약제학회지 (1987), 제 17권 제 4호
J. Kor. Pharm. Sci., Vol.17, No.4, 175~181 (1987)

Enhancement of Dissolution Properties of Poorly Soluble Drugs (III) Dissolution Enhancement of Furosemide from Ground Mixtures with Chitin or Chitosan

Sang-Chul Shin, In-Joon Oh, Kang-Choon Lee, Yong-Bok Lee and Ik-Bae Koh
College of Pharmacy, Chonnam National University
(Received October 27, 1987)

난용성 약물의 용출 증가 (제 3 보)
키틴 또는 키토산과의 혼합분쇄물로부터의 푸로세미드의 용출 증가

신상철·오인준·이강춘·이용복·고익배
전남대학교 약학대학
(1987년 10월 27일 접수)

To increase the dissolution rate of furosemide, chitin and chitosan which are widely occurring biodegradable natural materials were used as drug carriers. The ground mixtures of furosemide with chitin or chitosan were prepared by grinding in a ball mill. The ground mixture showed a faster and more enhanced dissolution rate than the physical mixture or intact furosemide. The crystalline peaks of furosemide disappeared in the ground mixtures indicating the production of amorphous form. The comparison of infrared spectra of the physical mixture and the ground mixture showed an interaction such as association between the functional groups of furosemide and chitin or chitosan in the molecular level. The weight losses in TGA curves showed all the same patterns. However, the endothermic peak due to the fusion of furosemide in DTA curve disappeared in the ground mixture indicating the different thermal property. The dissolution of furosemide from ground mixtures was fast in the order of chitosan and then chitin. The co-grinding technique with chitin or chitosan provided a promising way enhancing the dissolution rate of practically insoluble drug.

The dissolution step of practically insoluble drugs plays an important role in the drug absorption process. To increase the dissolution rate of practically insoluble drugs, great efforts have been made[1-9]. In the earlier studies, it was shown that polyvinylpyrrolidone and polyethylene glycol, in the form of coprecipitates with furosemide[10-12], allobarbital[13], and phenobarbital[14], enhanced markedly the rate of dissolution of these water insoluble drugs.

In manufacturing powdered preparations, grinding is generally used for reducing the particle size of drugs since the dissolution rate is strongly affected by the particle size. Recently, the ground mixtures of some drugs with crystalline cellulose[15,16], gelatin[17], chitin and chitosan[18-24] were reported to enhance the dissolution properties of practically insoluble drugs. In the previous studies, the dissolution rates of piroxicam[18] and ketoprofen[19] were enhanced markedly by grinding with chitin or chitosan.

In this study, the dissolution enhancement of furosemide was attempted using co-grinding technique with chitin or chitosan which is widely oc-

curing biodegradable natural material. The dissolution properties and physicochemical modification of ground mixtures of furosemide were investigated by dissolution test, infrared spectroscopy (IR), X-ray diffractometry, differential thermal analysis (DTA) and thermogravimetric analysis (TGA).

EXPERIMENTAL

Materials

Chitin and chitosan from Sigma Chemical Co. (U.S.A.) were ground in a ball mill and used after passing a 100 mesh sieve. All other chemicals used were reagent grade and used as received. Furosemide (100—200 mesh) was pharmaceutical grade from Il-yang Pharm. Co., Ltd. (Korea).

Apparatus

Dissolution tester (Prolabo dissolution tester), UV spectrophotometer (Perkin-Elmer, Lambda 5), X-ray diffractometer (Rigaku Geigerflex), IR spectrophotometer (Perkin-Elmer, 783), and TG-DTA apparatus (Rigaku Thermoflex) were used.

Preparation of Furosemide Test Systems

The furosemide and chitin or chitosan (1:2 w/w ratio) were mixed uniformly with care to avoid any grinding action. The ground mixtures of furosemide with chitin or chitosan were prepared by grinding in a ceramic mortar for 24 hours.

Dissolution Test

The dissolution test of furosemide from the different test preparations was carried out at 37°C and 150 rpm in K.P. IV disintegration medium No. 1 (pH 1.2). Each test preparation equivalent to 40 mg of furosemide, which is an excess amount of drug beyond its equilibrium solubility, was transferred into 300m*l* of dissolution medium. 3.0 m*l* of sample solution was withdrawn at appropriate time intervals and filtered through a 0.45 μm Millipore filter and immediately replaced with an equal volume of fresh dissolution medium. The amount dissolved was calculated by determining the absorbance of appropriately diluted solution at 274 nm.

