Chem. Pharm. Bull.
30(2) 673—678 (1982)

Factors affecting the Dissolution of Indomethacin dispersed in Various Water-Soluble Polymers[1,2]

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(Received July 14, 1981)

Dissolution profiles of indomethacin (IMC) dispersed in water-soluble polymers were investigated by the rotating disk method, and large differences in dissolution behavior were observed with different kinds of polymers. Therefore, the physico-chemical nature of the polymers might play a predominant role in the dissolution of IMC from these systems. The quantitative relationship of dissolution behavior with several properties of the polymers was investigated by the application of multiple regression analysis. A reasonably good fit, with statistical significance, between experimental and calculated values in the initial dissolution stage was obtained by taking into account factors such as water penetration of the compressed disk surface, hardness and gelation of polymers.

Keywords——indomethacin; water-soluble polymers; dissolution; water penetration; hardness; gelation; multiple regression analysis

Many studies have been carried out on enhancement of the solubility and dissolution rate of slightly soluble drugs by the utilization of a solid dispersion or molecular dispersion in water-soluble polymers such as polyethyleneglycol[3] and polyvinylpyrrolidone.[4] However, the quantitative relationship between dissolution profiles of drugs from such systems and fundamental factors such as physico-chemical properties of the polymers has not been studied in detail.

In the present study, we attempted to find a quantitative relationship between the dissolution profiles of indomethacin (IMC) dispersed in various water-soluble polymers by the freeze-dry method and some factors affecting the dissolution of IMC, such as water penetration of the compressed disk surface of samples, the hardness of compressed tablets of samples, gelation of polymers, pH, viscosity and apparent dissolution rate of polymers.

Experimental

Materials——IMC, generously supplied by S.S. Pharmaceutical Co., Ltd., was used after recrystallization from diethyl ether. The following water-soluble commercial polymers were used: carrageenan, methyl cellulose (13—18 cP, 2% in water, at 20°C), polyvinyl alcohol (degree of saponification, about 80%; number of unit molecules, about 2000), polyvinylpyrrolidones K-30 and K-90, sodium alginate, and sodium carboxymethyl cellulose (Tokyo Kasei Industrial Co., Ltd.); dextrans T-40 and T-70 (Pharmacia Fine Chemicals Co., Ltd.); gum arabic powder J.P.IX (Kanto Chemicals Co., Ltd.); gum tragacanth powder J.P.IX (Inuhinode Pharmaceutical Co., Ltd.); hydroxypropyl cellulose-SL (Nippon Soda Co., Ltd.); low methoxy pectin (Sunkist Growers Inc.); gelatin J.I.S. first grade (Nitta Gelatin Co., Ltd.); Guar gum was generously supplied by Sansho Co., Ltd.

Preparation Method for Freeze-dried Samples——Chart 1 shows the method for dispersion of IMC in various water-soluble polymers. IMC and each polymer in a weight ratio of 1: 2 were dissolved in aqueous ammonium solution, because IMC is only very slightly soluble in water,[5] and then freeze-dried. No ammonium ion was detected in the products by qualitative analysis using Nessler's reagent.

Identification of Compounds——Powder X-ray diffractometry and differential scanning calorimetry were employed in the same way as described in the previous paper.[6]

Procedure for Dissolution Study——The dissolution rate of IMC from the freeze-dried samples was determined by a rotating disk method. The procedure employed was the same as described in the previous paper.[7] Every experiment was carried out under the following conditions: 30 ml of 1/15 M phosphatebuffer solution, pH 6.0, at 37°C; the rotating velocity of the disks was 100 rpm; the disks were of 1.3 cm diameter,

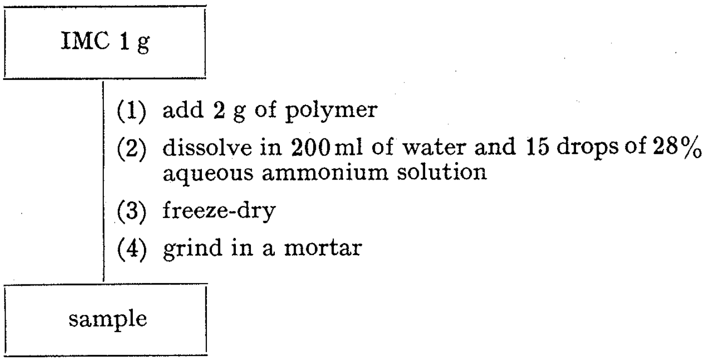

Chart 1. Preparative Method for Freeze-dried Sample

compressed under 200 kg/cm^2 by a Shimadzu hydraulic press for KBr tablets for infrared spectroscopy. At approproate intervals, 1 ml of 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 IMC was determined by the ultraviolet (UV) absorption method.

