Drug Development and Industrial Pharmacy, 25(11), 1205–1208 (1999)

COMMUNICATION

Formulation Development of Allopurinol Suppositories and Injectables

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ABSTRACT

Allopurinol was formulated into injectable and suppository dosage forms. The injectable formulation was prepared by dissolving allopurinol in a cosolvent system consisting of dimethyl sulfoxide (DMSO) and propylene glycol (v/v = 50/50). The stability of allopurinol in the cosolvent system was studied under accelerated storage conditions, and results indicate first-order degradation kinetics with an activation energy of 24.3 kcal/mol. The development of suppository dosage forms was performed by formulating allopurinol with polyethylene glycol (PEG) mixtures of different molecular weights. In vitro release profiles of suppositories formulated with different polyethylene bases were obtained in the pH 7.4 buffer solution using the USP 23 paddle method at 100 rpm. Results indicate that the release rate of the suppository formulations containing PEG 1500/PEG 4000 at the ratio (w/w) of 2.5/10 to 10/2.5 appeared to be similar. However, the addition of sodium lauryl sulfate in the suppository decreased the release rate of allopurinol significantly. A future study to establish in vitro/in vivo correlation (iv/ivc) is suggested.

INTRODUCTION

Allopurinol, chemically known as 1,5-dihydro-4H-pyrazolol[3,4-*d*] pyrimidin-4-one, is a xanthine oxidase inhibitor that acts on purine catabolism to reduce the production of uric acid. It is primarily indicated in the management of patients with signs and symptoms of primary or secondary gout. The effectiveness of allopurinol in the treatment of gout and hyperuricemia that results from hematological disorders and antineoplastic therapy has been demonstrated (1–4).

Allopurinol is a white to off-white, almost odorless

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powder, and it is very slightly soluble in water and ethanol, practically insoluble in chloroform and in ether, and dissolves in dilute solutions of alkali hydroxides. The sodium salt of allopurinol is soluble in water, but is incompatible with a number of drugs, as reported in the literature (5).

Current marketed products containing allopurinol include only an oral tablet dosage form primarily due to the low aqueous solubility of allopurinol. For pediatric or geriatric patients who encounter difficulties with oral ingestion of tablets, alternative dosage forms become an important route of administration. The purpose of this study was to develop injectable and suppository dosage forms that will demonstrate good physical/chemical stability and in vitro release profiles. This information should provide baseline information for further in vivo studies.

EXPERIMENTAL

Materials

Allopurinol was obtained from Siegfried Company, Limited, lot no. 9107J014; dimethyl sulfoxide (DMSO) was received from Ferak Laborat GmBH Berlin (West), lot no. 10654; propylene glycol was purchased from Rise Sun Trading Company, Limited, lot no. 870202. Polyethylene glycol (PEG) 1500 was acquired from Kanto Chemical Company Incorporated, lot no. 604A6036, and PEG 4000 was also acquired from Kanto Chemical Company, lot no.604A6032. Sodium lauryl sulfate was purchased from Kataya Chemical Company, Incorporated, lot no.8358; ammonium phosphate dibasic was purchased from E. Merck Company, Incorporated, lot no. 232A624207. Methanol was purchased from J. T. Baker Incorporated, lot no. 9093-3.

Preparation and Stability Study of Allopurinol Injectable

Because of the low solubility of allopurinol in water (0.48 mg/ml) and in ethanol (0.30 mg/ml) (6), a formulation containing 2.5 mg/ml of allopurinol in dimethyl sulfoxide (DMSO) was developed. The allopurinol injectable solution was then filled into 1-ml amber ampules and placed in 50°C ± 1°C, 60°C ± 1°C, and 70°C ± 1°C chambers for stability testing. Samples were withdrawn at designated time intervals and equilibrated to room temperature before analysis by high-performance liquid chromatography (HPLC).

Table 1

Formulations of Allopurinol Suppositories

	Composition (g)	
Base	Macrogol 4000	Macrogol 1500
A-1	10	2.5
A-1-A	10	2.5
A-2	7.5	5.0
A-3	5.0	7.5
A-4	2.5	10.0

Each suppository (1.21 g) contains 6.0 mg allopurinol.