X-ray Diffractometry

X-ray diffraction studies were carried out using Rigaku Geigerflex X-ray diffractometer. The target was Cu-tube (Ni-filter), 35 KV, 15mA and the detector was a proportional counter, which voltage was 1.7KV.

IR Spectroscopy

Infrared spectra for furosemide test systems were observed by potassium bromide disk method, with a double beam, infrared spectrophotometer.

Thermometric Measurements

Thermogravimetric and differential thermal analyses were carried out using TG-DTA apparatus, fitted with platinum dish. The reference material was 5mg of alpha-alumina. The heating rate was 10°C/min, and the upper temperature limit was 600°C.

RESULTS AND DISCUSSION

Stability of Furosemide in Dissolution Medium

To verify the chemical stability during the dissolution test, the change of furosemide concentration was tested in dissolution medium for 4 days.

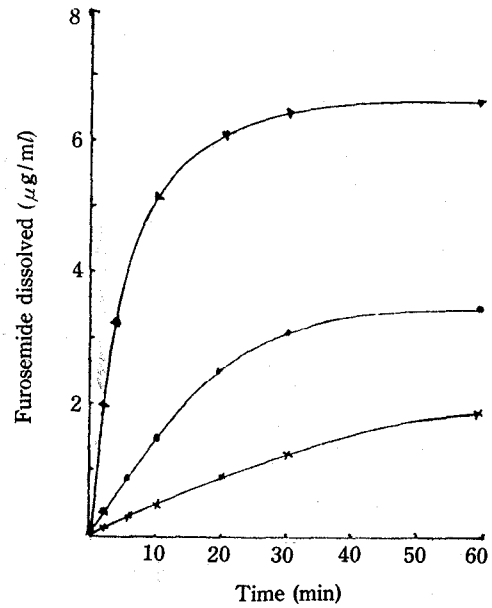

Figure 1—Dissolution rates of furosemide-chitin systems at 37°C and 150 rpm.
Key: ×, intact furosemide; ●, 1:2 furosemide-chitin physical mixture; ▲, 1:2 furosemide-chitin ground mixture

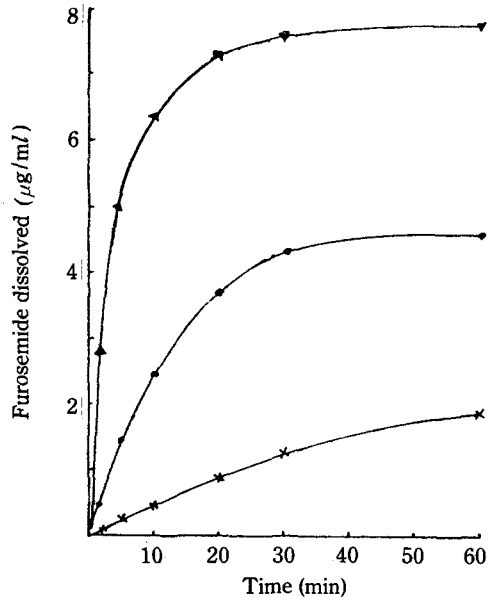

Figure 2—Dissolution rates of furosemide-chitosan systems at 37°C and 150 rpm.
Key: ×, intact furosemide; ●, 1:2 furosemide-chitosan physical mixture; ▲, 1:2 furosemide-chitosan ground mixture

The furosemide was stable in dissolution medium during the experiment.

Dissolution Rate Studies

The effect of chitin or chitosan on the dissolution behavior of furosemide was investigated. The dissolution properties of furosemide from the 1:2 furosemide-chitin ground and physical mixtures are shown in Fig. 1, in comparison with furosemide, and those for the furosemide-chitosan test systems are shown in Fig. 2. The amount of furosemide in solution from the chitin or chitosan physical mixture was slightly increased comparing with intact furosemide. This difference in dissolution of furosemide between the physical mixture and intact furosemide is considered to be simply due to the difference in wettability of hydrophobic furosemide particles. This was supported by the observation that intact furosemide floated on the surface of the dissolution medium longer than the physical mixture. The dissolution rate of furosemide from the chitin or chitosan ground mixture was significantly enhanced more greatly than that from the corresponding physical mixture.

