Chem. Pharm. Bull.
32(5)1936—1941(1984)

Factors Affecting the Dissolution of Griseofulvin Dispersed in Various Water-Soluble Polymers[1,2)]

TSUTOMU TAKAI,[3)] KOZO TAKAYAMA,* NAOKI NAMBU,
and TSUNEJI NAGAI

Faculty of Pharmaceutical Sciences, Hoshi University,[4)]
Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

(Received August 26, 1983)

Dissolution profiles of griseofulvin (GRF) dispersed in water-soluble polymers were investigated by the paddle method, and large differences in dissolution behavior were observed with different kinds of polymers. The quantitative relationship of dissolution behavior with several properties of the polymers was investigated by the application of multiple regression analysis. It was found that the degree of crystallinity of GRF, the wetting of samples, the solubility or insolubility of water-soluble polymers in methanol, the viscosity of polymer solution and the dissolution rate of polymers were important in the analysis of dissolution mechanisms and prediction of dissolution profiles of GRF from these systems.

Keywords——griseofulvin/water-soluble polymer solid dispersion; crystallinity-dissolution rate correlation; wetting-dissolution rate correlation; solubility-dissolution rate correlation; polymer viscosity-dissolution rate correlation; polymer pH-dissolution rate correlation

The application of solid dispersion techniques is a very effective way to enhance the solubility and dissolution rate of many of the poorly water-soluble drugs. In previous papers,[5-7)] we reported the quantitative relationships, determined by multiple regression analysis, of the dissolution properties of indomethacin,[5)] ketoprofen,[6)] and flufenamic acid[7)] dispersed in various kinds of polymers with the physico-chemical properties of the polymers. A reasonably good fit, with statistical significance, between experimental and calculated values of the dissolution data was obtained by taking into account such factors as water penetration to the samples, hardness and gelation of polymers. With regard to griseofulvin (GRF), a slightly soluble drug, dissolution is known to increase when the drug is dispersed in polyvinylpyrrolidone,[8)] polyethyleneglycol[9)] and some other kinds of carriers.[9,10)] However, the dissolution profiles of GRF from such systems have not been analyzed quantitatively. The purpose of this research was to identify the factors affecting the dissolution of GRF dispersed in water-soluble polymers.

Experimental

Materials——GRF was purchased from Nihon Kayaku Co., Ltd. Twenty-three water-soluble polymers used are listed in Table I. HPC-M was purchased from Nihon Soda Co., Ltd. PVP K-15 was purchased from Tokyo Kasei Industrial Co., Ltd. PEG-6000 was purchased from Wako Pure Chemical Industries, Ltd. Other polymers used were the same commercial products as described in the previous paper.[7)]

Preparation of Samples——Chart 1 shows the method for dispersion of GRF in water-soluble polymers. GRF and each polymer in a weight ratio of 1 : 2 were dissolved or suspended in methanol. The mixture was agitated well and evaporated to dryness under reduced pressure at about 45 °C. The residue was dried *in vacuo* at room temperature for 48 h, ground well in a mortar and sieved. The fraction retained on a 200 mesh sieve and passing through a 100 mesh sieve was used in the following experiments.

Procedure for Dissolution Study——Dissolution profiles of GRF from samples into 500 ml of JP X disintegration medium No. 1 (pH 1.2) were determined at 37 °C in a constant temperature water bath. The amount of GRF used

Table I. Water-Soluble Polymers Used in This Study

Gum arabic
Sodium alginate
Carrageenan
Locust bean gum
Guar gum
Gum tragacanth
Pectin
Carboxymethyl cellulose sodium (1050)$^{a)}$ (CMC-Na)
Methylcellulose (13—18 cP)$^{b)}$ (MC-I)
Methylcellulose (350—550 cP)$^{b)}$ (MC-II)
Methylcellulose (4000 cP)$^{b)}$ (MC-III)
Dextran T-40
Dextran T-70
Hydroxypropylcellulose-SL (HPC-SL)
Hydroxypropylcellulose-L (HPC-L)
Hydroxypropylcellulose-M (HPC-M)
Hydroxypropylcellulose-H (HPC-H)
Polyvinyl alcohol (2000)$^{a)}$
Polyvinylpyrrolidone K-15 (PVP K-15)
Polyvinylpyrrolidone K-30 (PVP K-30)
Polyvinylpyrrolidone K-90 (PVP K-90)
Polyethyleneglycol-4000 (PEG-4000)
Polyethyleneglycol-6000 (PEG-6000)

a) Data in parentheses indicate the degree of polymerization; supplied by Tokyo Kasei Industrial Co., Ltd.

