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Factors Affecting the Dissolution of Ketoprofen from Solid Dispersions in Various Water-soluble Polymers[1)]

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Dissolution profiles of ketoprofen (KPF) from solid dispersions in water-soluble polymers were investigated by the rotating disk method, and great differences in dissolution behavior were observed among different kinds of polymers. Therefore, the physico-chemical nature of the polymers might play a predominant role in the dissolution of KPF from these solid dispersions. The quantitative relationship of dissolution behavior with several properties of the polymers depended on a combination of such factors as the water penetration of the compressed disk surface, pH of polymer solution and the apparent dissolution rate of polymers.

Keywords——solid dispersion; ketoprofen; water-soluble polymers; dissolution; water penetration; pH; dissolution rate of polymers; multiple regression analysis

In a previous paper,[2)] the authors reported the quantitatibve relationship, determined by multiple regression analysis, between the dissolution of indomethacin (IMC) dispersed in various water-soluble polymers and the physico-chemical properties of the polymers. A reasonably good fit, with statistical significance, between experimental and calculated values in the initial dissolution stage was obtained by taking into account such factors as water penetration of the compressed disk surface of samples, hardness and gelation of polymers. To confirm the general validity of the results described in the previous paper, the factors affecting the dissolution of ketoprofen (KPF), a poorly water-soluble drug similar to IMC, dispersed in water-soluble polymers were analyzed by statistical procedures.

Experimental

Materials——KPF, generously supplied by SS Pharmaceutical Co., Ltd., was used after recrystallization from 50% aqueous ethanol solution. Seventeen water-soluble polymers used are listed in Table I. CGN, MC-I, MC-II and MC-III (13—18 cps, 80—120 cps and 350—550 cps, 2% in water, at 20°C), PVA (degree of saponification, about 80%; number of unit molecules, about 2000), PVP K-30 and PVP K-90, ALG-Na of JP X grade and PC were purchased from Tokyo Kasei Industrial Co., Ltd. ARG of JP X grade was purchased from Kanto Chemicals Co., Ltd. TRG of JP X grade was purchased from Inuhinode Pharmaceutical Co., Ltd. GLT of J.I.S. first grade was purchased from Nitta Gelatin Co., Ltd. GUG and LBG were generously supplied by Sansho Co., Ltd.

Preparative Method for Freeze-dried Samples——KPF and each polymer at a weight ratio of 1: 2 were dissolved in aqueous ammonium solution, because KPF is very slightly soluble in water,[3)] and then freeze-dried. No ammonium ion was detected in the products by qualitative analysis using Nessler's reagent. The other conditions were the same as described in the previous paper.[2)]

Identification of Compounds——Powder X-ray diffractometry and differential scanning calorimetry were employed in the same way as described in the previous paper.[4)]

Procedure for Dissolution Study——The dissolution rate of KPF from the freeze-dried samples was determined by a rotating disk method. The procedure employed was the same as described in the previous paper,[5)] and was carried out under the following conditions: 30 ml of 1/15 M phosphate buffer solution, pH 6.0, at 37°C; the rotating velocity of the disks was 100 rpm; the disks, which contained 66.7 mg of KPF, were of 1.3 cm diameter, compressed under 200 kg/cm^2 by a Shimadzu hydraulic press for KBr tablets for infrared spectroscopy. At appropriate intervals, 1 ml aliquots of the solution were taken, and the volume was kept constant by adding the same amount of fresh dissolution medium at the same temperature. The concentration of KPF was determined by the ultraviolet (UV) absorption method.

Table I. Water-soluble Polymers used in This Study

Polymer	Abbreviation
Dextran T-40	DEX T-40
Dextran T-70	DEX T-70
Polyvinylpyrrolidone K-30	PVP K-30
Polyvinylpyrrolidone K-90	PVP K-90
Carboxymethyl cellulose sodium	CMC-Na
Polyvinyl alcohol	PVA
Methyl cellulose (13—18 cP)[a]	MC-I
Methyl cellulose (80—120 cP)	MC-II
Methyl cellulose (350—550 cP)	MC-III
Sodium alginate	ALG-Na
Gelatin	GLT
Carrageenan	CGN
Pectin	PC
Gum arabic	ARG
Gum tragacanth	TRG
Guar gum	GUG
Locust been gum	LBG

a) Values in parentheses indicate the viscosity range of 2% aqueous solution at 20°C, supplied by Tokyo Kasei Industrial Co., Ltd.

Procedure for Determination of Factors Affecting the Dissolution of KPF——The following factors, based on the physico-chemical properties of the polymers or freeze-dried samples, were selected as possible factors affecting the dissolution of KPF from solid dispersions.