This result indicates that furosemide is not merely present in the ground mixture as compared with the physical mixture. The dissolution of furosemide from the ground mixture with chitin or chitosan was significantly greater than intact furosemide. The dissolution of furosemide from ground mixtures was fast in the order of chitosan and then chitin.

No difference of dissolution between intact and simply ground furosemide was observed. Consequently, co-grinding technique with chitin or chitosan gave the fast dissolution of furosemide. The role of chitin or chitosan in the different enhancement of dissolution rate of furosemide among the ground mixture and the physical mixture is quite interesting. Apparently, furosemide and chitin or chitosan act independently in the physical mixture, while the role of chitin or chitosan in the ground mixture alters the physico-chemical characteristics of furosemide. Therefore, one can postulate that there might be an interaction between furosemide and chitin or chitosan.

X-ray Diffraction Studies

In preparing the powdered products, grinding

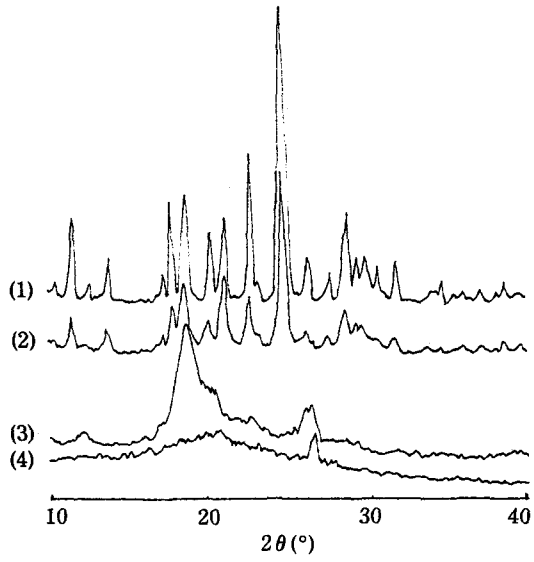

Figure 3—Comparison of X-ray diffraction patterns.
Key: (1), furosemide before grinding; (2), furosemide after grinding; (3), pure chitin; (4), pure chitosan

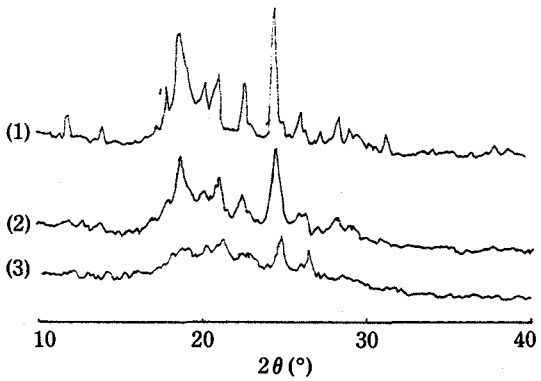

Figure 4—Comparison of X-ray diffraction patterns.
Key: (1), 1:2 furosemide-chitin physical mixture; (2), 1:2 furosemide-chitin ground mixture (16 hrs); (3), 1:2 furosemide-chitin ground mixture (24 hrs)

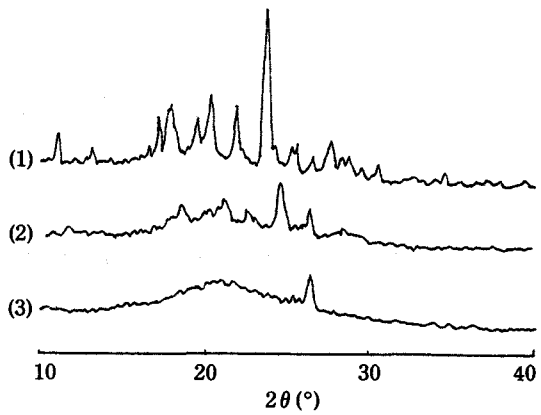

Figure 5—Comparison of X-ray diffraction patterns.
Key: (1), 1:2 furosemide-chitosan physical mixture; (2), 1:2 furosemide-chitosan ground mixture (16 hrs); (3), 1:2 furosemide-chitosan ground mixture (24 hrs)

is generally used for reducing the particle size, since the dissolution rate is strongly affected by the particle size.