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

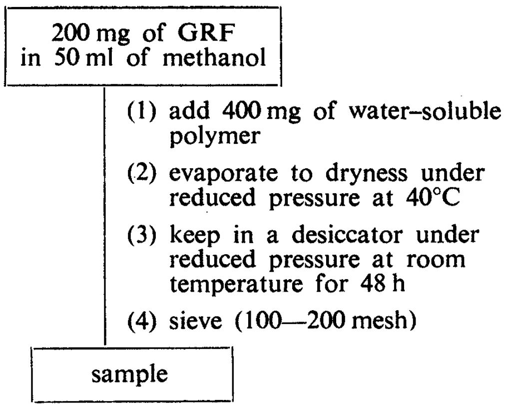

Chart 1. Preparation of Sample Powder

was 26 mg-eq. Each sample powder was transferred directly into the dissolution medium and stirred with a four-bladed stainless steel paddle at 300 rpm. Five ml of sample solution was withdrawn at appropriate intervals through a membrane filter (pore diameter 0.45 μm) and the volume was kept constant by adding the same amount of fresh dissolution medium at the same temperature. The concentration of GRF was determined by the ultraviolet spectrophotometry at 296 nm.

Procedure for Determination of Factors Affecting the Dissolution of GRF——The following factors, based on the physico-chemical properties of sample powders or polymers were selected as possible factors affecting the dissolution of GRF from these systems.

1) Apparent Degree of Crystallinity of GRF in the Sample Powder (X_1): The powder X-ray diffraction pattern of each sample powder containing 20% lithium fluoride (LiF) was measured with a Rigaku Denki Geigerflex model D-2 diffractometer with Ni-filtered Cu-K_α radiation. The ratio of the diffraction intensity of GRF crystal at $2\theta=16.6°$ to that of LiF at $2\theta=38.6°$ was used as the apparent degree of crystallinity of GRF in the sample powder.

2) Wetting of Sample by Water (X_2): The wetting of samples was determined as the rolling angle of a water droplet put on a compressed sample disk. The compressed disk was prepared in the same manner as for the rotating

disk method described in the previous paper.[5] The disk was attached to a hand-built holder which was kept horizontal. A droplet of water (100 μl) was put on the surface of the disk, and the holder was rotated slowly at a constant speed (5 °/s). At the time when the droplet rolled over, the rotation of the holder was stopped. The angle of the holder was measured as an index of wetting of the samples by water.

3) Solubilizing Effect of Polymers on GRF (X_3): One hundred mg of GRF and 10 ml of JP X disintegration medium No. 1 (pH 1.2) containing 0.1% polymer were put into a 25 ml test tube and shaken for 96 h at 37 °C. The solution was filtered with a membrane filter (pore diameter 0.45 μm). The concentration of GRF in the filtrate was determined by the ultraviolet absorption method.

4) Solubility or Insolubility of Polymers in Methanol (X_4): Three hundred mg of polymer was suspended in 100 ml of methanol, and the solution was agitated well at 45 °C for 5 min. The polymers were assigned the score 1 or 0 according to whether they were soluble in methanol as judged with the naked eye, or not, respectively.

Determinations of the following factors, based on the physico-chemical properties of polymers, were carried out exactly as described in the previous papers.[5,7] 5) angle of repose of sample powder (X_5),[7] 6) viscosity of polymer solution (X_6),[5] 7) pH of polymer solution (X_7),[7] 8) thickness of gel formed on the sample disk surface (X_8),[5] and 9) apparent dissolution rate of polymer (X_9).[5]

Results and Discussion

Dissolution Behavior of GRF Dispersed in Various Kinds of Polymers

The concentrations of GRF dispersed in various kinds of polymers in the dissolution medium at each sampling time are listed in Table II. In all cases, the dissolution rates of GRF from these systems were enhanced in comparison with that of the intact GRF. Large differences in dissolution behavior with the various kinds of polymers used were observed. In particular, a marked increase in the dissolution rate was observed in the cases of HPCs-SL, L, M and H. Therefore, the physico-chemical nature of the polymer may play a predominant

TABLE II. Amount Dissolved of GRF Dispersed in Water-Soluble Polymers at Each Sampling Time