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

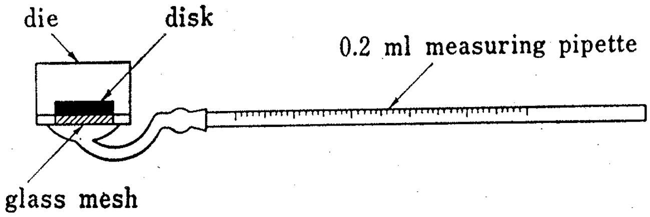

Fig. 1. Procedure for Determination of Water absorbed on the Disk Surface

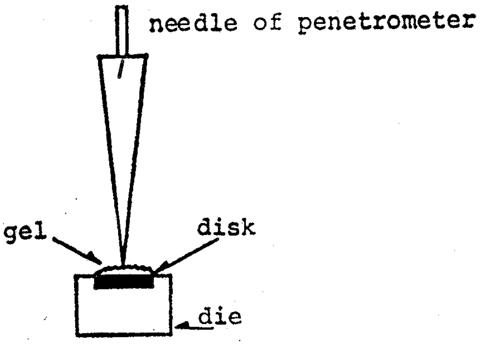

Fig. 2. Procedure for Determination of the Thickness of Gel formed on the Disk Surface

1) Amount of Water absorbed on Sample Disk Surface (*WA*): The value of *WA* was determined by means of the apparatus shown in Fig. 1. Sample powder (200 mg) was compressed in a cylindrical die of 1.3 cm inner diameter in a Shimadzu hydraulic press for KBr tablets for infrared spectroscopy, and the disk was not ejected. The compressed disk, still in the die, was put on a glass mesh (G-3) in the apparatus, as shown in Fig. 1, and the amount of water absorption of each sample was measured after 5 min at 20±2°C (the absorption process was apparently complete in 2—3 min).

2) Fracture Resistance Test of Compressed Tablet (*FR*): A tablet consisting of 150 mg of sample powder, which had been compressed directly under 200 kg/cm^2, was tested in a Kiya hardness tester using a specially[8)] designed accessory as described in the previous paper.[9)]

3) Thickness of Gel[10)] formed on the Polymer Disk Surface (*GF*): This measurement was carried out under the same conditions as the dissolution study using disks of polymers, as it had been confirmed in a preliminary experiment that there was a good correlation between the values observed for the disk containing the drug and that containing polymer alone. Reproducible data were obtained after 10 min, as confirmed by the preliminary experiment, so the thickness of gel formed on the disk surface was measured by the application of a Yoshida penetrometer (the tip angle of the needle was 15° and the needle weight was 21.1 g) after 10 min, as shown in Fig. 2.

4) pH of Polymer Solution (*PH*): The pH of 1% polymer aqueous solution was measured with a Corning model 130 digital pH meter at 20±2°C.

5) Viscosity of Polymer Solution (*VP*): The viscosity of 1% polymer aqueous solution was measured with a Ubbelohde viscometer and a Tokyo Keiki B-type viscometer at 37°C.

6) Apparent Dissolution Rate of Polymers (*DP*): This measurement was carried out under the same conditions as the dissolution study using polymer disks. After 10 min, the compressed disk (still in the die) was taken and dried *in vacuo* for 24 hr. The apparent dissolution rate of polymers was calculated from the decrease of the disk weight.

Results and Discussion

Dissolution Behavior of IMC dispersed in Various Polymers

Figure 3 shows the powder X-ray diffraction patterns of IMC/polyvinylpyrrolidone K-30 system. Several sharp diffraction peaks attributed to IMC crystals disappeared after freeze-drying. In differential scanning calorimetry, no endothermic peak accompanying the melting of IMC crystals was seen in this system. Therefore, IMC was considered to be in the amorphous state in the polymer. IMC was also in the amorphous state in other polymer systems.