In spite of the same combination ratio of drug to chitin or chitosan and the same particle size, the dissolution rate of furosemide from the ground mixture was markedly enhanced, while that from the physical mixture was not enhanced. At this point, X-ray diffraction studies were undertaken to unravel this phenomena. The pure furosemide showed the same diffraction peaks at 2θ degree of 18.0, 18.9, 22.8, 24.7, and 28.6 etc, indicating the presence of crystalline furosemide (Fig. 3).

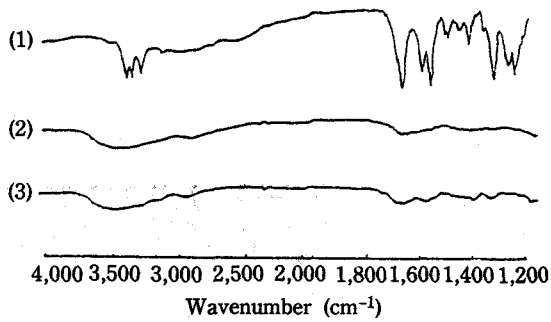

Figure 6—Comparison of infrared spectra.
Key: (1), pure furosemide (before and after grinding); (2), pure chitosan; (3), pure chitin

Interestingly, the physical mixture also showed crystallinity supposed to be due to the presence of crystalline furosemide and the intensity of diffraction peaks was dependent on the combination ratio of furosemide and chitin or chitosan (Figs. 4 and 5). Thus, the mere presence of chitin or chitosan in the physical mixture should not interfere with the crystallinity of co-existing furosemide.

On the other hand, X-ray diffraction peaks disappeared in the ground mixture indicating the formation of the amorphous state. It is also reported that amorphous states of drugs can be obtained by grinding drugs with microcrystalline cellulose. But when pure furosemide in the absence of chitin or chitosan was ground in a similar manner, the crystalline structure of furosemide was retained as judged by X-ray diffraction patterns. According to these results, furosemide is present as an amorphous form in the 1:2 ground mixture. The amorphous property of furosemide in the ground mixture is considered to be mainly responsible for the enhanced dissolution.

IR Spectra

When the drug was ground with chitin or chitosan, diffraction peaks of furosemide disappeared. In constrast, pure furosemide ground in a similar manner, in the absence of chitin or chitosan, showed crystallinity. To elucidate further physicochemical property, IR absorption spectra were investigated. From the IR spectrum of pure furosemide (Fig. 6), absorption bands are observed at 3340 cm^{-1} and 3260 cm^{-1}, and sharp bands at 1655 cm^{-1} and 1560 cm^{-1}. The 3340 cm^{-1} band is assigned to

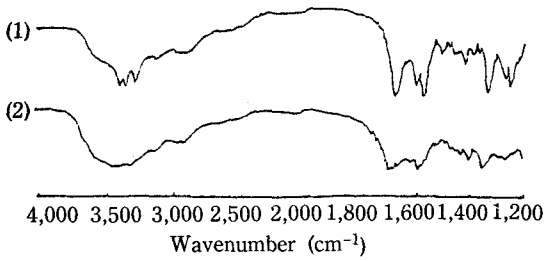

Figure 7—Comparison of infrared spectra.
Key: (1), 1:2 furosemide-chitin physical mixture; (2), 1:2 furosemide-chitin ground mixture

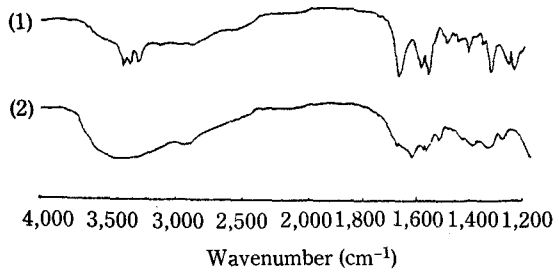

Figure 8—Comparison of infrared spectra.
Key: (1), 1:2 furosemide-chitosan physical mixture; (2), 1:2 furosemide-chitosan ground mixture

the NH stretching vibration of Ar-$NHCH_2$ and the 3260 cm^{-1} band to the NH stretching vibration of SO_2NH_2 and the 1655 cm^{-1} band which appears at such high frequency region is assigned to the bending vibration of amino group, the 1560 cm^{-1} band is to the asymmetric stretching vibration of carboxyl group and the 1318 cm^{-1} band is to the asymmetric stretching vibration of sulfonyl group in furosemide structure.

