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COMMUNICATION

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Dissolution Rate of Polymorphs and Two New Pseudopolymorphs of Sulindac

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ABSTRACT

This study reports the enhancement of sulindac dissolution rate by using the acetone and chloroform solvated forms. The intrinsic dissolution rates of polymorphs I and II and the influence of crystal habit on the drug dissolution process have also been studied. The dissolution properties were studied by calculating the intrinsic dissolution rate (k) by linear regression analysis from the amount dissolved versus time. The results indicated that the intrinsic dissolution rates of solvates in acetone and chloroform were much higher (k = 0.076 mg $min^{-1}cm^{-2}$, respectively) than those of polymorphs I and II (k = 0.036 mg $min^{-1}cm^{-2}$). However, the dissolution rates of the two solvates were found to be essentially the same and independent of the solvent nature. The intrinsic dissolution rates of form II recrystallized in methanol and ethanol differed (k = 0.031 and 0.036 mg $min^{-1}cm^{-2}$, respectively), which confirms the influence of crystal habit on sulindac dissolution rate. No significant difference in dissolution profiles were observed between forms I and II, in agreement with the similar values of fusion temperature (187 and 183°C, respectively).

INTRODUCTION

The ability of a drug to form solvates can greatly increase the number of available possibilities for modifying and controlling processing, dissolution, stability, and bioavailability (1).

A potential application of organic solvates in pharmaceutical formulation is as pharmaceutical derivatives to promote dissolution of poorly soluble drugs. Earlier studies have demonstrated the usefulness of solvates and polymorphic forms in improving the dissolution rate of nonsteroidal anti-inflammatory drugs.

It has been established that a dependency exists between polymorphism or pseudopolymorphism and dissolution rate for phenylbutazone (2–8), mefenamic acid (9), diflunisal (10), indomethacin (11), tenoxicam (12), and oxyphenbutazone (13).

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The crystal habit of drugs is also an important aspect of great pharmaceutical significance because this factor can modify the dissolution behavior of solids (14–17).

This study evaluates the effect of pseudopolymorphism, polymorphism, and crystal habit on sulindac dissolution rate from the solvates and polymorphs obtained in a previous paper (18). The corresponding intrinsic dissolution rates of compacted disks have been measured and compared.

MATERIALS AND METHODS

Materials

Sulindac was kindly supplied by Merck Sharp and Dohme of Spain S.A. The aqueous phosphate buffer of pH 6 was prepared with KH_2PO_4 and Na_2HPO_4 (Merck) of analytical reagent grade.

Dissolution Studies

When diffusion is the rate-determining step in a dissolution process, it can be presented by the general Noyes–Whitney (19) equation:

$$\frac{dC}{dt} = k'S(C_s - C)$$

where C is the concentration at time t, C_s is the concentration at saturation, k′ is the dissolution rate constant, and S is the solid surface area.

In order to obtain a zero-order kinetic and determine the intrinsic dissolution rate, disks of constant area, and "sink" conditions ($C < C_s$) have been used. For this purpose, powder samples (35 mg) were compressed by a hydraulic press for KBr tablets for infrared spectroscopy. It was confirmed by x-ray diffraction analysis that no phase transition occurred during compression. Disks of 13 mm diameter and 0.074–0.149 mm particle size were prepared. The compression force was 44 kN/cm^2.

The dissolution tests were performed according to the USPXXIII-NFXVIII (1995) paddle method with a Dissolutest 07170025 dissolution apparatus (Prolabo) using a rotational speed of 100 rpm at 37 ± 0.1°C and with 900 ml of aqueous phosphate buffer solution of pH 6. Samples of 5 ml of solution were taken with a glass syringe at suitable time intervals and filtered through a 0.8-μm membrane filter (Millipore). The filtrate was suitably diluted and sulindac concentration was spectrophotometrically determined at 285 nm using a Hewlet Packard HP 8452A diode array spectrophotometer. Dissolution runs for all samples were performed six times.

The plot of the amount dissolved as a function of time was linear. The intrinsic dissolution rate has been calculated from the slopes of the straight lines obtained.