Water-soluble polymer	Amount dissolved at each sampling time (mg/l)				
	$C_{t=2\,\text{min}}$	$C_{t=4\,\text{min}}$	$C_{t=6\,\text{min}}$	$C_{t=8\,\text{min}}$	$C_{t=10\,\text{min}}$
Gum arabic	0.443	0.876	1.17	1.55	1.76
Sodium alginate	0.707	1.20	1.61	2.07	2.28
Carrageenan	0.875	1.89	2.74	3.44	3.90
Locust bean gum	1.09	1.74	2.17	2.50	2.80
Guar gum	0.550	0.791	0.965	1.27	1.48
Gum tragacanth	1.92	2.42	2.65	2.98	3.17
Pectin	1.26	1.93	2.32	2.74	3.04
CMC-Na	1.12	1.74	2.26	2.81	3.37
MC-I	3.08	4.15	4.80	5.06	5.27
MC-II	3.09	3.72	4.16	4.51	4.74
MC-III	4.06	5.69	6.54	7.12	7.59
Dextran T-40	1.06	1.27	1.94	2.59	2.81
Dextran T-70	0.393	1.05	1.22	1.60	1.87
HPC-SL	8.39	12.3	13.2	13.4	13.6
HPC-L	9.91	14.7	15.3	15.7	16.0
HPC-M	10.4	13.3	15.4	16.2	16.5
HPC-H	9.51	13.9	14.8	15.5	15.9
Polyvinyl alcohol	3.88	6.19	7.20	7.66	8.01
PVP K-15	4.19	4.50	4.89	5.31	5.57
PVP K-30	3.37	4.48	5.22	5.83	6.29
PVP K-90	4.44	7.17	8.89	9.75	10.4
PEG-4000	1.96	2.86	3.54	4.00	4.38
PEG-6000	2.69	3.83	4.55	5.15	5.50

Each datum is the mean of two determinations.

role in the dissolution of GRF from these systems.

From a practical point of view, the relationship between the dissolution profile and physico-chemical properties of polymers should be evaluated as a basis for the systematic design of pharmaceutical formulations. Thus, we investigated the relationship quantitatively by the application of multiple regression analysis.[11)]

Factors Affecting the Dissolution of GRF

The concentration of GRF in the dissolution medium at each sampling time was used as the dependent variable ($C_{t=2-10\,\mathrm{min}}$). Nine factors (X_2-X_9) initially selected as predictors of $C_{t=2-10\,\mathrm{min}}$ are listed in Table III. Correlation coefficients adjusted doubly for degrees of freedom[12)] were used as an index for the selection of the optimum combination of factors. The dissolution behavior of GRF determined by the paddle method was fully explained by a combination of 6 factors as listed in Table IV, that is, degree of crystallinity of GRF (X_1), wetting of the sample by water (X_2), solubility or insolubility of the polymer in methanol (X_4), viscosity of polymer solution (X_6), pH of polymer solution (X_7), and dissolution rate of the polymer (X_9).

Good levels of statistical significance were obtained, as shown in Table IV. In order to determine the contribution of each factor to the dissolution of GRF, partial correlation coefficients of factors selected in the optimum regression equations were also calculated and are listed in Table V. Increase of wetting of samples by water and decrease of crystallinity of GRF in the samples were both important for enhancement of the dissolution rate of GRF. In particular, the wetting of samples is considered to be an important factor in the initial