1) Solubilizing Effect of Polymers on KPF (*SE*): One hundred mg of KPF and 10 ml of 1/15 M phosphate buffer solution (pH 6.0) containing 0.1% polymer were put into a 25 ml test tube and shaken for 72 h at 37°C. The solution was filtered with a Toyo TM-2 membrane filter (0.45 μm). The concentration of KPF in the filtrate was determined by the UV absorption method after dilution with the buffer solution. The ratio of this concentration to the solubility of KPF was used as the value of *SE*.

Determination of the following factors was carried out exactly as described in the previous paper:[2] 2) Amount of 1/15 M phosphate buffer solution (pH 6.0) absorbed on the sample disk surface (*WA*); 3) Fracture resistance test of a compressed tablet of sample (*FR*); 4) Thickness of gel formed on the sample disk surface (*GF*); 5) pH of polymer solution (*PH*): 6) Viscosity of polymer solution (*VP*); 7) Apparent dissolution rate of polymers (*DP*).

Results and Discussion

Figure 1 shows the powder X-ray diffraction patterns of KPF/PVP K-30 solid dispersion. Several sharp diffraction peaks attributed to KPF crystals disappeared after freeze-drying. In differential scanning calorimetry, no endothermic peak accompanying the melting of KPF crystals was seen in this solid dispersion. Therefore, KPF was considered to be in the amorphous state in the polymer. KPF was also in the amorphous state in the other polymers. As examples, the dissolution properties of KPF dispersed in DEXs T-40 and T-70 as determined by the rotaing disk method are shown in Fig. 2. The apparent dissolution rate (*DR*), which was calculated from the initial dissolution line in Fig. 2, is summarized in Table II, and large differences were observed among the various kinds of polymers used. In particular, a marked increase in *DR* was observed in the cases of DEXs T-40 and T-70. On the other hand, a decrease in *DR* was observed in the cases of CMC–Na, PVA, TRG, ALG–Na, MCs and CGN even though KPF was in the amorphous state in these polymers. Therefore, the physico-chemical properties of the polymers may play a predominant role in the dissolution of KPF, in accord with the findings in the previous paper.[2]

The relationship between *DR* and physico-chemical properties of polymers was investigated by stepwise multiple regression analysis.[6] Seven factors (*WA*, *FR*, *GF*, *VP*, *PH*, *DP* and *SE*) initially selected as predictors of *DR* are listed in Table II. *DP*, *WA* and *PH* were selected

as the optimum factors for the prediction of *DR* with a loglinear regression model (Table III). This result did not agree exactly with that obtained for IMC described in the previous paper.[2] The contribution of *DP* to *DR* is relatively great, so a mechanism similar to that of drug-release from suppositories and ointments may also operate in the dissolution of KPF from

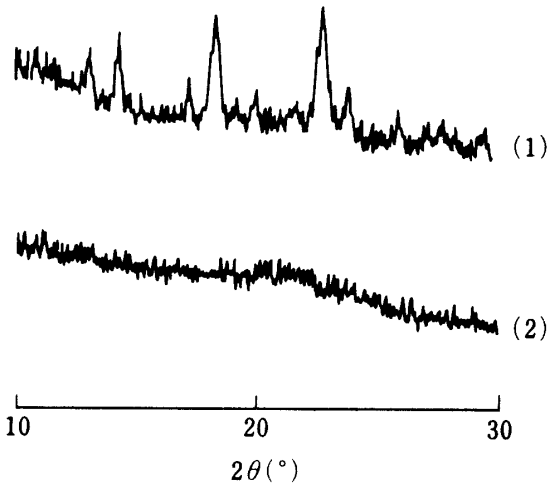

Fig. 1. Powder X-Ray Diffractin Patterns of KPF/PVP K-30 Solid Dispersions

(1) physical mixture, (2) freeze-dried sample.

