MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

Drug Development and Industrial Pharmacy, 28(6), 681–686 (2002)

RESEARCH PAPER

Enhancement of Dissolution Rate and Anti-inflammatory Effects of Piroxicam Using Solvent Deposition Technique

M. Barzegar-Jalali,[1] N. Maleki,[1] A. Garjani,[1] A. A. Khandar,[2] M. Haji-Hosseinloo,[1] R. Jabbari,[1] and S. Dastmalchi[3,*]

[1]*Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran*
[2]*Faculty of Chemistry, Tabriz University, Tabriz, Iran*
[3]*Faculty of Pharmacy, The University of Sydney, Sydney, NSW 2006, Australia*

ABSTRACT

Piroxicam solid depositions were prepared by means of the solvent deposition technique using different concentrations of microcrystalline cellulose as carrier material. The solvent deposition system (SDS) with drug to carrier ratio of 1:9 had a rapid dissolution rate in vitro. When this SDS was administered perorally to rats with a previous experimentally induced inflammation in their paws, it exhibited a pronounced anti-inflammatory action. X-ray diffraction and infrared (IR) spectroscopy showed no differences in the crystal state of piroxicam in SDS formulation and physical mixture of piroxicam and carrier. The increase in the dissolution rate and consequent enhancement of anti-inflammatory effect of piroxicam in SDS were attributed to the reduced particle size of drug deposited on the carrier and enhanced wettability of the particles brought about by the carrier.

Key Words: *Piroxicam; Solvent deposition; Dissolution rate; Anti-inflammatory effect*

*Corresponding author. Fax: +61 2 9351 4391; E-mail: siavoush@pharm.usyd.edu.au

INTRODUCTION

The poor dissolution characteristics of relatively insoluble drugs have long been a problem to the pharmaceutical industry. The solubility characteristic of a drug is a good indicator of gastrointestinal absorptivity. Poorly soluble drugs are characterized by low absorption and weak bioavailability. For such drugs, reduction of particle size generally increases the dissolution rate and hence improves the absorption and bioavailability. Among the various approaches to improve the dissolution of poorly soluble drugs, the solvent deposition technique (SDS) has proven to be very successful (1–7).

A brief study reported rapid dissolution rate of piroxicam from a SDS without additional physicochemical and in vivo studies (8). In the present investigation we have employed the solvent deposition technique for piroxicam, a poorly soluble drug, with the objective of improving its dissolution rate and consequently its anti-inflammatory efficiency. Different SDSs and simple physical mixtures of piroxicam and carrier were prepared and assessed for their dissolution characteristics and in vivo anti-inflammatory effects. Anti-inflammatory effects were detected in the carrageenan paw oedema assay in rats (9). Carrageenan-induced paw oedema in rats closely resembles the pharmacological mechanism of non-steroidal anti-inflammatory drugs (NSAIDs) in humans and, furthermore, an added advantage of this model is the effectiveness of single oral doses of drugs at non-toxic level (10). X-ray diffraction and infrared (IR) spectroscopy methods were used to elucidate possible crystal change in the SDS and drug–carrier interaction.

MATERIALS AND METHODS

Preparation of SD Systems and Physical Mixtures

Microcrystalline cellulose (PH-101 Avicel, FMC, Brussels, Belgium) was used as an inert carrier. The solvent deposition system was prepared by dissolving piroxicam (used as received from Quimica, Spain) in methylene chloride (Merck, Darmstadt, Germany) to produce a clear solution (2,11,12). The carrier was dispersed in the solution by stirring and the solvent was evaporated at 38±0.5°C. The resultant mass was dried for 24 hr at 40°C, pulverized, and passed through a sieve with a mesh number of 120. The ratios of drug to carrier were 1:1, 1:9, and 1:19 in the SDSs. A physical mixture containing one part drug and nine parts carrier was prepared using the bottle method. Two samples containing 20 mg piroxicam were taken and analyzed for the drug content by ultraviolet (UV) spectroscopy at a wavelength of 334.8 nm (UV-160, Shimadzu, Kyoto, Japan) using an appropriate Beer's plot. The drug contents in the samples were between 97% and 103% of the expected value.

Dissolution Rate Studies

The dissolution rate of piroxicam in powder form, physical mixture, and SDSs was studied using Levy's beaker and stirrer method. A sample equivalent to 20 mg of piroxicam was added to 1000 mL of dissolution medium (0.1 N hydrochloric acid). The mixture was stirred at 75 rpm with a two-bladed stirrer, 7.5 cm in diameter positioned 4 cm from the bottom of the beaker, at 37±0.3°C. Five milliliter samples of dissolution mixture were withdrawn and filtered at different time intervals and assayed at 334.8 nm on the spectrophotometer. The drug concentration in each sample was corrected considering the concentrations in the previous samples. Each dissolution test was repeated at least three times.

