Drug Development and Industrial Pharmacy, 27(4), 359–364 (2001)

COMMUNICATION

Molecular Properties of Propranolol Hydrochloride Prepared as Drug-Resin Complexes

Prasert Akkaramongkolporn[1,*] Katsuhide Terada,[2] and Etsuo Yonemochi[2]

[1]*Department of Pharmaceutical Technology, Faculty of Pharmacy, Silpakorn University, Nakorn Pathom, Thailand*
[2]*Department of Pharmaceutics, School of Pharmaceutical Sciences, Toho University, Japan*

ABSTRACT

Drug-resin complexes, as well as physical dispersions, containing varying contents of propranolol were prepared. The molecular properties of samples were investigated by differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), and infrared (IR) spectroscopy. In addition, the USP paddle method was used to determine the release behavior of drug from various formulations prepared from the samples. The data from DSC and XRPD indicated that the molecular state of drug in the complexes was amorphous, whereas that in the physical dispersions exhibited the crystalline state of pure drug. These results suggested that the molecule of drug prepared as drug-resin complexes was monomolecularly dispersed in the resin bead. The IR study provided evidence that demonstrated the interaction between the drug and resin in the complexes. The release behavior of drug from the complexes was governed by the cross-linkage structure and equilibrium treatment of drug exchange of resin.

KEY WORDS: *Differential scanning calorimetry; Infrared spectroscopy; Ion exchange; Propranolol hydrochloride; Release behavior; X-ray diffraction.*

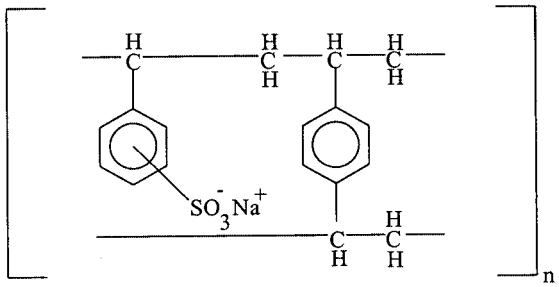
*Corresponding author.

INTRODUCTION

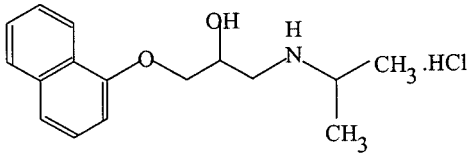
A drug can be loaded onto an ion-exchange resin by an exchanging reaction, and hence a drug-resin complex is formed (1,2). Some pharmaceutical properties of a drug prepared as a drug-resin complex are modified from pure drug, including decreased drug release, taste, and toxicity and stability enhancement of the drug (3,4). Moreover, the coating of the complex with some polymers has been claimed to change some of these properties more than the uncoated complex (5,6).

Molecular properties can be affected in several variable ways, which exerts a profound influence on the release behavior of drug. For example, the decrease in crystallinity of glibenclamide and oxazepam prepared as inclusion complexes with cyclodextrins significantly enhanced the dissolution of drugs (7,8). Felodipine surface solid dispersions had an improvement of drug dissolution that was caused partly by the amorphous state of the drug (9). Depending on the grinding time, the grinding of the drug with and without some substances decreased the crystallinity of the drug. Increased dissolution of drug was observed in the ground mixture than in the intact drug (10).

Owing to limited information on the molecular properties of drug prepared as drug-resin complex, our study investigated the molecular properties of drug in the complex in comparison with pure drug and that prepared as physical dispersions. Propranolol hydrochloride, a crystalline and cationic drug, and Amberlite® IRP 69, a cationic exchanger widely used in pharmaceutical applications, were used as the model drug and resin, respectively (Fig. 1). The methods used for characterizing the molecular property of samples included differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), and infrared (IR) spectroscopy. The release behavior of drug from the samples was also determined using the USP paddle method.



Resin



Propranolol HCl

Figure 1. Structure of resin and propranolol HCl.

EXPERIMENTAL

Materials

The chemical materials and drug used were as follows: Amberlite® IRP 69 (Sigma, St. Louis, MO), propranolol HCl (Sigma), monobasic potassium phosphate (Wako, Japan), and sodium hydroxide (Jensei, Japan).

