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Preparation and evaluation of a dry elixir for the enhancement of the dissolution rate of poorly water-soluble drugs

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Abstract

Various products of microcapsules containing a drug and ethanol in a dextrin wall were prepared using a spray dryer to improve the dissolution rate of poorly water-soluble drugs. Indomethacin (IMC), ketoprofen (KPF) and ibuprofen (IPF) were selected as model compounds. The microcapsules were spherical in shape with a smooth surface and small pieces of broken shells were adhered to large particles regardless of the type of drugs. A cross-sectional view of the dry elixir indicates a large inner cavity containing the ethanolic drug solution in a dextrin shell. The thickness of the dextrin wall (1–3 μm) is sufficient to hold the ethanol solution in the dextrin wall. The geometric mean diameters of L and H microcapsules prepared at low (95°C) and high (140°C) inlet temperatures were about 5.59 and 5.11 μm, respectively. As the ethanol contents increased, the mean diameter of the dry elixir also slightly increased. When the inlet air temperatures (140 vs 95°C) increased, the ethanol contents in the microcapsules decreased due to heat damage, a ballooning effect on the drying droplets and rapid volatilization of ethanol. Ethanol contents were greatest at an inlet air temperature of 90–100°C. The amounts of ethanol in the microcapsules were primarily controlled by the type and concentration of dextrin and inlet air temperature. Ethanol contents in the microcapsules were unchanged during 2 months storage in a sealed glass bottle at 25 ± 1°C. In dissolution studies of microcapsules, the drug dissolution rate within the first 5 min (k_1) from microcapsules increased dramatically. The k_1 of IPF, KPF and IMC in microcapsules was increased 2–3-, 3–4- and 4–9-fold when compared to drug alone. This result suggests that drugs encapsulated in microcapsules dissolve and disperse quickly as a result of the cosolvent effect of ethanol. However, the amounts of IPF and KPF in microcapsules dissolved for 60 min increased slightly whereas those of IMC were doubled when compared to drug only. The amounts of drugs dissolved from microcapsules were related to the ethanol content in microcapsules. The dissolution of drugs in microcapsules was satisfactorily described by a second-order kinetic process. The second-order dissolution rate constant (k_2) of drug in microcapsules was much greater than that of drug except for IPF. In the case of IPF, the k_2 of drug in microcapsules decreased appreciably although k_1 was larger compared to drug alone. Microcapsules simultaneously containing ethanol and drug in water-soluble dextrin membranes might be useful to improve the solubility, dissolution rate and bioavailability of poorly water-soluble drugs as a novel dosage form.

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1. Introduction

Poorly water-soluble drugs involve many difficulties in the development of pharmaceutical dosage forms for oral delivery systems due to low bioavailability. Several methods have been used to increase the solubility and dissolution rate of drugs for enhancing gastrointestinal absorption (Kawashima et al., 1975; Yamamoto et al., 1976; Kedzierewicz et al., 1990; Vudathala and Rogers, 1992). The spray-drying technique has been widely applied for drying heat-sensitive substances, preparing granules for tabletting, coating drugs with suitable polymers to produce dust-free powders and improving the solubility of poorly water-soluble drugs (Raff et al., 1961; Newton, 1966; Kawashima et al., 1975; Tanaka et al., 1980). Spray drying is also useful for the preparation of microcapsules, since coated particles can be produced from droplets via a single process. A powder alcohol, which is a microcapsule containing ethanol in a solid outlayer wall, was previously produced by use of the spray-drying technique (Sato and Kurusu, 1974; McCormick, 1977; Sato et al., 1982). An alcohol-containing powder has good water solubility, taste and storage stability. Alcohol or aroma is held in water-soluble materials such as gelatin, dextrin or the like having the ability to form coatings when three components of alcohol, water-soluble material and water are spray-dried at the lowest possible temperature. As a result, a solid product from which almost all of the water has been removed and in which the alcohol is held in water-soluble material is produced, since the diffusion coefficient of ethanol is very low in water-soluble dextrin as compared to water (Menting and Hoogstad, 1967; Menting et al., 1970). However, no attempt has previously been made on microcapsules simultaneously containing ethanol and drug in a solid dextrin wall using the spray-drying technique to improve solubility and dissolution rate of poorly water-soluble drugs in aqueous medium.