Preparation and In Vitro Release Rate Study of Allopurinol Suppository

Various suppositories containing 6.0 mg of allopurinol in a total 1.21 gram suppository were prepared by the hot melt method according to the formulas listed in Table 1. Selected formulations, wrapped with synthetic membrane, were used in the release rate testing following USP 23 dissolution method II at 100 rpm. The dissolution medium was 900 ml of pH 7.4 phosphate buffer solution, and it was maintained at 37°C ± 1°C throughout the experiment. Samples of 1 ml from each vessel were withdrawn at designated intervals and analyzed by HPLC.

High-Performance Liquid Chromatography Analysis

The HPLC equipment was equipped with a dual-piston pump (model LC-6A, Shimadzu, Kyoto, Japan), an ultraviolet (UV) detector set at 254 nm, and a C_{18} column (3.9 mm × 15 cm with 5-μm packing, Waters Associates).

The mobile phase, consisting of 70.9% (v/v) 0.01 M ammonium phosphate dibasic and 29.1% methanol, was pumped at a flow rate of 0.7 ml/min. The stability-indicating nature of the HPLC method is depicted in the representative chromatograms shown in Fig. 1, which depicts a sample of allopurinol (2.5 mg/ml) injectable was degraded at 70°C for 90 days. The peaks shown in the chromatograms indicate that the degradation compounds were eluted separately and were detected without apparent interference with the peak of interest.

RESULTS AND DISCUSSION

The results of the stability study of allopurinol in DMSO/propylene glycol (50:50) solvent system subjected to different temperature conditions are shown in

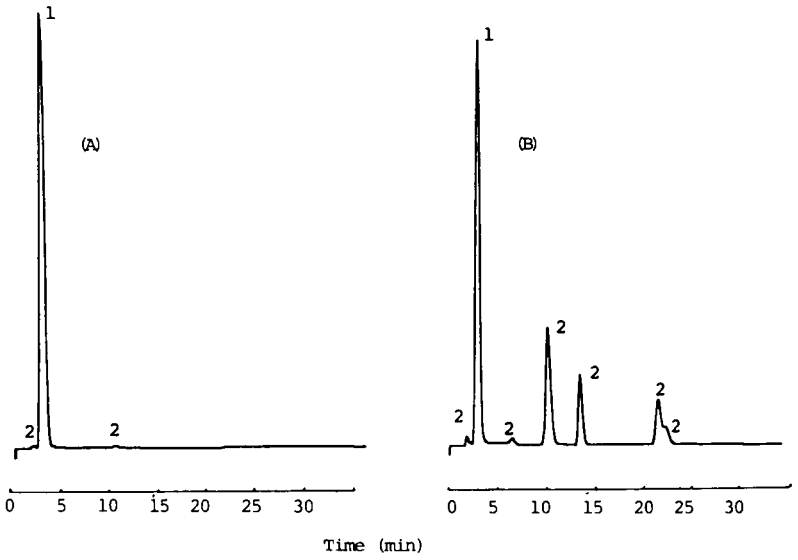

Figure 1. HPLC chromatogram of allopurinol (2.5 mg/ml) in DMSO:propylene glycol (50:50) solvent (A) immediately after preparation and (B) after 90 days of storage at 70°C: (1) allopurinol; (2) degradation products.

Fig. 2. The linearity between the logarithm of percentage remaining versus time indicates first-order degradation kinetics for allopurinol. The Arrhenius plot of allopurinol against 1/temperature is shown in Fig. 3. A straight line was obtained from this graph, and the activation energy was determined to be 24.33 kcal/mol. The estimated stability half-life at room temperature, determined to be 39.55 years, indicates a stable formulation was achieved.

The dissolution profiles of various suppository formulations containing 6.0 mg of allopurinol and different amounts of PEG 1500 and PEG 4000 are shown in Fig. 4. Results indicated that 100% of allopurinol was released from the suppository within 5 hr for all the formulations tested. The release rate of the formulations containing different ratios of PEG 1500/PEG 4000 (2.5/10 to 10/2.5) appeared to be similar. However, the addition of sodium lauryl sulfate in the suppository decreased the release rate of allopurinol significantly.