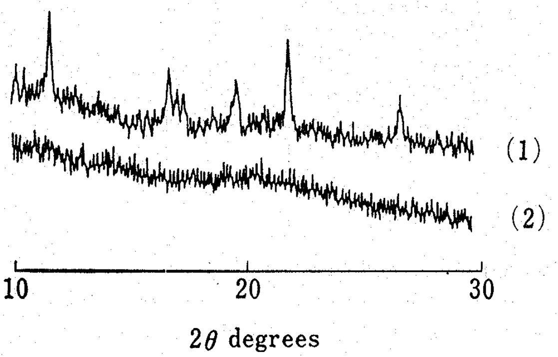

Fig. 3. Powder X-Ray Diffraction Patterns of IMC/Polyvinylpyrrolidone K-30 System

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

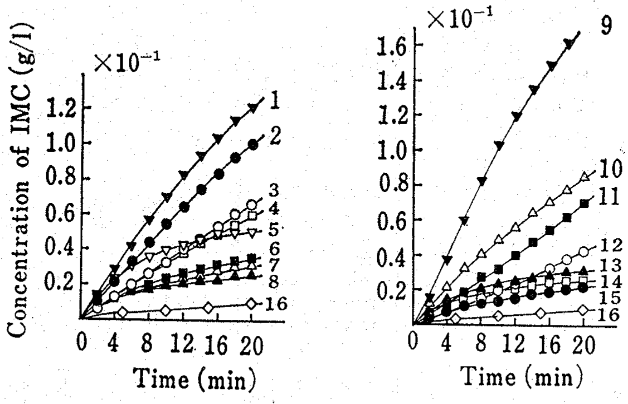

Fig. 4. Dissolution Profiles of IMC from Freeze-dried Samples with Various Water-Soluble Polymers according to the Rotating Disk Method in 1/15 M, pH 6.0 Phosphate Buffer Solution at 37°C

1, dextran T-40; 2, polyvinylpyrrolidone K-30; 3, polyvinylpyrrolidone K-90; 4, hydroxypropyl cellulose; 5, dextran T-70; 6, methyl cellulose; 7, sodium carboxymethyl cellulose; 8, polyvinyl alcohol; 9, gelatin; 10, gum arabic; 11, pectin; 12, sodium alginate; 13, guar gum; 14, gum tragacanth; 15, carrageenan; 16, IMC form I.

The dissolution properties of IMC from these systems and of form I (the most stable form)[11] as determined by the rotating disk method are shown in Fig. 4. Large differences in dissolution behavior among the various kinds of polymers used were observed. In particular, a marked increase in the dissolution rate was observed in the cases of gelatin, dextran T-40 and polyvinylpyrrolidone K-30. Therefore, the physico-chemical nature of the polymers may play a predominant role in the dissolution of IMC from these systems, though further detailed investigations seem necessary.

For practical purposes, the relationship between the dissolution profile and physico-chemical properties of polymers should be evaluated as a bases for systematic design of pharmaceutical formulations. Thus, we investigated the relationship quantitatively by the application of multiple regression analysis.[12]

Factors affecting the Dissolution of IMC

In the first plase, the concentrations of IMC in the dissolution medium at the sampling times shown in Fig. 4 were used as dependent variables ($C_{t=2-20\,\mathrm{min}}$). Six factors (*WA*, *ER*, *GF*, *PH*, *VP* and *DP*) initially selected as predictors of $C_{t=2-20\,\mathrm{min}}$ are listed in Table I. In view of the values of the correlation matrix among the factors shown in Table II, the problem of multi-colinearity among the factors may not arise, because each correlation coefficient was relatively small. Correlation coefficients with doubly adjusted degrees of freedom[13] were used as an index for the selection of the optimum combination of factors, and *WA*, *FR* and *GF* were selected as the optimum factors for the prediction of $C_{t=2-20\,\mathrm{min}}$ with a loglinear