The purpose of this research was to prepare microcapsules containing a poorly water-soluble drug elixir termed a 'dry elixir' by varying the compositions and manufacturing conditions, and to evaluate the enhancement of the dissolution properties of poorly water-soluble drugs encapsulated in dextrin microcapsules. The three nonsteroidal anti-inflammatory agents, indomethacin (IMC), ketoprofen (KPF) and ibuprofen (IPF), were selected as model drugs. The physicochemical properties of the dry elixirs such as shape, size and stability were also investigated.

2. Materials and methods

2.1. Materials

Indomethacin (IMC), ketoprofen (KPF) and ibuprofen (IPF) were purchased from Sumitomo Pharm. Co. (Osaka, Japan), Rhone-Plounce Pharm. Co. (Seoul, Korea) and Samil Pharm. Co. (Seoul, Korea), respectively. Dextrin (TK-16®) was obtained from Matzdani Chem. Co. (Tokyo, Japan). Ethanol was of food grade. All other chemicals were of reagent grade and used without further purification.

2.2. Preparation of microcapsules

A Büchi 190 nozzle type minispray dryer (Flawil, Switzerland) was used for the preparation of microcapsules. Drug (1 g) was dissolved in 40 g of ethanol-water cosolvent (50% w/w). The resulting drug solution was prewarmed to 60°C and blended with dextrin (20 g) and sodium lauryl sulfate (0.2 g). The final solution was delivered to the nozzle at a flow rate of 5 ml/min using a peristaltic pump and thereafter spray-dried at 95°C inlet and 60°C outlet temperature. The microcapsules were accumulated in a cyclone separator. Microcapsules containing IPF, IMC and KPF were designated as L-IPFMC, L-IMCMC and L-KPFMC, respectively. When 120 g of ethanol-water cosolvent (50% w/w), and 140°C

inlet and 110°C outlet temperature were used, microcapsules of IPF, IMC and KPF prepared were also designated as H-IPFMC, H-IMCMC and H-KPFMC, respectively. The pressure of the spray air was 3 kg/cm^2 and the flow rate of dry air was maintained at an aspirator setting of 10. The direction of air flow was the same as that of sprayed product. Sodium lauryl sulfate was used to avoid attaching microcapsules to the inner wall of spray drying chamber. A schematic diagram representing the preparation of microcapsules is shown in Fig. 1.

2.3. Shape and size distribution of microcapsules

The shape and the surface of microcapsules were examined using a scanning electron microscope (Jeol, JJM-35, Tokyo, Japan). The microcapsules were coated with gold (Jeol Fine Coater, Japan) before taking photographs at an accelerating voltage of 2.4 kV. The size distribution of microcapsules was also determined using a laser particle analyzer (Fritsch Co., Ider-Oberstein, Germany).

2.4. Ethanol contents in microcapsules

Absolute ethanol (2 ml) and acetonitrile (2 ml) as an internal standard were mixed and adjusted to 50 ml with purified water in a 50 ml volumetric flask for the preparation of standard solutions. About 5 g of microcapsules accurately weighed and acetonitrile (2 ml) were dissolved in purified water in a 50 ml volumetric flask and adjusted to 50 ml with purified water for the preparation of sample solutions. The concentration of ethanol in microcapsules was determined using gas chromatography with a Porapak Q, Chromosorb 101 column. Nitrogen was used as a carrier gas. The temperatures of column, detector and injector were 150, 170 and 170°C, respectively.