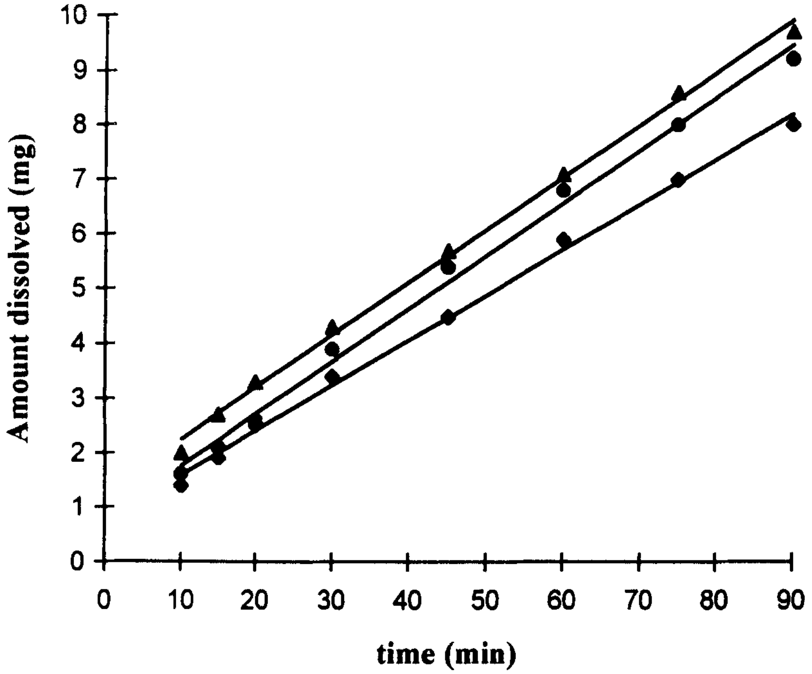

Figure 1. Dissolution profiles of sulindac: (●) form I, (▲) form II in ethanol, (◆) form II in methanol.

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RESULTS AND DISCUSSION

The dissolution rates of two new solvates in acetone and chloroform and the polymorphic forms (I and II) of sulindac, which were prepared and characterized in a previous paper (18), have been studied. The influence of form II crystal habit on the dissolution rate has been also reported.

The dissolution profiles of polymorph II recrystallized in methanol and ethanol and polymorph I are shown in Fig. 1. The plots of the amount of drug dissolved as a function of time were linear ($r > 0.99$) and in consequence, the intrinsic dissolution rates (k) per unit area of sulindac polymorphs could be calculated and expressed in milligrams minute^{-1} centimeter^{-2}. The results are presented in Table 1. The highly significant linear correlation coefficients revealed a zero-order kinetics.

Form II obtained by recrystallization in methanol (tabular habit) showed a lower dissolution rate than form II obtained in ethanol (hexagonal habit). The difference in the k values shown in Table 1 confirms the importance of crystal habit in controlling the dissolution rate of sulindac and must be due to different values of the overall surface energy of crystals.

The dissolution rate of form II in methanol was lower than that of form I. However, no difference was found between the intrinsic dissolution rates of form I and form II recrystallized in ethanol.

Table 1

Intrinsic Dissolution Rates of Sulindac Polymorphs and Pseudopolymorphs

Form	k (mg min^{-1}cm^{-2})[a]
I	0.036 ± 0.002
II[b]	0.031 ± 0.001
II[c]	0.036 ± 0.001
A	0.076 ± 0.001
B	0.076 ± 0.002

[a] Average range of uncertainty of six determinations.

[b] Tabular habit.

[c] Hexagonal habit.

A = Acetone solvate.

B = Chloroform solvate.

The dissolution characteristics of polymorphs I and II were alike; this is in agreement with the similar values of fusion temperature and enthalpy reported in the previous paper (18). Martínez (10) also obtained similar dissolution rates for three polymorphic forms of diflunisal.

In Fig. 2 the dissolution profiles of sulindac solvates are plotted. The significant increase in the intrinsic dis-

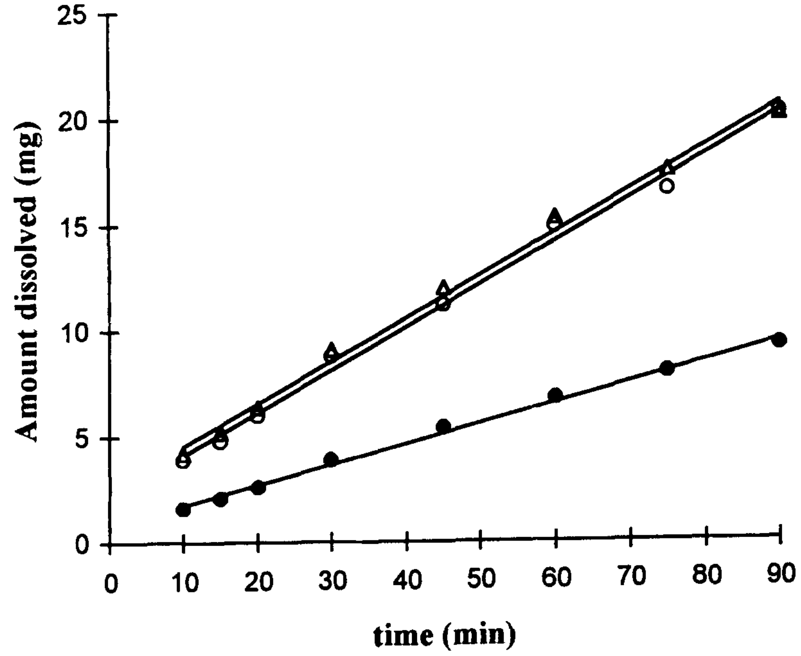

Figure 2. Dissolution profiles of sulindac: (●) form I, (○) chloroform solvate, (Δ)acetone solvate.