TABLE III. Physico-Chemical Properties Selected as Predictors

Water-soluble polymer	X_1	X_2 (°)	X_3 (mg/l)	X_4	X_5 (°)	X_6 (cP)	X_7	X_8 (mm)	X_9 (mg/l)
Gum arabic	0.745	16.5	70.6	0	59.2	1.12	4.90	1.11	4.11
Sodium alginate	0.673	30.0	74.8	0	59.0	213	7.33	1.78	1.58
Carrageenan	0.589	29.7	72.9	0	64.6	401	9.00	2.15	1.26
Locust bean gum	0.714	18.0	76.2	0	47.9	64.2	6.67	0.682	1.84
Guar gum	0.621	17.0	79.5	0	57.2	1940	6.40	0.442	2.13
Gum tragacanth	0.684	20.0	77.9	0	60.0	140	5.13	1.59	1.76
Pectin	0.764	22.8	91.6	0	50.6	8.64	3.77	0.876	2.79
CMC-Na	0.781	19.3	103	0	49.9	21.0	6.79	1.80	1.78
MC-I	0.537	13.3	109	0	49.6	2.34	6.58	0.554	2.02
MC-II	0.625	13.5	107	0	51.6	19.8	5.23	0.524	3.11
MC-III	0.464	13.0	107	0	59.4	43.2	5.42	1.19	4.08
Dextran T-40	0.740	15.8	61.2	0	60.8	0.805	7.34	0.618	5.72
Dextran T-70	0.900	12.5	63.3	0	56.4	0.840	7.72	1.11	3.61
HPC-SL	0.616	10.5	103	1	43.4	1.37	5.66	0.632	2.61
HPC-L	0.735	9.00	107	1	45.2	1.86	6.87	0.768	1.05
HPC-M	0.644	16.5	103	1	49.5	3.56	4.01	0.675	1.23
HPC-H	0.647	21.0	106	1	43.4	104	5.93	0.868	0.492
Polyvinyl alcohol	0.316	14.0	114	0	47.6	1.40	6.35	0.620	1.68
PVP K-15	0.810	10.0	82.6	1	50.6	0.826	5.13	0.420	15.9
PVP K-30	0.590	15.5	106	1	54.3	0.802	4.56	0.718	4.35
PVP K-90	0.462	22.0	111	1	38.8	2.30	6.07	0.824	2.64
PEG-4000	1.09	10.3	66.9	1	55.4	0.824	6.19	0.455	25.7
PEG-6000	0.778	8.50	62.8	1	54.4	0.882	5.43	0.370	11.5

X_1, apparent degree of crystallinity of GRF in sample powder; X_2, wetting of samples by water; X_3, solubilizing effect of polymers on GRF; X_4, solubility or insolubility of polymer in methanol; X_5, angle of repose of sample powder; X_6, viscosity of polymer solution; X_7, pH of polymer solution; X_8, thickness of gel formed on the sample disk surface; X_9, apparent dissolution rate of polymers.

TABLE IV. Optimum Regression Equation for Amount Dissolved of GRF at Each Sampling Time by the Paddle Method

Dependent variable	$\log C_t = aX_1 + bX_2 + cX_4 + d(\log X_6)^2 + e\log X_6 + fX_7^2 + gX_7 + h(\log X_9)^2 + i\log X_9 + \text{constant}$					
	a	*b*	*c*	*d*	*e*	*f*
$\log C_{t=2\,\mathrm{min}}$	−1.28	−0.0287	0.548	−0.178	0.497	—
	(±0.44)[d]	(±0.0123)	(±0.155)	(±0.063)	(±0.201)	
$\log C_{t=4\,\mathrm{min}}$	−1.09	−0.0229	0.489	−0.148	0.377	—
	(±0.33)	(±0.0093)	(±0.117)	(±0.048)	(±0.151)	
$\log C_{t=6\,\mathrm{min}}$	−1.18	−0.0256	0.482	−0.157	0.408	0.0309
	(±0.28)	(±0.0093)	(±0.106)	(±0.044)	(±0.141)	(±0.0199)
$\log C_{t=8\,\mathrm{min}}$	−1.05	−0.0218	0.445	−0.137	0.349	0.0290
	(±0.27)	(±0.0087)	(±0.100)	(±0.042)	(±0.133)	(±0.0187)
$\log C_{t=10\,\mathrm{min}}$	−0.983	−0.0206	0.433	−0.132	0.338	0.0383
	(±0.243)	(±0.0080)	(±0.092)	(±0.038)	(±0.121)	(±0.0171)

Dependent variable	$\log C_t = aX_1 + bX_2 + cX_4 + d(\log X_6)^2 + e\log X_6 + fX_7^2 + gX_7 + h(\log X_9)^2 + i\log X_9 + \text{constant}$						
	g	*h*	*i*	const.	*s*[a]	*r*[b]	*F*[c]
$\log C_{t=2\,\mathrm{min}}$	—	0.404	−0.578	1.47	0.140	0.964	28.2
		(±0.355)	(±0.437)	(±0.41)			
$\log C_{t=4\,\mathrm{min}}$	—	0.379	−0.660	1.54	0.106	0.975	41.5
		(±0.268)	(±0.330)	(±0.31)			
$\log C_{t=6\,\mathrm{min}}$	−0.351	0.384	−0.590	2.63	0.087	0.983	42.4
	(±0.242)	(±0.233)	(±0.295)	(±0.87)			
$\log C_{t=8\,\mathrm{min}}$	−0.326	0.339	−0.538	2.49	0.082	0.982	39.1
	(±0.228)	(±0.220)	(±0.277)	(±0.82)			
$\log C_{t=10\,\mathrm{min}}$	−0.314	0.308	−0.497	2.41	0.075	0.983	42.2
	(±0.208)	(±0.201)	(±0.254)	(±0.75)			

a) Standard deviation.
b) Multiple correlation coefficient.
c) Level of significance ($p < 0.01$).
d) 95% confidence intervals.