2.5. Drug contents in microcapsules

Microcapsules were completely dissolved in 100 ml of methanol-water cosolvent solution (50%, v/v). The drug concentration was determined using a Pye Unicam 1750 UV/Vis spectrophotometer (Kyoto, Japan) at wavelengths of 221 nm (IPF), 260 nm (KPF) and 317 nm (IMC), respectively.

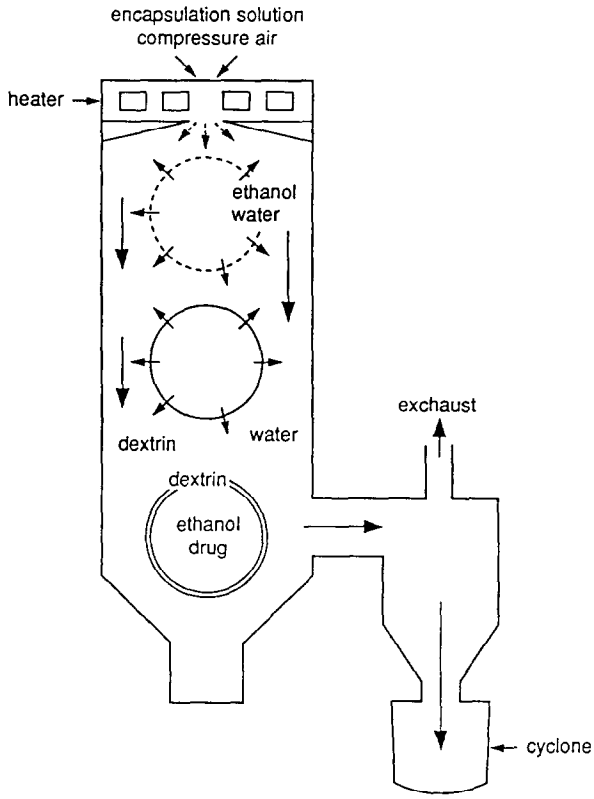
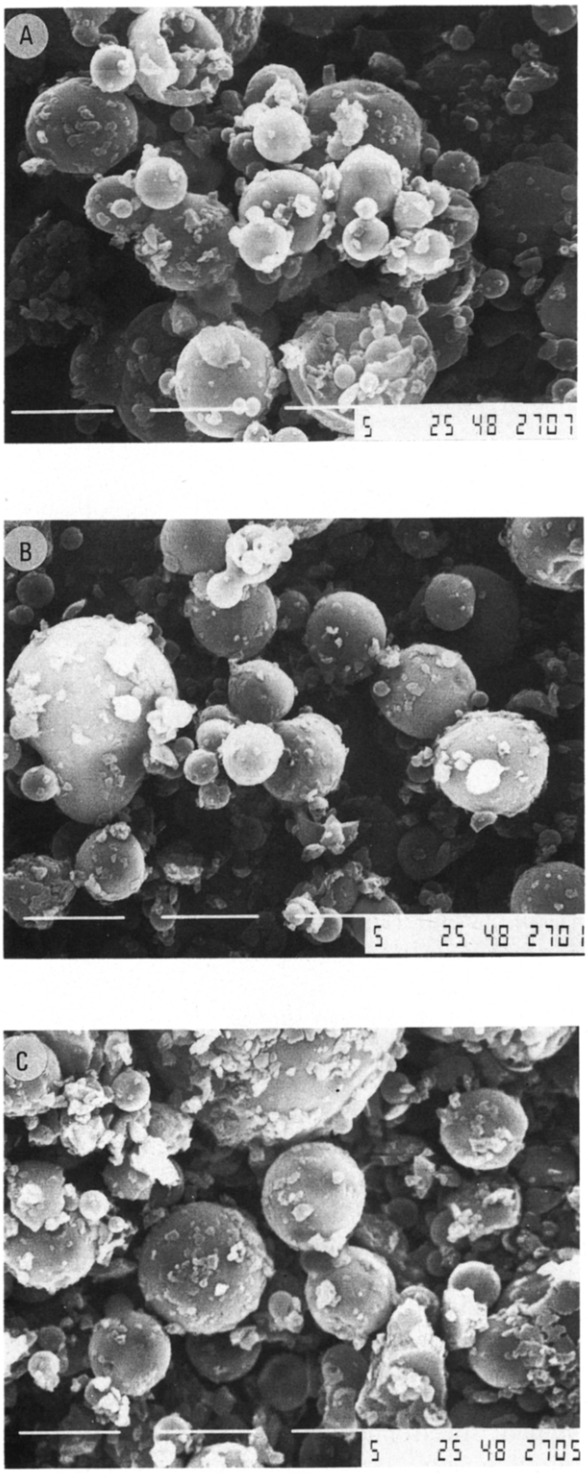


