** 873 (1979)
10 Cedarbaum, M.: Clin. Pharmacokin. **13**, 141 (1987)
11 Dash, R. J.; Ajmani, A. K.; Sialy, R: Hor. Metab. Res. **26**, 164 (1994)
12 Vermesh, M.; Fossum, G. T.; Kletzky, O. A.: Obstet. Gynecol. **72**, 693 (1988)
13 Ginsburg, J.; Hardiman, P.; Thomas, M.: Lancet **338**, 1205 (1991)
14 Sutinen, R.; Bilbao-Revoredo, B.; Urtti, A.; Paronen, A.: Int. J. Pharm. **57,** 155 (1989)
15 Di. Colo, G.; Carelli, V.; Nanipieri, E; Serafini, M. F.; Vitale, D.: Int. J. Pharm. **30,** 1 (1986)
16 Rehula, M.: Pharmazie **48**, 126 (1993)
17 Carelli, V.; Di Colo, G.; Guerrini, G.; Nannipieri, E.: Int. J. Pharm. **50**, 181 (1989)
18 Richardson, J. L.; Illum, L.; Thomas, N. W: Pharm. Res. **9**, 878 (1992)
19 Imai, T.; Tetsuguki, N.; Ueno, M.; Otagiri, M.: Chem. Pharm. Bull. **37**, 2251 (1989)
20 Acartürk, F.; Şencan, A.; Çelebi, N.: S.T.P. Pharma Sciences **3**, 369 (1993)
21 Ağabeyoğlu, I. T.: XVIII'eme Semaine Medicale Balkanique, Resumes II, 327, 30 Aout-4 Septembre, Istanbul 1984
22 Higuchi, T.: J. Pharm. Sci. **52**, 1145 (1963)
23 Roseman, T. J.: J. Pharm. Sci. **64**, 46 (1972)
24 Acartürk, F.; Kıslal, Ö.; Çelebi, N.: Int. J. Pharm**. 85**, 1 (1992)

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