Method

Washing of Resin

The resin (20 g) was placed in a 250-ml beaker to which 200 ml of deionized water was added. The slurry was stirred with a magnetic bar for 5 min and left to settle for 15 min; thereafter, the supernatant was removed by decantation. The resin was washed two more times according to the above procedure. The washed resin was collected by filtration and dried overnight in a hot air oven at 50°C. The dried resin was kept in a tight vial.

Preparation of Drug-Resin Complexes and Physical Dispersions

Drug-resin complexes PC I, PC II, and PC III containing varying contents of drug were prepared by placing the washed resin (1 g) in 100 ml of 0.15%, 0.5%, and 2.0% w/v of propranolol HCl solution, respectively. The mixtures were left in the dark at room temperature (25°C) for 48 h and shaken periodically. The complexes were retrieved from the filtrates by filtration and washed with an excess amount of deionized water, which was then collected and added to the previous filtrates. The complexes were dried overnight in a hot air oven at 50°C and then stored in a tight vial. The drug content in the final filtrate, which was the sum of the filtrate and washing water, was analyzed by ultraviolet (UV) spectroscopy (UV-160, Shimadzu, Kyoto, Japan) at 288.5 nm. The amount of drug loaded on the complexes was obtained

by subtracting the remaining amount of drug in the final filtrate from the initial amount.

The physical dispersions PD I, PD II, and PD III were prepared with the same drug contents as the above complexes, respectively, by shaking each portion of drug and resin in a vial.

Differential Scanning Calorimetry

The DSC curves from the samples were determined by a differential scanning calorimeter (DSC 7, Perkin Elmer, USA). Each sample was placed in an aluminum pan and then crimped with an aluminum cover (Perkin Elmer). The heating and cooling rates were 20°C/min and 200°C/min, respectively. All measurements were performed over 25°C–250°C under a nitrogen purge.

X-ray Powder Diffraction

A Rigaku X-ray powder diffractometer was used. The measuring conditions were as follows: CuK_α radiation, nickel filtered; graphite monochromator; 35 kV voltage; and 10 mA current. All samples were run at 1° (2θ) min^{-1} from 5° to 35° (2θ).

Infrared Spectroscopy

The IR spectra of the samples were obtained using a Fourier transform infrared spectrometer (FTIR-7300, Jasco, Japan). The measurements were carried out according to the KBr disk method.

Dissolution Study

The dissolution of various formulations was conducted using the USP paddle apparatus (11). A portion of samples that contained 20 mg of drug was weighed and added to 450 ml of phosphate buffer (pH 7.0 ± 0.2) consisting of 29.1 and 10.0 mN of sodium hydroxide and monobasic potassium phosphate, respectively (12). The temperature and paddle speed were set at 37°C ± 0.1°C and 50 ± 1 rpm, respectively. At correcting times, aliquots of the medium (5 ml) were taken and then measured for drug content by UV spectroscopy.