Fig. 1. Schematic diagram representing the preparation of microcapsules by spray-drying techniques.

2.6. In vitro dissolution studies

In vitro dissolution of drug encapsulated in microcapsules was performed using the USP XXII dissolution apparatus II (paddle method) at 37 ± 0.5°C. Microcapsules equivalent to 25 mg of drug were dispersed in the 900 ml of enzyme-free distilled water at a paddle stirring speed of 100 rpm. The samples (3 ml) were collected at 5, 10, 20, 30, 45 and 60 min with replacement of equal volume of temperature-equilibrated media and filtered through a membrane filter (0.22 μm). The concentration of drug released was determined spectrophotometrically. The dissolution profiles were further examined to evaluate the



dissolution kinetics of drugs in microcapsules (Vudathala and Roger, 1992).

3. Results and discussion

Generally, on drying dextrin dissolved in an ethanol-water cosolvent system on a rotary evaporator, the ethanol and water evaporate simultaneously and dextrin is finally dried. However, microcapsules containing ethanol in the dextrin shell are produced by spray-drying the above solution as follows. Spraying the dextrin dissolved in a ethanol-water mixture through a fluid pressure nozzle into the drying chamber at the appropriate temperature, ethanol and water are initially evaporated within the chamber of the spray dryer at the same time. However, when the outlayer wall of dextrin is completely formed, ethanol does not pass through the wall, due to the hydrophilicity of dextrin and the permeability difference between ethanol and water (menting and Hoogstad, 1967; Menting et al., 1970). As a result, ethanol is captured inside the dextrin shell and powder alcohol is produced. Employing the same principle of producing the powder alcohol, microcapsules containing a poorly water-soluble drug elixir (dry elixir) can be produced by spray-drying the drug and dextrin dissolved in the ethanol-water mixture.

Electron scanning micrographs of microcapsules are illustrated in Fig. 2. The microcapsules were spherical in shape with a smooth surface and small pieces of broken shells were found to adhere to large particles regardless of the drug used. A magnified view of dry elixirs (L-IPFMC) is also shown in Fig. 3. Fig. 3A also demonstrates the dry elixir to be spherical in shape with its outer surface surrounded by an intricate layer of dextrin. The cross-sectional view of dry elixirs in Fig. 3B shows the large inner cavity containing ethanolic drug solution in the dextrin wall. The log normal number distribution of particle size is

Fig. 2. Scanning electron micrograph of microcapsules (magnification, 200×0. (A) L-IPFMC; (B) L-IMCMC; (C) L-KPFMC.

commonly used to predict the geometric mean diameter and geometric standard deviation from a linear relationship between the logarithm of particle size and cumulative percent frequency on a probability scale (Martin et al., 1983). The log-probability plots of the number-based size distribution of microcapsules are given in Fig. 4. The geometric mean diameters of L-IMCMC and H-IMCMC were about 5.59 and 5.11 μm, respectively. The mean diameters of other dry elixirs were almost identical with those above (data not shown). As the ethanol contents increased, the mean diameter of the dry elixir also increased slightly. From these findings, the mean diameter may be mainly dependent on the manufacturing conditions (i.e., temperature, concentration of dextrin, etc.) irrespective of the drug. The wall thickness was calculated based on the weight of ethanol, drug and dextrin, mean diameter and density of microcapsules. This wall thickness