X-ray Crystallography and IR Spectroscopy

X-ray diffraction patterns of the samples were obtained by an automatic powder diffractometer (Siemens-850, Munich, Germany) using Cu Kα radiation at a scan rate of $2^\circ\,\mathrm{min}^{-1}$ in terms of 2θ angle. The KBr disk sample preparation technique was used to obtain the IR spectra of the formulations on an IR spectrophotometer (FTIR 3400, Shimadzu, Kyoto, Japan).

Carrageenan-Induced Paw Oedema

Female wistar rats (180–220 g) with free access to water but that had fasted overnight (18 hr) received a subplantar injection in the right-hand paw of 100 μL of 1% λ-carrageenan (Sigma, Munich, Germany). Paw thickness was measured from ventral to dorsal surfaces, using a dial calipers (13) immediately prior to carrageenan injection, and then at hourly intervals for 7 hr. The mean swelling for six rats was calculated. Drugs or carrier were administered perorally

as a suspension in tap water 1 hr before carrageenan injection. The control group received only tap water. The inflammation responses are expressed as percentage increase in paw thickness compared with pre-injection values, and plotted against time. A total oedema (percentage of mean response) for each group is defined as the normalized area under the curve relative to that of the control group.

RESULTS AND DISCUSSION

Dissolution Rate of Different Formulations of Piroxicam

The dissolution curves of the drug powder, its physical mixture with microcrystalline cellulose in ratios of 1:9, and different SDSs are given in Fig. 1. A model-independent parameter, the mean dissolution time (MDT), was employed for comparison of dissolution profiles (14), calculated by:

$$\mathrm{MDT}_{\text{in vitro}} = \frac{\sum_{i=1}^{n} t_{\text{mid}} \Delta M}{\sum_{i=1}^{n} \Delta M} \quad (1)$$

where i is the dissolution sample number, n is the number of dissolution sample times, t_{mid} is the time at the midpoint between times t_i and t_{i-1}, and ΔM is the amount of drug dissolved between t_i and t_{i-1}. The MDT values for different formulations are given in Table 1. The order of increase in dissolution rate was

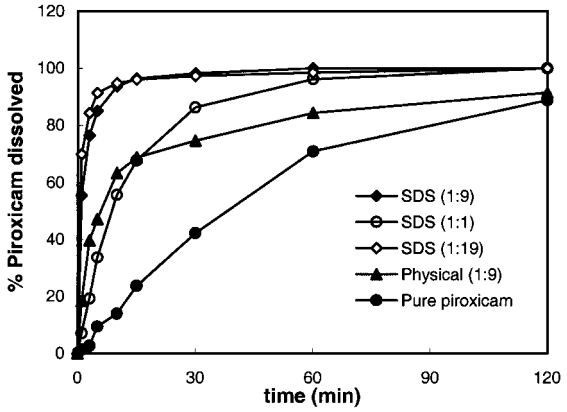

Figure 1. The dissolution curve of the piroxicam powder, its physical mixture with microcrystalline cellulose (1:9), and different SDS formulations. Each data point is the average of three values.

Table 1

Dissolution Parameters of Various Formulations of Piroxicam

Formulation	Drug:Excipient Ratio	MDT (min)
Powder form	—	39.48
Physical mixture	1:9	20.79
SDS	1:1	9.97
SDS	1:9	3.24
SDS	1:19	3.48

as follows:

$$\mathrm{SDS(1:19)} \approx \mathrm{SDS(1:9)} > \mathrm{SDS(1:1)} > \text{physical mixture(1:9)} > \text{drug powder}$$

The adsorption of hydrophilic colloidal particles of microcrystalline cellulose onto the hydrophobic piroxicam particles in the physical mixture might enhance the wettability of the latter particles and increase their dissolution in comparison with the drug powder. The drug dissolution was increased considerably from the SDSs. The drug dissolution for the 1:9 and 1:19 SDSs was more than 10 times that of the drug powder, as judged from MDT values. The increase in ratio of the carrier to piroxicam from 9 to 19 in SDS formulation did not further improve the dissolution of piroxicam, possibly due to enclosure of drug particles in the polymer matrix.