The IR spectra of the physical mixture (Figs. 7 and 8) showed the absorption bands illustrating the presence of furosemide and chitin or chitosan. However, in the spectra of the ground mixture, the sharp band observed in the region of 3500-3200 cm^{-1} became broad and weak. From the comparison of the spectra of physical, and ground mixtures, the stretching bands assigned to the non-bonded aromatic imino group and sulfonylamide group in furosemide molecule became weak and broad in the ground mixture, whereas the physical mixture showed the stretching vibrations.

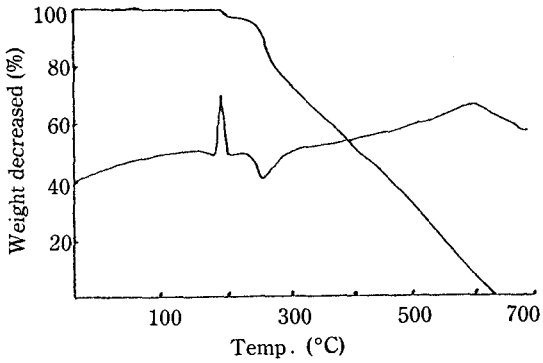

Figure 9—DTA and TGA thermogram of furosemide.

Therefore, it is presumed that the ground mixture shows an interaction such as association between the functional groups of furosemide and chitin or chitosan in the molecular level. The association between furosemide and chitin or chitosan is expected to be most probable between the imino group of furosemide and hydroxyl group of chitin or chitosan.

DTA and TGA Studies

The DTA and the TGA thermograms for furosemide test systems are shown in Figs. 9-12. The TGA thermograms of furosemide (Fig. 9) showed a weight loss of about 3.3% at 205° which was within the reported melting point range of 203-206° with decomposition, and the weight loss until 300° was about 22%. The DTA curves of intact furosemide exhibited a single, sharp exothermic peak at temperature of 220°, and an endothermic peak at about 280°C. The weight loss of about 3.3% at 205° in TGA thermograms seems most probably to be due to the ammonia decomposition in the furosemide molecule. Visual observations of the melting state suggested that a dark brown caramelized melting mass was observed at approximately 206°, and both peaks in DTA curves should be due to the degradation of furosemide (Fig. 9).

The weight loss of about 12% until 100°C in TGA curves of chitin and chitosan (Fig. 10) shows dehydration. TGA curves of the physical, and ground mixtures (Fig. 11) showed all the same patterns. The single endothermic peak due to the fusion of furosemide was observed in the physical

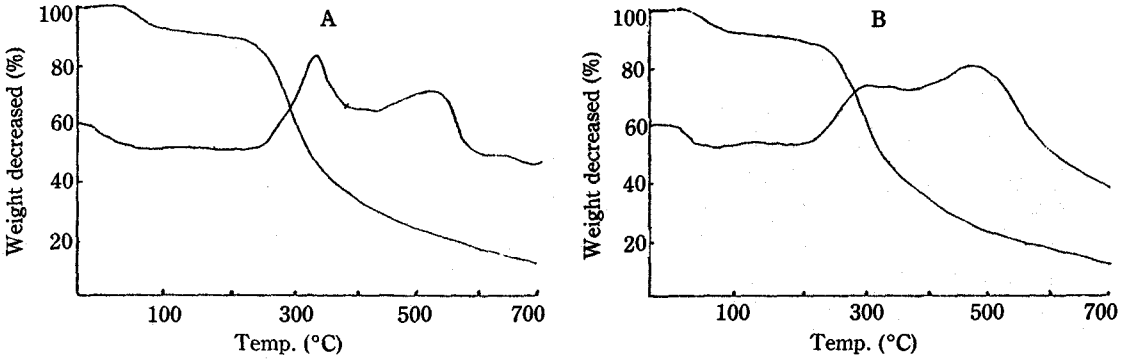

Figure 10—DTA and TGA thermograms of chitin (A) and chitosan (B).