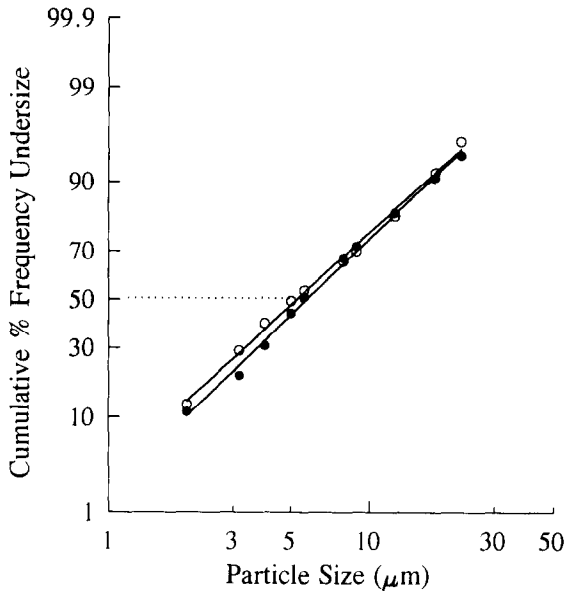


Fig. 4. Log-probability plots of number-based size distribution of microcapsules. The geometric mean diameter is the logarithm of particle size equivalent to 50% on the probability scale. (●———●) L-IMCMC; (○———○) H-IMCMC.

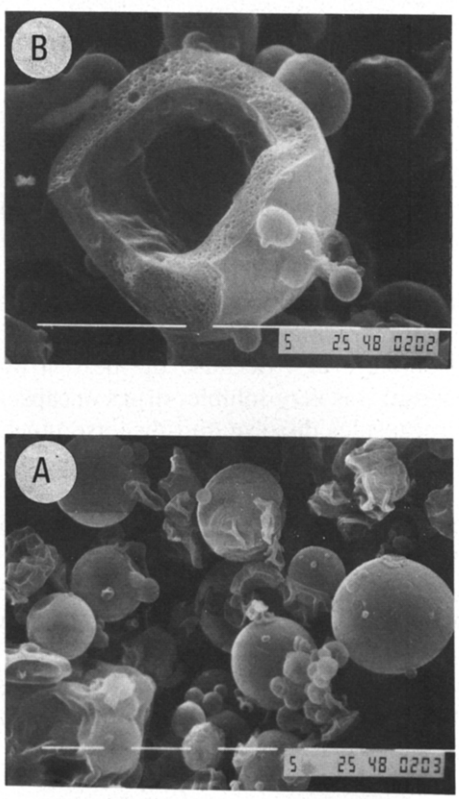


Fig. 3. Scanning electron micrograph of microcapsules (L-IPFMC). (A) surface; (B) cross-sectional view.

(about 1–3 μm) is large enough to hold the ethanol solution until dry elixirs are dissolved in aqueous medium. The detailed relationship between the cavity size of microcapsules and the dextrin wall thickness is of interest in order to maximize the encapsulation of elixir and optimize the manufacturing conditions of microcapsules.

It is desirable to maximize the ethanol contents in the dry elixir to improve the solubility and dissolution rate of poorly water-soluble drugs as a result of the cosolvent effect of ethanol. Selection of the type and concentration of dextrin and inlet air temperature was primarily important for maximization of the ethanol contents in the dry elixir. The ethanol and drug contents encapsulated in microcapsules are listed in Table 1. The dextrin having 16 of dextrous equivalence (TK-16®) led to greater ethanol contents in the dry elixir as compared to other grades of dextrin (data not shown). The more diluted dextrin solution was spray-dried, the smaller amount of ethanol being encapsulated as a result of the longer period required to form the dextrin outlayer. The higher the manufacturing tempera-