TABLE I. Physico-chemical Properties selected as Predictors

Polymer	WA[a] $\times 10^2$ (ml)	FR[a] (kg/mm)	GF[b] (mm)	PH	$VP \times 10^{-1}$ (cP)	DP[a] (mg/min)
Dextran T-40	3.50	0.994	0.618	7.35	0.0815	5.72
Dextran T-70	4.35	1.25	1.11	7.72	0.0840	3.61
Polyvinylpyrrolidone K-30	2.55	0.741	0.718	4.56	0.0802	4.35
Polyvinylpyrrolidone K-90	3.83	1.93	0.824	6.07	0.230	2.64
Polyvinyl alcohol	2.70	3.42	0.620	6.35	0.140	1.68
Sodium carboxymethyl cellulose	3.30	1.79	1.79	6.79	3.60	1.78
Methyl cellulose	1.00	1.17	0.552	6.58	0.234	2.02
Gum arabic	3.50	1.17	1.11	4.90	0.112	4.11
Gum tragacanth	3.45	1.23	1.59	5.13	14.0	1.76
Sodium alginate	1.30	1.12	1.78	7.33	21.3	1.58
Pectin	0.650	0.473	0.876	3.77	0.980	2.79
Gelatin	2.90	0.704	0.450	6.11	0.103	8.25
Carrageenan	2.80	2.45	2.15	9.00	40.1	1.26
Hydroxypropyl cellulose	1.60	1.15	0.632	5.66	0.137	2·61
Guar gum	0.950	1.20	0.442	6.40	216[c]	2.13

a) Each datum is the mean of three determinations.
b) Each datum is the mean of five determinations.
c) The value was obtained with a Tokyo Keiki B-type viscometer.

TABLE II. Correlation Matrix among the Factors

	$\ln WA$	$\ln FR$	$\ln GF$	$\ln PH$	$\ln VP$	$\ln DP$
$\ln WA$	1	—	—	—	—	—
$\ln FR$	0.424	1	—	—	—	—
$\ln GF$	0.283	0.272	1	—	—	—
$\ln PH$	0.313	0.579	0.242	1	—	—
$\ln VP$	−0.348	0.164	0.420	0.250	1	—
$\ln DP$	0.238	−0.543	−0.127	−0.202	−0.259	1

TABLE III. Loglinear Regression Equations for $C_{t=2-20\,\mathrm{min}}$

Dependent variable	$\ln WA$	$\ln FR$	$\ln GF$	Intercept	n	r	s	F
$\ln C_{t=2\,\mathrm{min}}$	0.659	−0.442	−0.457	−2.94	15	0.896	0.207	14.9
	(±0.188)[a]	(±0.299)	(±0.202)	(±0.18)				
$\ln C_{t=4\,\mathrm{min}}$	0.659	−0.586	−0.555	−2.39	15	0.962	0.144	45.9
	(±0.131)	(±0.160)	(±0.161)	(±0.12)				
$\ln C_{t=6\,\mathrm{min}}$	0.660	−0.734	−0.553	−2.00	15	0.973	0.131	64.3
	(±0.199)	(±0.145)	(±0.128)	(±0.11)				
$\ln C_{t=8\,\mathrm{min}}$	0.651	−0.817	−0.551	−1.78	15	0.964	0.159	47.9
	(±0.144)	(±0.176)	(±0.155)	(±0.13)				
$\ln C_{t=10\,\mathrm{min}}$	0.671	−0.853	−0.551	−1.57	15	0.958	0.177	41.0
	(±0.161)	(±0.197)	(±0.170)	(±0.15)				
$\ln C_{t=12\,\mathrm{min}}$	0.672	−0.902	−0.550	−1.43	15	0.947	0.206	31.7
	(±0.187)	(±0.228)	(±0.201)	(±0.18)				
$\ln C_{t=14\,\mathrm{min}}$	0.657	−0.939	−0.536	−1.29	15	0.933	0.236	24.7
	(±0.214)	(±0.261)	(±0.230)	(±0.20)				
$\ln C_{t=16\,\mathrm{min}}$	0.654	−0.985	−0.518	−1.19	15	0.926	0.254	22.2
	(±0.231)	(±0.282)	(±0.248)	(±0.22)				
$\ln C_{t=18\,\mathrm{min}}$	0.640	−0.991	−0.502	−1.09	15	0.907	0.288	17.0
	(±0.261)	(±0.319)	(±0.281)	(±0.24)				
$\ln C_{t=20\,\mathrm{min}}$	0.617	−1.01	−0.501	−0.998	15	0.891	0.318	14.1
	(±0.289)	(±0.35)	(±0.310)	(±0.271)				

a) 95% confidence interval.