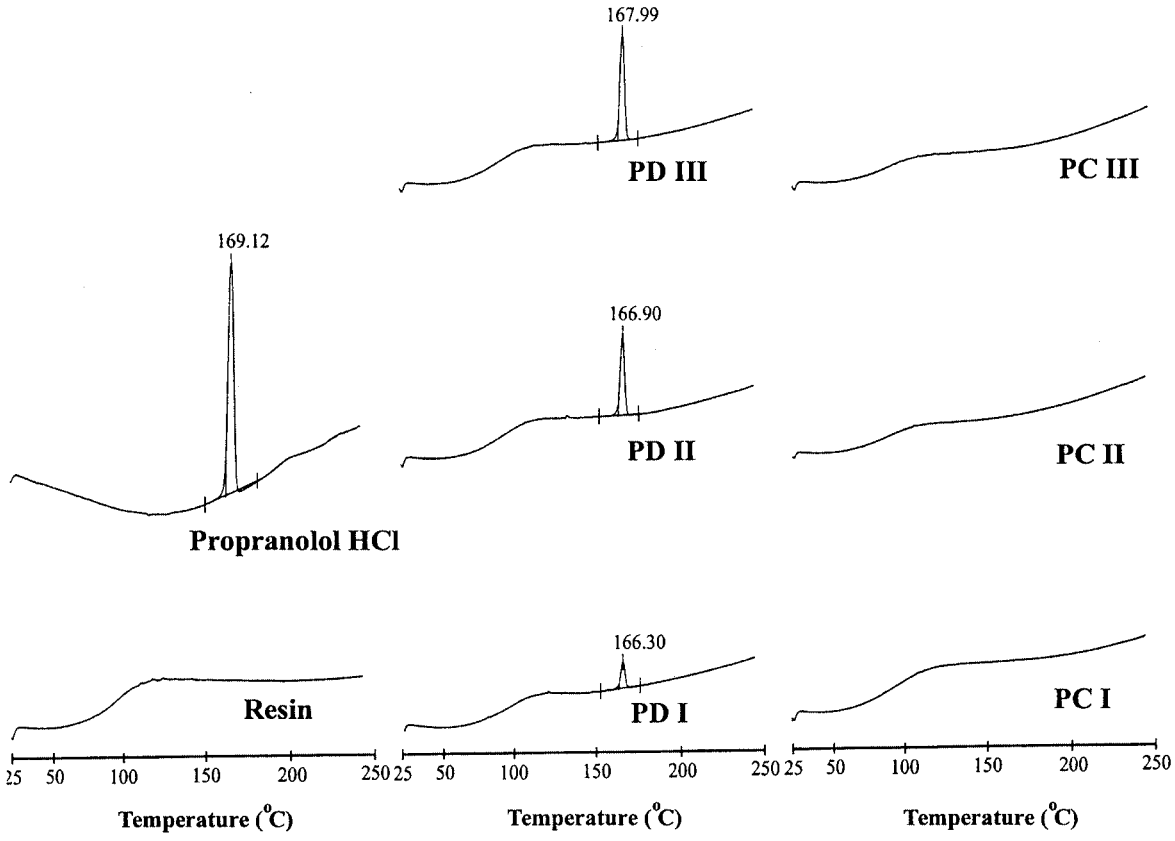


Figure 2. DSC curves of samples.

RESULTS AND DISCUSSION

The drug-resin complexes containing varying contents of drug were obtained successfully. PC I, PC II, and PC III had 15.5%, 32.4%, and 45.0% w/w of drug loading, respectively. This evidence followed a previous report that the drug loading onto drug-resin complexes increased with increasing concentration of loading solution (2). PD I, PD II, and PD III had the same drug contents as the respective complexes obtained.

Figure 2 shows the DSC curves of all samples. A sharp endothermic peak was observed at 169.12°C for pure drug, indicating the melting point of propranolol hydrochloride. The endothermic peak of pure drug was also shown in the case of physical dispersions at 166°C–168°C. On the other hand, no peak over the range 25°C–250°C was found in the DSC curves of the resin and all complexes.

The XRPD pattern of pure drug contained a number of sharp peaks, while the resin showed a diffused peak or halo pattern (Fig. 3). The XRPD patterns of the physical dispersions showed simply the sum of the characteristic peaks of pure drug and the diffused peak of the resin, whereas only a diffused peak was observed in the XRPD patterns for the complexes regardless of drug loading.

According to the data from DSC and XRPD, the molecular state of pure drug was crystalline, but that of the resin was amorphous. The molecular state of the drug prepared as drug-resin complexes was changed from the crystalline to the amorphous state. These results demonstrated that the entrapped molecule of drug was dispersed monomolecularly in the resin bead (13). In the case of physical dispersions, the molecule of drug, which was outside the resin bead, did not disperse monomolecularly, so the crystalline state of the pure drug was presented.