tures (inlet temperature, 140°C; outlet temperature, 110°C), the smaller were the ethanol contents observed owing to heat damage, ballooning effect on the drying droplets and rapid volatilization of ethanol, however, the drug contents in microcapsules increased slightly (L- vs H-microcapsules). The ethanol content in the dry elixir was greatest at an inlet air temperature of 90–100°C. The amounts of ethanol and drug in the microcapsules were governed by the compositions and manufacturing conditions of the microcapsules. When microcapsules were stored in a sealed glass bottle for 2 months at 25 ± 1°C, the elixir contents (alcohol and drug) remained unchanged compared to the initial contents encapsulated in microcapsules. This result suggests that microcapsule-encapsulating elixirs are stable at least for 2 months.

The dissolution profiles of three model drugs in microcapsules are compared in Fig. 5–7. The percentages of drugs dissolved for 5 and 60 min and the drug dissolution rate within the first 5 min (k_1) are summarized in Table 2. k_1 increased dramatically compared to the case of drug alone. k_1 of IPF, KPF and IMC was increased 2–3-, 3–4- and 4–9-fold compared to drug alone. The percentages of IPF and KPF dissolved from microcapsules for 60 min were slightly increased compared to drug alone (72.0, 63.9 vs 59.4%; 97.5, 92.8 vs 82.3%). However, the percentage of IMC dissolved from microcapsules for 60 min was approximately double in comparison to drug alone (96.6, 88.3 vs 40.5%). These results suggest that microcapsules containing ethanol and drugs are useful for improving the dissolution rate of poorly water-soluble drugs. Because the dextrin wall of microcapsules is very soluble, drugs encapsulated in microcapsules dissolve and disperse quickly as a result of the cosolvent effect of ethanol. The amounts of drugs dissolved and dispersed into aqueous medium were related to the ethanol contents in microcapsules.

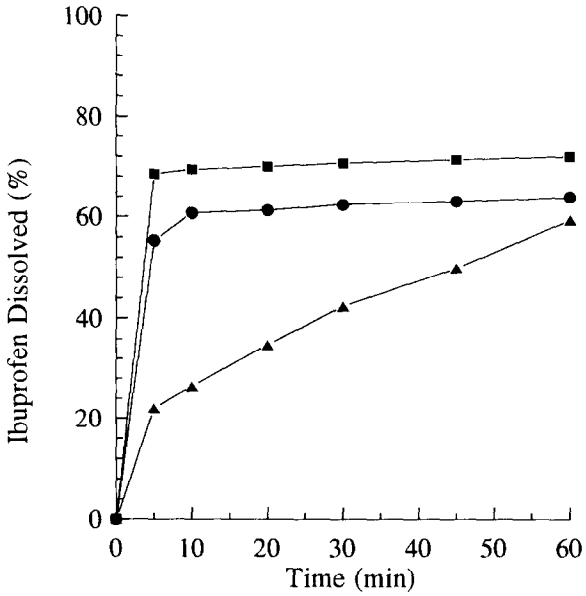


Fig. 5. Comparison of dissolution profiles of ibuprofen (IPF) microcapsules. The standard deviation was too small to show (▲——▲) IPF alone; (●——●) H-IPFMC; (■——■) L-IPFMC.

Table 1
The percentages of drug and ethanol contents encapsulated in various microcapsules

Products [a]	Drug content (%)		Ethanol content (%)	
	$t = 0$	$t = 60$ days [b]	$t = 0$	$t = 60$ days [b]
L-IPFMC	2.90	2.89	39.2	38.5
L-IMCMC	2.96	2.97	35.1	33.7
L-KPFMC	2.95	2.94	35.0	34.8
H-IPFMC	3.83	3.79	20.0	19.8
H-IMCMC	4.02	4.01	15.2	15.5
H-KPFMC	3.98	3.90	16.1	14.9

[a] In the preparation of L-IPFMC, L-IMCMC and L-KPFMC, drugs dissolved in 40 g of ethanol-water cosolvent (50% w/w) were spray-dried at 95°C inlet and 60°C outlet temperature. In the preparation of H-IPFMC, H-IMCMC and H-KPFMC, drugs dissolved in 120 g of ethanol-water cosolvent (50% w/w) were spray-dried at 140°C inlet and 110°C outlet temperature.