TABLE V. Partial Correlation Coefficients of Factors Selected in the Optimum Regression Equation

Dependent variable	X_1	X_2	X_4	$(\log X_6)^2$	$\log X_6$	X_7^2	X_7	$(\log X_9)^2$	$\log X_9$
$\log C_{t=2\,\mathrm{min}}$	−0.340	−0.382	0.728	−0.385	−0.283	—	—	0.000610	−0.177
$\log C_{t=4\,\mathrm{min}}$	−0.349	−0.343	0.724	−0.393	−0.289	—	—	−0.0571	−0.242
$\log C_{t=6\,\mathrm{min}}$	−0.359	−0.305	0.717	−0.396	−0.292	−0.303	−0.288	−0.0594	−0.243
$\log C_{t=8\,\mathrm{min}}$	−0.359	−0.287	0.723	−0.393	−0.293	−0.283	−0.270	−0.0676	−0.254
$\log C_{t=10\,\mathrm{min}}$	−0.355	−0.280	0.724	−0.389	−0.288	−0.272	−0.260	−0.0726	−0.260

dissolution stage, because the partial correlation coefficient of X_2 was large in the initial dissolution stage and decreased gradually with the progress of dissolution time. Further, polymers soluble in methanol, which was used as the solvent for sample preparation, should be chosen as good carriers for solid dispersions with GRF since the value of the partial correlation coefficient of factor X_4 was largest, as shown in Table V.

A parabolic relation was observed between the viscosity of polymers (X_6) and the dissolution of GRF. A contribution of polymer viscosity (X_6) to the dissolution of GRF may be explained in terms of the balance between its inhibiting effects on crystallization and on diffusion of GRF from the surface of the sample powder as discussed in the previous paper.7)

The pH of the polymer solution (X_7) and its square (X_7^2) were both significant in the optimum regression equation except in the early dissolution stages ($C_{t=2-4\,\text{min}}$). This result is consistent with the fact that GRF is more soluble in the lower pH region, though the relation between dissolution and pH was not linear. The dissolution rate of polymer (X_9) was significant in the optimum regression equation, and its contribution to the dissolution of GRF increased gradually with increase of dissolution time (Table V). The square of X_9 was also included in the optimum regression equation. These results indicate that parabolic functions of X_7 or X_9 with respect to the dissolution of GRF might give better approximations to the true functions, though the true functions of X_7 or X_9 with respect to the dissolution of GRF were not obvious and the value of the partial regression coefficient of the square term of X_9 was small.

In any case, the statistical significance of each regression equation was high, so it was considered that the factors strongly affecting the dissolution of GRF in these systems could be defined quantitatively by the application of multiple regression analysis.

Acknowledgements A part of this study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan. The authors are very grateful to Miss Yumiko Kurihara and Mr. Toshihisa Noguchi for their assistance in the experimental work.

References and Notes

1) This paper forms Part XLVI of "Pharmaceutical Interactions in Dosage Forms and Processing." The preceding paper, Part XLV: E. Fenyvesi, K. Takayama, J. Szejtli, and T. Nagai, *Chem. Pharm. Bull.*, **32**, 670 (1984).
2) A part of this work was presented at the 102nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, 1982.
3) Present address: *Tanabe Pharmaceutical Co., Ltd., Kashima 3–16–89, Yodogawa-ku, Osaka 532, Japan.*
4) Formerly, *Hoshi Institute of Pharmaceutical Sciences.*
5) K. Takayama, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **30**, 673 (1982).
6) K. Takayama, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **30**, 3013 (1982).
7) K. Takayama, H. Imaizumi, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **30**, 3701 (1982).
8) M. Mayersohn and M. Gibaldi, *J. Pharm. Sci.*, **55**, 487 (1966).
9) W. L. Chiou and S. Riegelman, *J. Pharm. Sci.*, **58**, 1505 (1969).
10) W. L. Chiou and S. Niazi, *J. Pharm. Sci.*, **65**, 1212 (1976); K. Y. Yang, R. Glemza, and C. I. Jarowski, *ibid.*, **68**, 560 (1979).
11) This calculation was carried out on a Toshiba PA-7010 personal computer with a program written by the authors.
12) T. Haga, H. Takeuchi, and T. Okuno, *Quality, J.S.Q.C.*, **6**, 35 (1976).