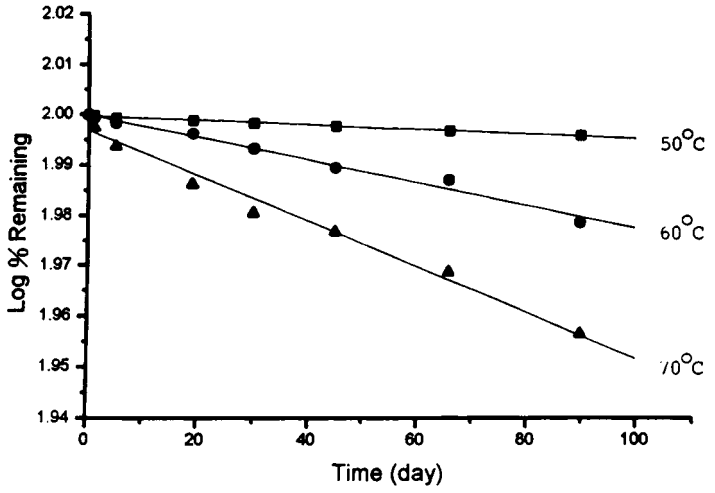

Figure 2. First-order profile of allopurinol from DMSO:propylene glycol (50:50) solvent at different temperatures.

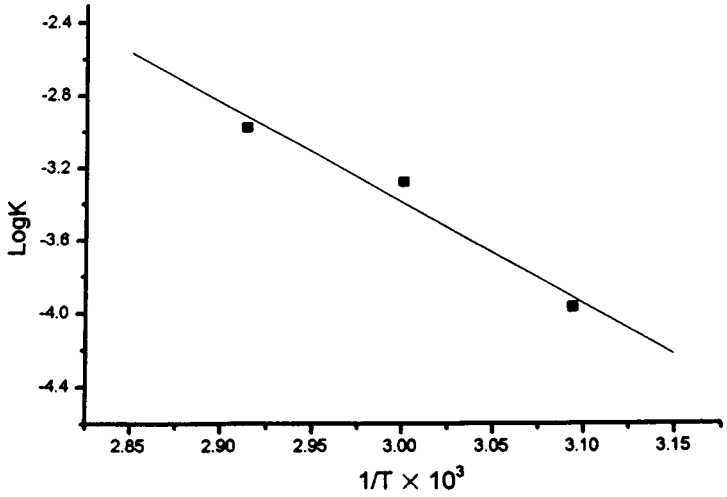

Figure 3. Arrhenius plot of the degradation of allopurinol (2.5 mg/ml) in DMSO:propylene glycol (50:50) solvent.

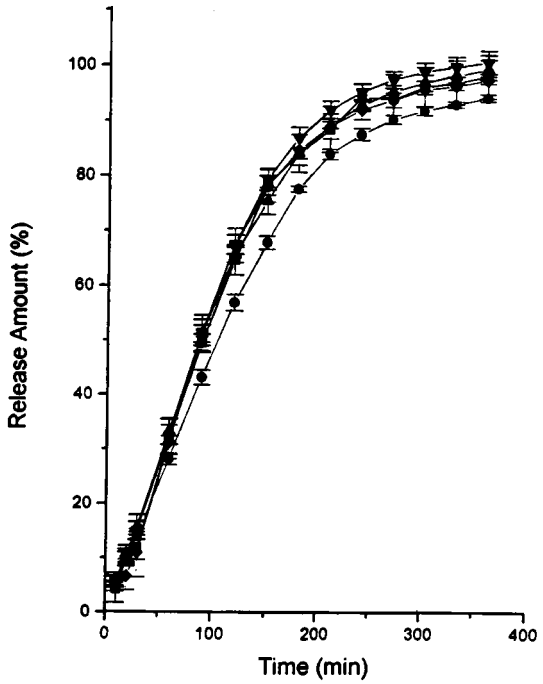

Figure 4. Release profile of allopurinol from suppositories containing Macrogol 4000 and Macrogol 1500: ■, A-1; ●, A-1A; ▲, A-2; ▼, A-3; ◆, A-4.

CONCLUSION

An injectable allopurinol formulation was developed using a DMSO and propylene glycol mixture at a 50/50 (v/v) ratio as the cosolvent system to overcome the low water solubility of allopurinol. Degradation kinetics of the injectable solution were determined to follow a first-order reaction with an estimated stability half-life of 39.55 years at room temperature. PEG-based allopurinol suppository formulations were developed. In vitro release rate profiles of various formulations containing varying amounts of PEG 1500 and PEG 4000 were found to be similar. Sodium lauryl sulfate added to the PEG-based formulation was found to decrease the release rate of allopurinol. A future study in vivo study is suggested.

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