[b] Microcapsules were stored at room temperature (25 ± 1°C) for 60 days and ethanol contents were determined thereafter.

The dissolution of drugs in microcapsules behaved in accordance with second-order kinetics after an initial burst-out as shown in Fig. 8. There was a linear relationship between $W/W_e(W_e-W)$ and time according to the following equation (Vudathala and Roger, 1992):

$$\frac{W}{W_e(W_e - W)} = k_2 t$$

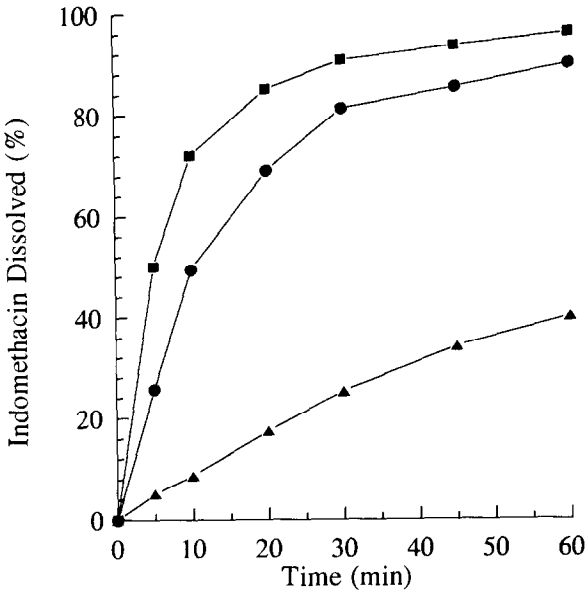


Fig. 6. Comparison of dissolution profiles of indomethacin (IMC) microcapsules. The standard deviation was too small to show. (▲——▲) IMC alone; (●——●) H-IMCMC; (■——■) L-IMCMC.

Table 2
Comparison of percentages of drugs dissolved from various microcapsules for 5 and 60 min

Products	% dissolved		k_1 [a]
	5 min	60 min	
IPF	21.6	59.4	1.08
L-IPFMC	68.4	72.0	3.42
H-IPFMC	50.4	63.9	2.52
IMC	5.4	40.5	0.27
L-IMCMC	50.4	96.6	2.52
H-IMCMC	23.4	88.3	1.17
KPF	25.2	82.3	1.26
L-KPFMC	90.0	97.5	4.50
H-KPFMC	68.4	92.8	3.42

[a] Drug dissolution rate within first 5 min (mg/min).

where W, W_e and k_2 indicate the amount of drug dissolved at time t, maximum amount of drug available for dissolution (equivalent to 25 mg of drug) and apparent second-order dissolution rate constant, respectively. The k_1 and k_2 of drug