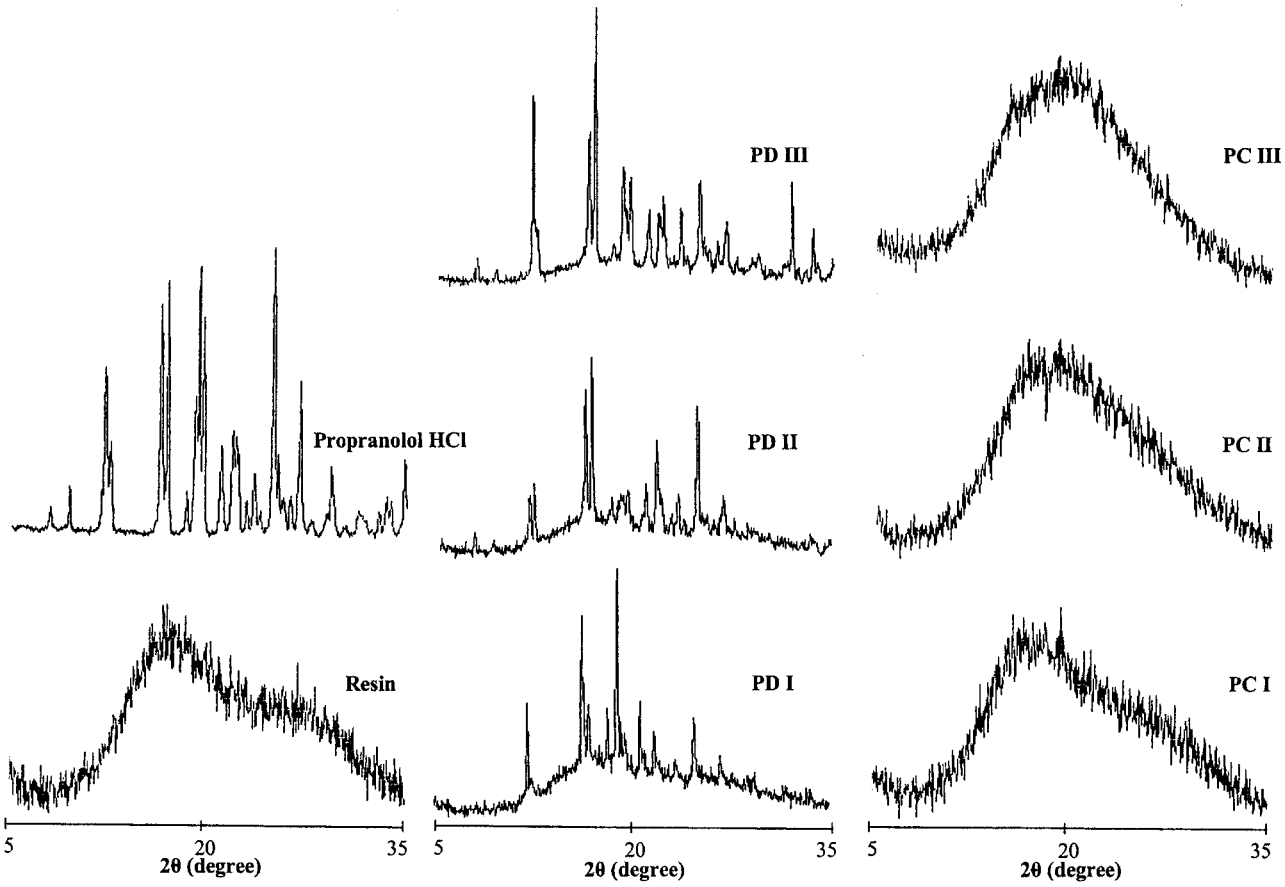


Figure 3. XRPD patterns of samples.

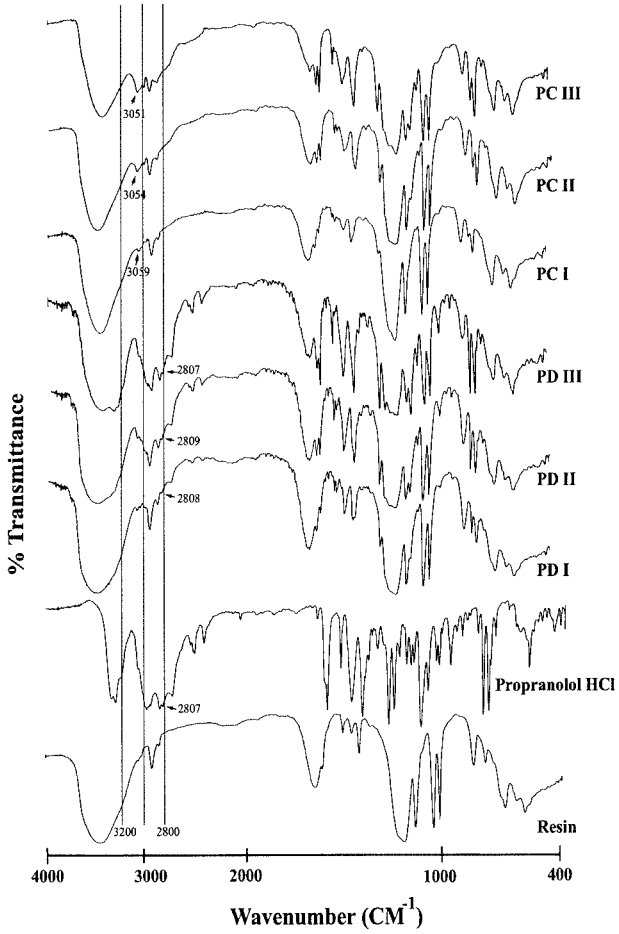


Figure 4. IR spectra of samples.