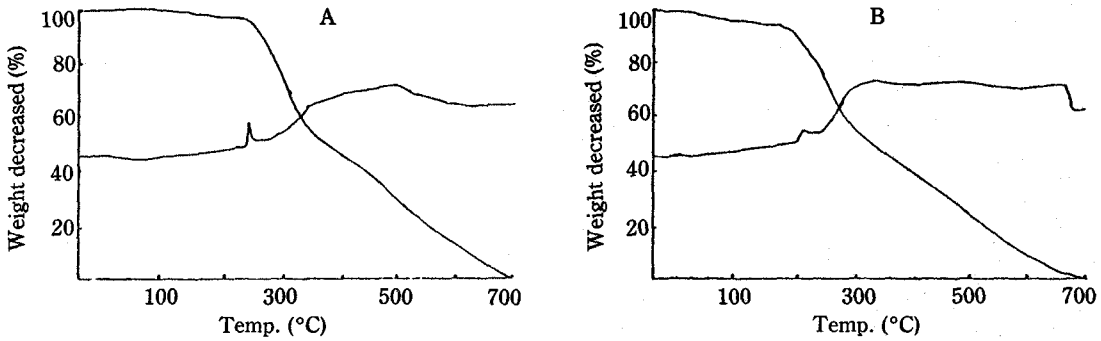

Figure 11—DTA and TGA thermograms of 1:2 furosemide-chitin physical (A) and ground (B) mixtures.

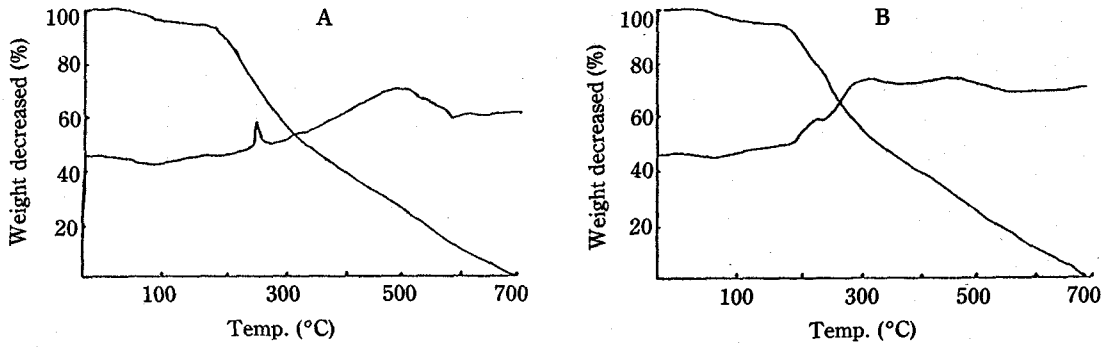

Figure 12—DTA and TGA thermograms of 1:2 furosemide-chitosan physical (A) and ground (B) mixtures.

mixture with chitin or chitosan, but the endothermic peak, heat of fusion due to the crystalline furosemide, disappeared in the ground mixture (Figs. 11 and 12).

This phenomena can be explained by the concept that the ground mixture may be regarded as an "entropy frozen solution" that a drug dissolved into chitin or chitosan without the ability of molecules to move throughout the whole system. It was reported that an apparent amorphous state of benzoic acid on vibrational ball milling with microcrystalline cellulose has been demonstrated by its lack of melting point from differential thermal calorimetric measurements. Some of the possible transformation that may take place during the ball milling process seems to be the formation of an amorphous structure either by partial melting of the crystalline furosemide powder and its interaction with chitin or chitosan or to be production of lattice defect due to the shear stress and impact

stress.

The effects of grinding on the heat of fusion, and the crystalline peaks of X-ray diffraction are closely correlated to each other. The relative enthalpy change may be considered to correspond to the disappearance of crystallinity. It may be said that the drug molecules were dispersed in the chitin or chitosan matrix of the ground mixture and the thermal property was changed.