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solution rate values (Table 1) with respect to the polymorphic forms I and II is due to presence of solvent in the crystal lattice. Similar results have been obtained with solvates of oxyphenbutazone (13) and tenoxicam (12). The intrinsic dissolution rates were alike for the acetone and chloroform solvates in accordance with the similar values of desolvation temperature and enthalpy reported in the previous paper (18), which indicated that the dissolution rate is independent of the solvent nature.

CONCLUSIONS

The results obtained in this study support the concept that an increase in the dissolution rate of poorly soluble compounds can be obtained using the solvated form of the drug. Differences in the in vitro dissolution characteristics of sulindac released were found, showing a very fast dissolution rate of the solvated forms versus the nonsolvated forms. However, the intrinsic dissolution rates of solvates were independent of the solvent nature.

These results confirm that crystal habit is an important factor that determines the intrinsic dissolution rate of sulindac because the k-values of form II recrystallized in methanol (tabular habit) and ethanol (hexagonal habit) were different.

Polymorphs I and II showed no difference in their intrinsic dissolution rates due to their similar values of fusion temperature and enthalpy (18).

REFERENCES

1. J. K. Haleblian, J. Pharm. Sci., 64(8), 1269–1288 (1975).
2. J. Matsunaga, N. Nambu, and T. Nagai, Chem. Pharm. Bull., 24(6), 1169–1172 (1976).
3. H. G. Ibrahim, F. Pisano, and A. Bruno, J. Pharm. Sci., 66(5), 669–673 (1977).
4. B. W. Müller, Pharm. Acta Helv., 53, 333–340 (1978).
5. Y. Matsuda, S. Kawaguchi, H. Kobayashi, and J. Nishijo, J. Pharm. Pharmacol., 32, 579–580 (1980).
6. M. D. Tuladhar, J. E. Carless, and M. P. Summers, J. Pharm. Pharmacol., 35, 208–214 (1983).
7. T. Matsumoto, J. Ichikawa, N. Kaneniwa, and M. Otsuka, Chem. Pharm. Bull., 36(3), 1074–1085 (1988).
8. N. Kaneniwa, J. Ichikawa, and T. Matsumoto, Chem. Pharm. Bull., 36(3), 1063–1073 (1988).
9. A. J. Aguiar, and J. E. Zelmer, J. Pharm. Sci., 58, 8, 983–987 (1969).
10. M. C. Martínez-Ohárriz, C. Martin, M. M. Goñi, C. Rodríguez-Espinosa, M. C. Tros de Ilarduya, and M. Sánchez, J. Pharm. Sci., 83(2), 174–177 (1994).
11. N. Kaneniwa, M. Otsuka, and T. Hayashi, Chem. Pharm. Bull., 33(8), 3447–3455 (1985).
12. L. Nabulsi, L. Owais, T. A. Arafat, H. Al-Kaysi, M. Sheikh Salem, and A. A. Badwan, The Jordanian Pharmaceutical Manufacturing Company, Faculty of Pharmacy, University of Jordan, 203–212 (1992).
13. M. Stoltz, A. P. Lötter, and J. G. Van Der Watt, J. Pharm. Sci., 77(12), 1047–1049 (1988).
14. J. T. Carstensen, *Theory of Pharmaceutical Systems*, vol. 2, Academic Press, New York, 1973, pp. 145 and 147.
15. H. M. Burt, and A. G. Mitchell, Int. J. Pharm., 5, 239–251 (1980).
16. H. M. Burt, and A. G. Mitchell, Int. J. Pharm., 9, 137–152 (1981).
17. A. H. Chow, and D. J. W. Grant, Int. J. Pharm., 51, 129–135 (1989).
18. M. C. Tros de Ilarduya, C. Martin, M. M. Goñi, and M. C. Martínez-Ohárriz, J. Pharm. Sci., 86(2), 248–251 (1997).
19. A. Noyes, and W. Whitney, J. Am. Chem. Soc., 19, 930–936 (1897).

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