Figure 4 shows the IR spectra of the samples. It was seen that the IR spectra of the physical dispersions showed superimposition of the drug and resin spectra. This indicated that there was no appreciable interaction between the drug and resin in these mixtures, coinciding with the results from DSC and XRPD. The spectra of drug-resin complexes in the region 400–2000 cm^{-1} had a similar result, demonstrating the presence of drug in the complexes. However, for the rest, around 2000–4000 cm^{-1} the spectra of complexes obviously differed from the combination of each component. A peak at 2807 cm^{-1} and multiple combination peaks extending to 2350 cm^{-1}, which were assigned to the stretching vibrations of the NH_2^+ group of drug interacting with chloride ion, disappeared (or shifted). In addition, new peaks emerged around 3051–3059 cm^{-1} in the complex spectra. In comparison with certain peaks around this wavelength position, a distinguishing increase in intensity of the new peaks in the complex spectra ensures that they are not the usual peaks associated with either pure drug or resin. The formation of new chemical bonds would be expected to result in the emergence of additional peaks or alterations in wavenumber position (14). From this standpoint, the above finding can be interpreted that the NH_2^+ group of drug, which originally bound chloride ion in pure drug, was transformed to interact with the sulfonate group of resin in the complexes.

The dissolution profiles of drug from various formulations are reported in Fig. 5. As compared to pure drug and physical dispersions, the complexes provided slower rates of drug release even though the molecular state of drug in the complexes was amorphous. This indicated that the molecular property of drug was not a major determinant of the release behavior of drug for the complexes. The sustaining of drug release from the complexes was caused by the cross-linkage structure of the resin, which delayed the diffusion of drug from the interior and toward the surface of the resin bead. This unique cross-linkage structure has been considered a major cause of the sustained release of drug from drug-resin complexes (4,15,16).

Determining the equilibrium position of drug exchange can solve whether the drug release from various formulations attains equilibrium. The position of the equilibrium is commonly measured by the selectivity coefficient, defined as follows (17):

$$K_M^D = \frac{[D]_r[M]_s}{[D]_s[M]_r}$$

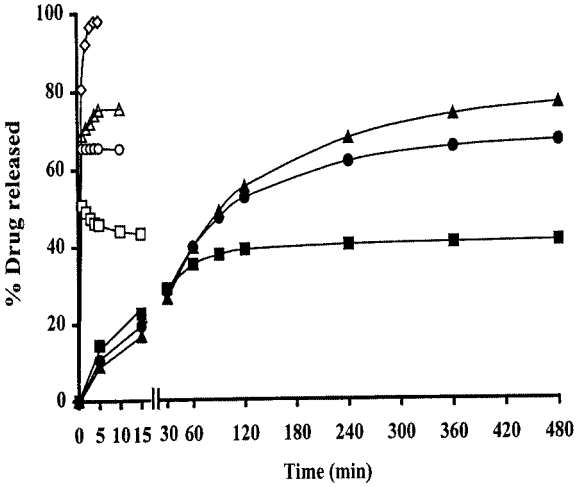


Figure 5. Dissolution profiles of ◇ propranolol HCl; □ PD I; ○ PD II; △ PD III; ■ PC I; ● PC II; ▲ PC III.