Infrared spectroscopy and x-ray diffraction of piroxicam powder and piroxicam obtained after evaporation of its solution in CH_2Cl_2 showed no changes in the drug molecule and crystal (Fig. 2). Also, no alterations were obtained in the IR spectra and x-ray diffraction patterns of SDS (1:9) and physical mixture (1:9) as shown in Fig. 3. These observations led us to the conclusion that the enhanced dissolution for SDSs was due to the increase of effective surface area of piroxicam as a result of the reduction of its particle size, as well as an increase of its wettability by the carrier.

Effects of Different Formulations of Piroxicam on Carrageenan-Induced Paw Oedema

Induction of acute inflammation in control rats resulted in a prominent increase in paw thickness,

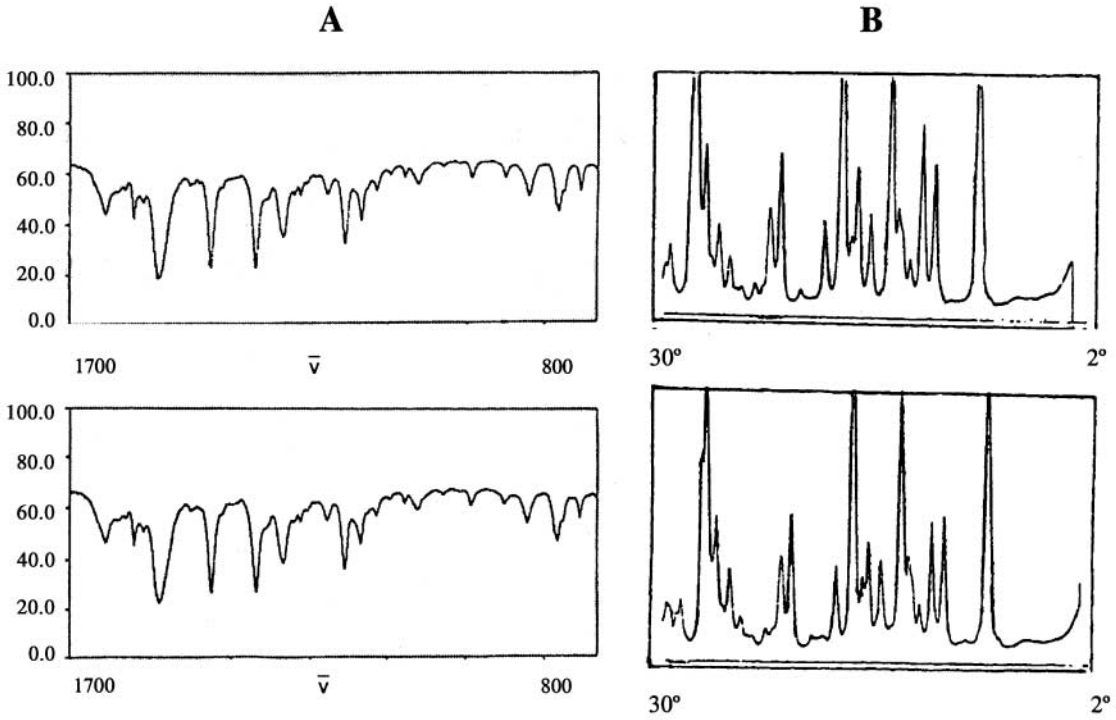

Figure 2. Infrared spectra (panel A) and x-ray diffraction pattern (panel B) of the pure piroxicam (top) and piroxicam obtained after evaporation of its solution in CH_2Cl_2 (bottom).

