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Development of Dissolution Medium for Rofecoxib in Pharmaceutical Formulations

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Rofecoxib is a non-steroidal antiinflammatory drug and selective cox-2 inhibitor, used in the treatment of rheumatoid arthritis especially in gastritis and ulcerative conditions. It is chemically designated as 4-[4-(methylsulfonyl) phenyl]-3-phenyl-2-(5H)-furanone. In this present study, dissolution of rofecoxib from two commercial formulations was studied in two different media to evaluate their discriminating power.

Key Words: Rofecoxib, Dissolution, Formulation medium.

INTRODUCTION

Approaches usually used in the design of dissolution media for poorly soluble drugs to maintain sink condition (*i.e.*, a large difference in the dissolved drug concentration and saturation drug concentration) include (a) bringing about drug solubility by increasing the volume of the aqueous sink or removing the dissolved drug[1, 2], (b) solubilization of the drug by co-solvents[3, 4] up to 40%, by anionic[4, 5] or non-ionic[6] surfactants added to the dissolution medium in post-micellar concentration, and (c) alteration of pH to enhance the solubility of ionizable drug molecules.

Solubility plays a prime role in the dissolution of a drug substance from the solid dosage form. Correlation between solubility and dissolution rate of different drug substances in various media are well established[7]. In this study, solubility data was used as a basis for the development of dissolution medium for rofecoxib. Surfactants SLS and Tween 80 were tried for increasing the solubility of rofecoxib.

Rofecoxib[8] is chemically 4-[4-(methylsulfonyl) phenyl]-3-phenyl-2-(5H)-furanone. It is a diaryl substituted pyrazole derivative containing a sulfonamide substituent. It is a selective inhibitor of the cox-2 isoform of prostaglandin endoperoxide synthase and exhibits many of the pharmacological actions of prototypical NSAIDS, including antiinflammatory, analgesic and antipyretic activity. It is sparingly soluble in acetone, slightly soluble in methanol and isopropyl acetate, very slightly soluble in ethanol, practically insoluble in octanol and insoluble in water. It is not official in any pharmacopoeia.

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Rofecoxib is not yet official in any pharmacopoeia, official dissolution rate test is not available and also no other dissolution rate test or medium is reported. Like many non-steroidal antiinflammatory drugs, rofecoxib is very sparingly soluble (*ca.* 0.04 mg/mL) in water. Hence, in the present study initially a suitable dissolution medium is developed for rofecoxib.

EXPERIMENTAL

Rofecoxib was obtained from M/s. Cadila Pharmaceuticals Ltd. Sodium lauryl sulfate (SLS) and Tween 80 were obtained from S.D. Fine Chemical Ltd., Mumbai. The following commercial rofecoxib tablet formulations were used:

(1) ROFICA, 25 mg; M/s Micro-Nova, batch No. RXPT001; Mfg. date January 2003, Exp. date January 2005, (CT1).

(2) ROFEB, 25 mg; M/s Aristo, batch No. 213K013; Mfg. date September 2003, Exp. date September 2005, (CT2).

Solubility Determination: Solubility of rofecoxib in various fluids was determined and shown in Table-1. Excess rofecoxib (50 mg) was added to 15 mL of each fluid taken in a 25 mL stoppered conical flask and the mixtures were shaken for 15 h at room temperature (28 ± 1°) on a rotary flask shaker. After 15 h of shaking the samples were allowed for equilibrium for another 15 h. 2 mL aliquots were withdrawn and filtered immediately using a 0.45 μ disk filter. The filtered samples were diluted suitably and assayed for rofecoxib by measuring absorbance at 211 nm using the corresponding fluid as blank. The solubility experiments were conducted in triplicate.

TABLE-1
SOLUBILITY (μg/mL) OF ROFECOXIB IN VARIOUS FLUIDS

Fluid composition	Solubility (μg/mL)						
	Per cent of surfactant (% w/v)						
	0	0.5	1.0	1.5	2.0	2.5	3.0
Purified water (pH 6.4)	40 (4.2)	—	—	—	—	—	—
0.1 N HCl (pH 1.2)	38.4 (2.6)	—	—	—	—	—	—
Phosphate buffer (pH 7.4)	26.75 (7.7)	—	—	—	—	—	—
0.1 N HCl-SLS	38.4 (2.6)	68.0 (1.7)	90.0 (0.8)	125.0 (0.9)	192.4 (4.2)	285 (3.5)	370 (0.4)
0.1 N HCl-Tween 80	38.4 (2.6)	52.1 (2.4)	73.0 (2.1)	96.10 (1.7)	130 (1.0)	181 (0.9)	245 (1.2)
Purified water-SLS	40 (4.2)	96.75 (1.3)	180.2 (0.3)	243.0 (0.5)	363.4 (1.8)	448.4 (1.4)	621 (0.5)
Purified water-Tween 80	40 (4.2)	60.2 (3.4)	94.0 (2.6)	120 (1.4)	161 (1.7)	211 (0.9)	302 (1.5)

Figures in parentheses are coefficient of variation (%) values.