CONCLUSIONS

The present investigations on the ground mixture of furosemide with chitin or chitosan showed the following results;

1. The dissolution rate of furosemide was rapid and markedly enhanced by co-grinding with chitin or chitosan and the extent of enhancing the dissolution of furosemide from the ground mixtures was fast in chitosan, followed by chitin.

2. X-ray diffraction study revealed that intact furosemide and furosemide contained within the physical mixture were crystalline in nature, whereas furosemide in the ground mixture system was not crystalline.

3. A comparison of the IR spectra showed that an association between the functional groups of furosemide and chitin or chitosan might occur in the molecular level.

4. The weight loss of pure furosemide, its physical and ground mixtures in TGA curves showed all the same patterns, however, the endothermic peak due to the fusion of furosemide disappeared in both chitin and chitosan ground mixtures, indicating the change of thermal property in DTA curves.

5. The co-grinding technique with chitin or chitosan provides a promising way of enhancing the dissolution rate of practically insoluble drugs.

ACKNOWLEDGEMENT

This work was supported by the research grant of Chonnam National University.

REFERENCES

1) W.L. Chiou, *J. Pharm. Sci.*, **66**, 980 (1977)
2) O.I. Corrigan, R.F. Timoney and M.J. Whelan, *J. Pharm. Pharmacol.*, **28**, 703 (1976)
3) O.I. Corrigan and R.F. Timoney, *J. Pharm. Pharmacol.*, **27**, 759 (1975)
4) M.B. Dexter, *J. Pharm. Pharmacol.*, **27**, Supp. 1-2, 58 (1975)
5) A.P. Simonelli, S.C. Metha and W.I. Higuchi, *J. Pharm. Sci.*, **59**, 633 (1970)
6) A.P. Simonelli, S.C. Metha, and W.I. Higuchi, *J. Pharm. Sci.*, **58**, 538 (1969)
7) J.C. Anderson and G.M. Boyce, *J. Pharm. Sci.*, **58**, 1425 (1969)
8) P. Molyneux and H.P. Frank, *J. Am. Chem. Soc.*, **83**, 3169 (1961)
9) R.E. Phares, *J. Pharm. Sci.*, **57**, 53 (1968)
10) S.C. Shin, *Arch. Pharm. Res.*, **2**, 49 (1979)
11) S.C. Shin, *Arch. Pharm. Res.*, **2**, 35 (1979)
12) S.C. Shin, M.H. Lee and C.H. Woo, *J. Kor. Pharm. Sci.*, **6**, 48 (1976)
13) S.C. Shin, M.H. Lee and S.K. Kim, *J. Kor. Pharm. Sci.*, **8**, 11 (1978)
14) S.C. Shin, Y.B. Kim and M.H. Lee, *Seoul Univ. J. Pharm. Sci.*, **2**, 95 (1977)
15) K. Yamamoto, M. Nakano, T. Arita, Y. Takayama and Y. Nakai, *J. Pharm. Sci.*, **65**, 1484 (1976)
16) K. Yamamoto, M. Nakano, T. Arita and Y. Nakai, *J. Pharmacokin. Biopharm.*, **2**, 487 (1974)
17) K. Kigasawa, K. Maruyama, M. Tanaka, K. Watabe and O. Koyama, *Yakugaku Zasshi*, **101**, 733 (1981)
18) I.B. Koh, S.C. Shin and Y.B. Lee, *Arch. Pharm. Res.*, **9**, 55 (1986)
19) I.B. Koh, S.C. Shin and Y.B. Lee, *J. Kor. Pharm. Sci.*, **16**, 36 (1986)
20) Y. Sawayanagi, N. Nambu and T. Nagai, *Chem. Pharm. Bull.*, **31**, 2507 (1983)
21) Y. Sawayanagi, N. Nambu and T. Nagai, *Chem. Pharm. Bull.*, **30**, 2935 (1982)
22) S. Miyazaki, K. Ishii and T. Nakai, *Chem. Pharm. Bull.*, **29**, 3067 (1981)
23) Y. Nakai, *Farumashia*, **17**, 601 (1981)
24) Y. Sawayanagi, N. Nambu and T. Nagai, *Chem. Pharm. Bull.*, **30**, 4464 (1982)