regression model. Other factors such as *PH*, *VP* and *DP* were not important for the analysis. A linear regression model for the prediction of $C_{t=2-20\,\mathrm{min}}$ was also investigated with the combination of the same factors, but the results were not as good as those of the loglinear regression. Loglinear regression equations for $C_{t=2-20\,\mathrm{min}}$ are listed in Table III. Good levels of statistical significance and quite good coincidence between experimental and calculated values were obtained in the initial dissolution stage (*i.e.*, $C_{t=4-10\,\mathrm{min}}$). Therefore, it might be considered that the water penetration and the gelation rate of polymers was the rate-determining step of the initial dissolution of IMC from these systems. The hardness, tested as *FR*, might contribute indirectly to the dissolution of IMC, in so far as it reflects the state of the exposed surface (*e.g.*, the porosity).

Based on the above considerations, the initial dissolution rate of IMC from these systems might be predicted with the same factors, *WA*, *FR* and *GF*. Then, the apparent dissolution rates (*DR* [mg/min]) were calculated from the slopes of the initial dissolution lines in Fig. 4, and the following loglinear equation was obtained.

$$\begin{aligned} \ln DR &= 0.678(\pm 0.177)\ln WA - 0.899(\pm 0.216)\ln FR \\ &\quad - 0.542(\pm 0.190)\ln GF + 0.731(\pm 0.166) \\ &\quad n=15 \quad r=0.952 \quad s=0.195 \quad F=35.2 \end{aligned}$$

There was quite good coincidence, with statistical significance, between experimental and calculated values as shown in Fig. 5. In the following dissolution stage ($C_{t=12-20\,\mathrm{min}}$), however, the levels of significance gradually decreased with the progress of the dissolution. One reason may be the phase transition of amorphous IMC to stabler forms in these systems with the progress of the dissolution. In any case, other suitable factors should be also taken into consideration for the general prediction of dissolution properties of IMC from these systems.

From the viewpoint of the systematic design of pharmaceutical formulations, it may be possible to utilize some of the factors investigated in this paper in conjunction with statistical treatment to estimate the efficiency of various water-soluble polymers.

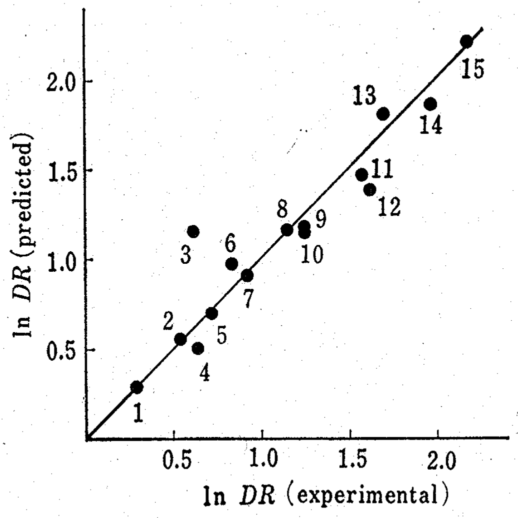

Fig. 5. Relationship between Experimental and Predicted Values of *DR*

1, carrageenan; 2, polyvinyl alcohol; 3, gum tragacanth; 4, sodium alginate; 5, sodium carboxymethyl cellulose; 6, guar gum; 7, methyl cellulose; 8, hydroxypropyl cellulose; 9, pectin; 10, polyvinylpyrrolidone K-90; 11, dextran T-70; 12, gum arabic; 13, polyvinylpyrrolidone K-30; 14, dextran T-40; 15, gelatin.

Acknowledgement The authors are grateful to S.S. Pharmaceutical Co., Ltd., for supplying materials. Thanks are also due to Miss Sachiko Uehara and Miss Naoko Tai for their assistance in the experimental work.

References and Notes

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