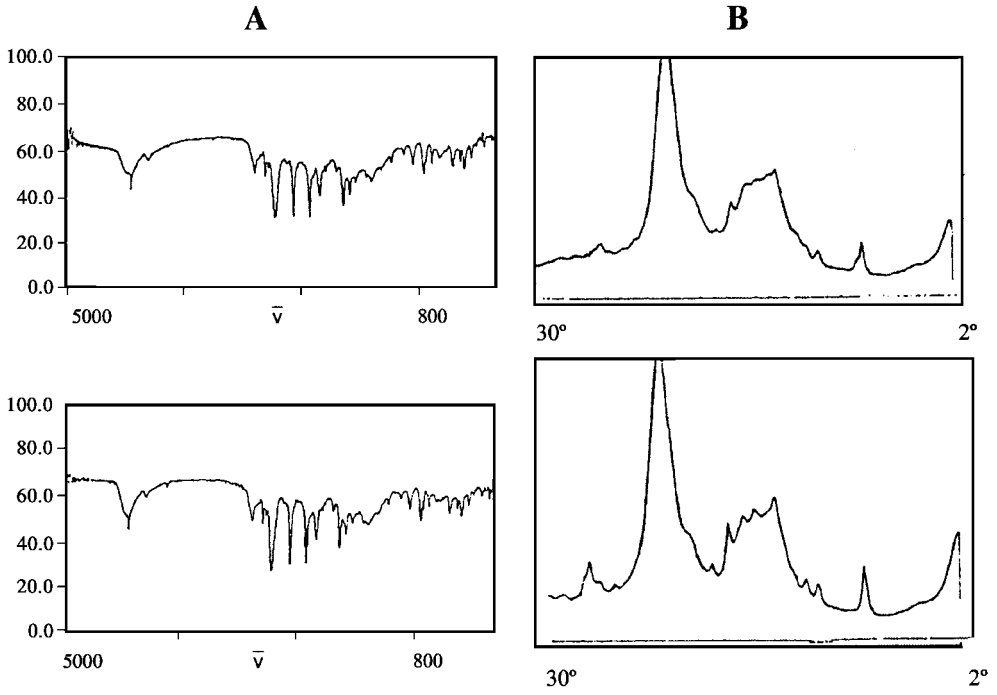

Figure 3. Infrared spectra (panel A) and x-ray diffraction pattern (panel B) of SDS (1:9) (top) and physical mixture (1:9) (bottom) formulations of piroxicam and microcrystalline cellulose.

beginning 1 hr after intraplantar injection of carrageenan and reaching a peak of inflammation after 4 hr. Pretreatment with Avicel (54 mg kg^{-1}, p.o.), as carrier, had no effect on paw thickness. A dose of 4 mg kg^{-1} of piroxicam in physical mixture formulation produced no anti-inflammatory effects. Administration of SDS (1:9) containing 4 mg kg^{-1} of piroxicam, however, significantly ($p < .05$) suppressed the maximal oedema responses attained during 7 hr, from 67% to 45% (Fig. 4). The results also showed greater suppressive effect on maximal oedema with a stronger dose of 6 mg kg^{-1} of piroxicam, delivered in SDS (1:9) (Fig. 5). Although administration of 6 mg kg^{-1} of pure piroxicam significantly ($p < .05$) reduced the total oedema to 75% of that in the control group, the same dose of piroxicam delivered in SDS showed significantly more anti-inflammatory effects and suppressed the total oedema to 51% (Table 2). This pronounced anti-inflammatory effect of SDS (1:9) was attributed to the increased availability due to enhanced gastrointestinal (GI) absorption of the drug as a result of its improved dissolution rate.

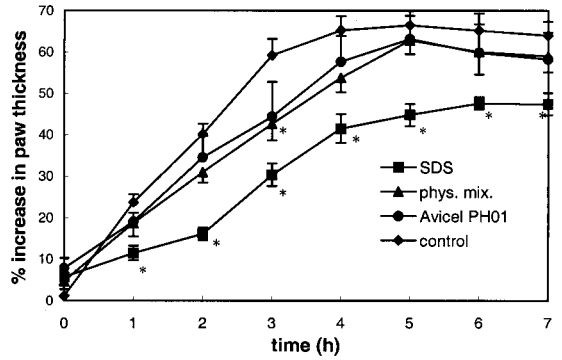

Figure 4. Effects of different formulations of piroxicam on carrageenan-induced paw oedema on rat. A dose of 4 mg kg^{-1} of piroxicam was delivered in SDS (1:9) and physical mixture (1:9) formulations and the anti-inflammatory effect was evaluated based on suppression of increase in paw thickness and compared to that in the control group. Data points labeled with asterisks are significantly ($p < .05$) different from the corresponding points in the control group. Each data point is the mean ± SE from six experiments.

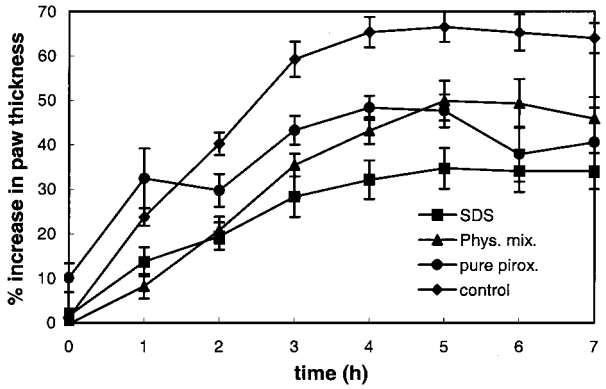

Figure 5. Effects of different formulations of piroxicam on the carrageenan-induced paw oedema in rats. A dose of 6 mg kg^{-1} of piroxicam (in pure, SDS (1:9) and physical mixture (1:9) formulations) was delivered and the anti-inflammatory effect was evaluated based on suppression of increased paw thickness and compared to that in the control group. Each data point is the mean ± SE from six experiments.