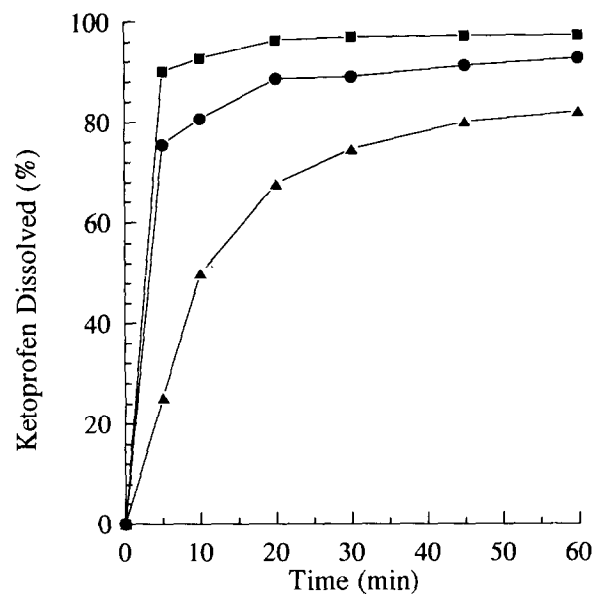


Fig. 7. Comparison of dissolution profiles of ketoprofen (KPF) microcapsules. The standard deviation was too small to show. (▲——▲) KPF alone, (●——●) H-KPFMC, (■——■) L-KPFMC.

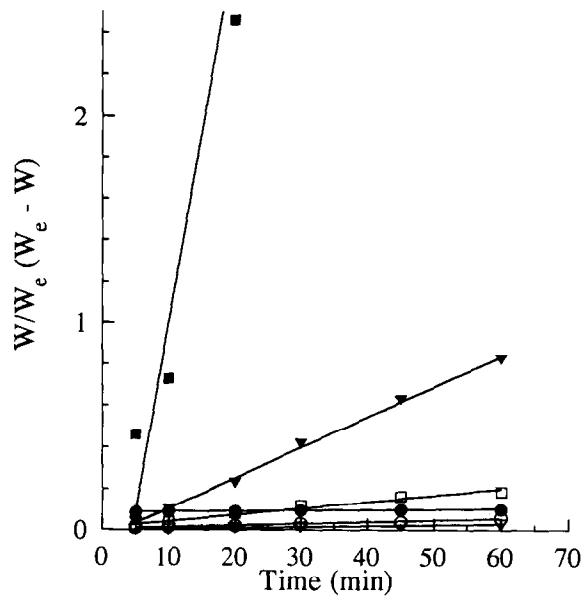


Fig. 8. A plot for the second-order dissolution kinetics of drugs from dissolution profiles. (△——△) IPF alone; (□——□) IMC alone; (○——○) KPF alone; (▲——▲) L-IPFMC; (■——■) L-IMCMC; (●——●) L-KPFMC.

Table 3
Comparison of the second order dissolution kinetics of drugs in microcapsules

Products	k_2 ($\times 10^4$) [a]	k_1 [b]
IPF	7.27 (0.99) [c]	1.08
L-IPFMC	3.05 (0.96)	3.42
IMC	4.72 (0.99)	0.27
L-IMCMC	145.2 (0.99)	2.52
KPF	37.4 (0.98)	1.26
L-KPFMC	1834.2 (0.97)	4.50

[a] Second-order dissolution rate constant (mg/min).
[b] Drug dissolution rate within first 5 min.
[c] Correlation coefficient from a linear regression analysis.

entrapped in microcapsules, and coefficient of determination (r) obtained from linear regression analysis are compared in Table 3. This result suggests that the dissolution of poorly water-soluble drugs in microcapsules was satisfactorily expressed on the basis of second-order kinetics. The dissolution rate constant of drug in microcapsules was much greater than that of drug except for IPF. In the case of IPF, k_2 of drug in microcapsules was decreased appreciably although the dissolution rate of drug within the first 5 min was greater compared to drug alone.

Microcapsules simultaneously containing ethanol and drug in water-soluble materials such as gelatin and dextrin might be useful to improve the solubility, dissolution rate and bioavailability of poorly water-soluble drugs in dosage form design. Poorly water-soluble and poorly bioavailable potent drugs may be good candidates for the preparation of dry elixirs using a spray-drying technique, especially to improve bioavailability in terms of clinical applications. The in vitro and in vivo relationships between dissolution and bioavailability of drugs are currently under investigation. In addition, scaling up of the production of microcapsules may be considered, since the spray-drying method currently used can provide simple and efficient manufacturing procedures.

4. Acknowledgements

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