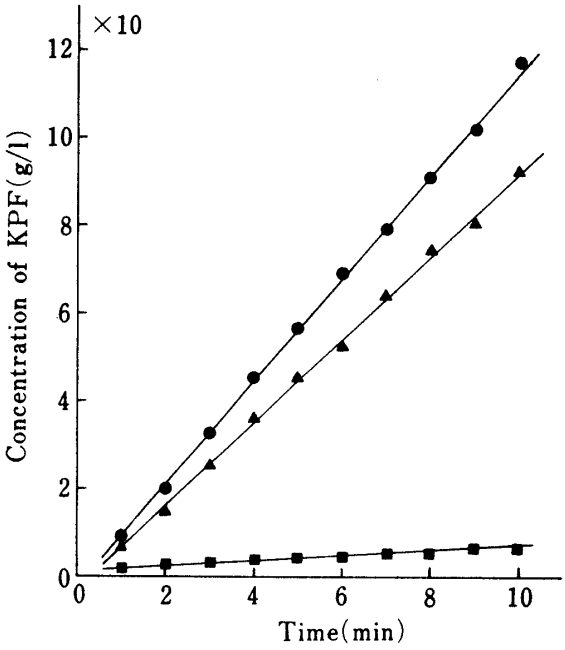

Fig. 2. Dissolution Profiles of KPF from Freeze-dried Samples with DEX T-40 (●) and DEX T-70 (▲) according to the Rotating Disk Method in 1/15 M Phosphate Buffer Solution (pH 6.0) at 37°C (■, intact KPF as reference)

TABLE II. Physico-chemical Properties Selected as Predictors of the Dissolution Rate of KPF (Dependent Variable)

Water-soluble polymer	$DR^{a)}$ (g/l·min)	$WA^{b)} \times 10^2$ (ml)	$FR^{b)}$ (kg/mm)	$GF^{c)}$ (mm)	$VP \times 10^{-1}$ (cP)	PH	$DP^{b)}$ (mg/min)	$SE^{a)}$
Not added	0.558	—	—	—	—	—	—	—
DEX T-40	12.0	3.25	0.388	0.686	0.0815	7.34	5.72	1.04
DEX T-70	9.73	3.40	0.583	0.278	0.0840	7.72	3.61	1.10
PVP K-30	6.60	3.10	0.838	0.458	0.0802	4.56	4.35	1.17
PVP K-90	0.684	4.15	1.71	0.614	0.230	6.07	2.64	1.06
CMC-Na	0.477	2.80	2.81	1.33	2.10	6.79	1.78	1.05
PVA	0.415	2.50	0.392	0.824	0.140	6.35	1.68	1.04
MC-I	0.470	3.15	2.20	0.348	0.234	6.58	2.02	1.03
MC-II	0.342	3.25	2.21	0.362	1.17	4.96	3.61	1.04
MC-III	0.339	2.00	2.34	0.432	1.98	5.23	3.11	1.08
ALG-Na	0.463	2.85	3.97	1.35	21.3	7.33	1.58	1.03
GLT	1.34	1.40	3.01	0.795	0.103	6.11	8.25	1.00
CGN	0.471	3.40	0.965	2.00	40.1	9.00	1.26	0.997
PC	0.764	4.40	1.13	1.42	0.980	3.77	2.79	0.943
ARG	3.17	3.80	1.65	0.688	0.112	4.90	4.11	1.04
TRG	0.0260	1.00	2.65	1.27	14.0	5.13	1.76	1.02
GUG	0.963	1.75	1.87	0.938	194	6.40	2.13	1.00
LBG	1.13	1.55	2.63	1.00	6.42	6.67	1.84	1.00

a) Each datum is the mean of two determinations.
b) Each datum is the mean of three determinations.
c) Each datum is the mean of five determinations.

Table III. Stepwise Development of the Correlation Equation for DR

Equation	$\log DR = a\log DP + b\log WA + c\log PH -$ constant							
	a	b	c	constant	n	s	r	F
1	1.74 (±1.02)[a]			0.806 (±0.490)	17	0.530	0.600	8.44
2	1.67 (±0.90)	1.50 (±1.10)		1.40 (±0.61)	17	0.467	0.733	8.13
3	2.02 (±0.84)	1.52 (±0.97)	2.56 (±1.95)	3.56 (±1.73)	17	0.412	0.816	8.63

a) 95% confidence intervals.

these solid dispersions. In any case, the statistical significance was not high, so other factors must be taken into consideration for the general prediction of dissolution properties of KPF from these systems.

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References and Notes

1) This paper forms Part XXVIII of "Pharmaceutical Interactions in Dosage Forms and Processing." The preceding paper, Part XXVII: Y. Sawayanagi, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **30**, 2935 (1982).
2) K. Takayama, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **30**, 678 (1982).
3) It was ascertained by thin-layer chromatography of the products that KPF was not degraded during the procedure.
4) K. Takayama, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **25**, 2608 (1977).
5) H. Nogami, T. Nagai, and A. Suzuki, *Chem. Pharm. Bull.*, **14**, 329 (1966).
6) This calculation was carried out on a SHARP MZ-80C micro computer with a program written by the authors.