Table 2

Effects of Different Treatments on Total Oedema Response in Rats

Test Group	Dose of Piroxicam (mg/kg)	Total Oedema±SE (% of mean control response)[a]	Significantly Different from Groups[b]
Control (a)	—	100±5.12	c,e,f,g
Avicel (b)	—	88.41±9.71	f,g
Powder form (1:9) (c)	6	74.95±5.59	a,g
Physical mixture (1:9) (d)	4	85.78±5.56	e,f,g
Physical mixture (1:9) (e)	6	65.03±4.80	a,d,g
SDS (1:9) (f)	4	61.98±3.50	a,b,d
SDS (1:9) (g)	6	51.06±3.88	a,b,c,d,e

[a]Total oedema for each group is defined as the normalized area under the curve generated by plotting the percentage of increased paw thickness vs. time relative to that of the control group.
[b]Groups are considered significantly different with $p < .05$ in Mann–Whitney test.

A solvent deposition formulation containing one part piroxicam and nine parts microcrystalline cellulose could enhance the drug solution rate in vitro. Upon peroral administration of the formulation to the rats with subsequently induced inflammation in their paws, it exhibited a significant increase in anti-inflammatory activity.

REFERENCES

1. Yang, K.Y.; Glemza, R.; Jarowski, C.I. Effects of Amorphous Silicon Dioxides on Drug Dissolution. J. Pharm. Sci. **1979**, *68* (5), 560–565.
2. Van der watt, J.G.; Parrott, E.L.; Devilliers, M.M. A Comparison of Interaction and Solvent Deposition Mixing. Drug Dev. Ind. Pharm. **1996**, *22* (7), 741–746.
3. Yakou, S.; Yajima, Y.; Sonobe, T.; Sugihara, M.; Fukuyama, Y. Effect of Manufacturing Procedures on the Dissolution and Human Bioavailability of Diphenylhydantoin. Chem. Pharm. Bull. **1982**, *30* (1), 319–325.
4. Monkhouse, D.C.; Lach, J.L. Use of Adsorbents in Enhancement of Drug Dissolution. Int. J. Pharm. Sci. **1972**, *61* (9), 1430–1435.
5. Alsaidan, S.M.; Alsughayer, A.A.; Eshra, A.G. Improved Dissolution Rate of Indomethacin by Adsorbents. Drug Dev. Ind. Pharm. **1998**, *24* (4), 389–394.
6. Bansal, A.K.; Kakkar, A.P. Solvent Deposition of Diazepam over Sucrose Pellets. Indian J. Pharm. Sci. **1990**, *52* (4), 186–187.
7. Johansen, H.; Moller, N. Solvent Deposition Method for Enhancement of Dissolution Rate: Importance of Drug to Excipient Ratio. J. Pharm. Sci. **1978**, *67*, 134–137.
8. Chowdary, K.P.R.; Madhusudhan, P.; Studies on the Preparation and Evaluation of Solvent Deposited Systems of Piroxicam. Indian J. Pharm. Sci. **1990**, *52* (1), 32–33.
9. Duwiejua, M.; Zeitlin, I.J.; Waterman, P.G.; Gray, A.I. Anti-inflammatory Activity of *Polygonum bistorta*, *Guaiacum officinale* and *Hamamelis virginiana* in Rats. J. Pharm. Pharmacol. **1994**, *46* (4), 286–290.
10. Otterness, I.G.; Gans, D.J. Nonsteroidal Anti-inflammatory Drugs: An Analysis of the Relationship Between Laboratory Animal and Clinical Doses, Including Species Scaling. J. Pharm. Sci. **1988**, *77* (9), 790–795.
11. Khan, K.A. The Concept of Dissolution Efficiency. J. Pharm. Pharmacol. **1975**, *27* (1), 48–49.
12. Yen, S.Y.; Chen, C.R.; Lee, M.T.; Chen, L.C. Investigation of Dissolution Enhancement of Nifedipine by Deposition on Superdisintegrants. Drug Dev. Ind. Pharm. **1997**, *23* (3), 313–317.
13. Al-Haboubi, H.A.; Zeitlin, I.J. Re-appraisal of the Role of Histamine in Carrageenan-Induced Paw Oedema. Eur. J. Pharmacol. **1983**, *88* (2/3), 169–176.
14. Polli, J.E.; Rekhi, G.S.; Augsburger, L.L.; Shah, V.P. Methods to Compare Dissolution Profiles and a Rationale for Wide Dissolution Specifications for Metoprolol Tablets. J. Pharm. Sci. **1997**, *86* (6), 690–700.