Table 1

Amount and Equilibrium of Drug Release

Formulations[a] Prepared From	Drug Released (%)	$[M]_r$[b] (mN)	$[D]_r$ (mN)	$[M]_s$ (mN)	$[D]_s$ (mN)	K_M^D
Physical dispersions						
PD I	44.07	0.959	0.084	39.184	0.066	51.83
PD II	65.24	0.346	0.052	39.152	0.098	60.23
PD III	75.53	0.197	0.037	39.137	0.113	64.49
Drug-resin complexes						
PC I	14.19	0.961	0.088	39.038	0.062	58.02
PC II	67.11	0.354	0.049	38.999	0.101	54.07
PC III	76.77	0.198	0.035	38.985	0.115	59.48

[a] Each contained 20 mg of drug.
[b] Total ionized sites of resin are 4.3 mEq/g.

where $[D]_s$, $[M]_s$, and $[D]_r$, $[M]_r$ represent the concentration (mN) of drug and cations, respectively, in the solution and resin phase at equilibrium. The total cations, which equals the sum of $[M]_s$ and $[M]_r$, includes ions from both the dissolution medium and those contributed by the resin in a tested formulation. $[M]_r$ is equal to the concentration of ionized sites on the resin less those occupied by the entrapped drug. Then, $[M]_s$ can be obtained by subtracting $[M]_r$ from the total cations. The similar value of selectivity coefficients (Table 1) suggested that the drug release of the formulations prepared from both physical dispersions and drug-resin complexes reached the same equilibrium. An increase in the amount of drug released in each series of formulations, which ranged from PD, PC I to II and III, was due to the decreasing quantity of resin, which directly reflected on the magnitude of $[M]_r$, as described above. This can be explained by virtue of the equilibrium treatment of drug exchange. As $[M]_r$ decreased (Table 1), other species had to change in such a way as to make the equilibrium position once again equal to K_M^D. Consequently, it required the decrease of $[D]_r$ and $[M]_s$ and the increase of $[D]_s$. In summary, this finding revealed that the release behavior of drug from drug-resin complexes was supplementarily governed by the equilibrium treatment of drug exchange aside from the cross-linkage structure of resin.

ACKNOWLEDGMENT

We are grateful to the Japan Society for the Promotion of Science and National Research Council of Thailand (JSPS-NRCT) for the financial support of this work.

REFERENCES

1. Schlichting, D. A. J. Pharm. Sci. **1962**, *51*, 134.
2. Kanhere, S. S.; Shah, R. S.; Bafna, S. L. J. Pharm. Sci. **1968**, *57*, 342.
3. Borodkin, S.; Sundberg, D. P. J. Pharm. Sci. **1971**, *60*, 1523.
4. Irwin, W. J.; MacHale, R.; Watts, R. P. Drug Dev. Ind. Pharm. **1990**, *16*, 883.
5. Ranghunatan, Y.; Amsel, L. P.; Hinsvark, O.; Bryant, W. J. Pharm. Sci. **1981**, *70*, 379.
6. Sriwongjanya, M.; Bodmeier, R. Int. J. Pharm. **1997**, *158*, 29.
7. Sanghavi, N. M.; Venkatesh, H.; Tandel, V. Drug. Dev. Ind. Pharm. **1994**, *20*, 1275.
8. Moyano, J. R.; Gines, J. M.; Arias, M. J.; Rabasco, A. M. Int. J. Pharm. **1995**, *114*, 95.
9. Kerc, J.; Srcic, S.; Kofler, B. Drug. Dev. Ind. Pharm. **1998**, *24*, 359.
10. Yonemochi, E.; Oda, K.; Saeki, S.; Oguchi, T.; Nakai, Y.; Yamamoto, K. Chem. Pharm. Bull. **1994**, *42*, 1948.
11. U.S. Pharmacopeial Convention, Dissolution. In *The United States Pharmacopeia 23/National Formulary 18*; Author: Rockville, MD, 1995; <711>, 1791–1792.
12. U.S. Pharmacopeial Convention, Buffer solutions. In *The United States Pharmacopeia 23/National Formulary 18*; Author: Rockville, MD, 1995; 2049–2050.
13. Oguchi, T.; Terada, K.; Yamamoto, K.; Nakai, Y. Chem. Pharm. Bull. **1989**, *37*, 1881.
14. Jenquin, M. R.; MaGinity, J. W. Int. J. Pharm. **1994**, *101*, 23.
15. Irwin, W. J.; Belaid, K. A.; Alpar, H. O. Drug Dev. Ind. Pharm. **1987**, *13*, 2047.
16. Burke, G. M.; Mendes, R. W.; Jambhekar, S. S. Drug. Dev. Ind. Pharm. **1986**, *12*, 713.
17. Borodkin, S.; Yunker, M. H. J. Pharm. Sci. **1970**, *59*, 481.