Dissolution Rate Study: The dissolution rate of rofecoxib from commercial formulations was studied in 900 mL of dissolution medium using a USP XXI Dissolution Rate Test Apparatus (M/s Campbell Electronics) with a paddle stirrer. One rofecoxib tablet, a speed of 75 rpm and a temperature of 37 ± 1° were used in each test. The dissolution media used were 0.1 N hydrochloric acid containing 1.0% SLS (DM 1) and distilled water containing 1.0% SLS (DM 2). Samples of dissolution media were withdrawn at different time intervals, filtered through 0.45 μ nylon disc filter and assayed for rofecoxib by measuring absorbance at 211 nm. The dissolution experiments were conducted in triplicate. The results are given in Table-2.

TABLE-2
MEAN ± S.D. DISSOLUTION PROFILES OF ROFECOXIB FROM COMMERCIAL FORMULATIONS IN DISSOLUTION MEDIA 1 & 2 (N = 3)

Time (min)	Per cent of rofecoxib dissolved			
	Dissolution medium-1 (DM1)		Dissolution medium-2 (DM2)	
	CT1	CT2	CT1	CT2
5	36.2 ± 3.6	30.6 ± 3.3	55.9 ± 1.0	48.7 ± 1.3
10	44.3 ± 6.9	43.5 ± 2.6	67.6 ± 0.8	60.2 ± 1.0
15	55.1 ± 2.7	49.9 ± 2.6	78.6 ± 1.0	72.5 ± 1.4
30	66.9 ± 1.7	59.2 ± 2.0	85.0 ± 0.7	81.5 ± 1.9
45	75.5 ± 1.5	68.7 ± 1.1	92.7 ± 0.5	88.6 ± 0.8
60	83.4 ± 0.5	74.2 ± 0.1	99.9 ± 1.2	95.7 ± 0.9

RESULTS AND DISCUSSION

The solubility of rofecoxib was determined at room temperature (28 ± 1°C) in different fluids (Table-1). The solubility of rofecoxib was 40, 38.4 and 26.75 μg/mL, respectively in purified water (pH 6.4), 0.1 N hydrochloric acid (pH 1.2) and phosphate buffer pH 7.4. These results indicated that rofecoxib is poorly soluble at both acidic and alkaline pH ranges. Hence, alteration of pH of the dissolution fluid cannot be used for rofecoxib to maintain sink condition.

The solubility of rofecoxib in purified water and 0.1 N HCl was increased in the presence of surfactants. The solubility was increased as the concentrations of surfactants were increased. Improvement in the solubility is more in case of SLS compared to Tween 80 solutions. There is a 15-fold and 10-fold increase of solubility in purified water and 0.1 N HCl both containing 3% SLS respectively. However, these solutions containing 3% SLS pose problems like frothing, entrapment of air, etc. during dissolution. Purified water and 0.1 N HCl containing 1% SLS are nearly satisfying the sink condition. Hence, these two were selected for testing their suitability as dissolution medium for rofecoxib. The stirring rate was fixed at 75 rpm.

Accordingly, the dissolution of rofecoxib from two commercial formulations was studied[9] in the above dissolution media to evaluate their discriminating power. The dissolution of rofecoxib from CT1 and CT2 in dissolution medium-2 was higher when compared to the dissolution of rofecoxib in dissolution medium-1 (Fig. 1). The observed improvement in the dissolution rate of commercial formulations may be due to high solubility of the drug in purified water compared to HCl containing SLC. The release from CT1 was rapid and complete when compared to CT2, which exhibited low dissolution initially. This indicates the good discriminating power of dissolution medium-2. Thus, based on the results of the study dissolution medium-2, *i.e.*, distilled water containing 1% SLS can be selected as a dissolution medium for rofecoxib.

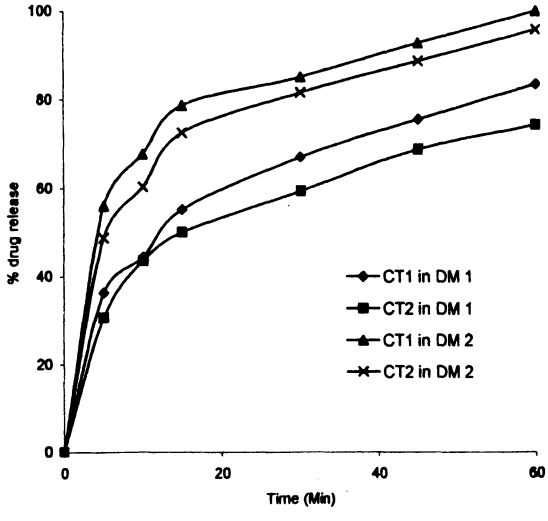

Fig. 1. Dissolution profiles of rofecoxib from commercial formulations in dissolution media 1 and 2

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