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Formulation Development Studies of Rofecoxib

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The present paper, attempts at highlighting, the need for proper preformulation study leading to good formulation development of poorly water-soluble drugs, such as rofecoxib. However, this drug shows poor water solubility resulting in problems such as difficulty in formulation and poor release in gastric media. A study was conducted on five marketed formulations of rofecoxib to estimate their dissolution characteristics and these were compared with two laboratory made test formulations. The dissolution medium was also optimized for the study. It was found that the marketed preparations selected for study showed poor drug release characteristics as compared to the laboratory-made formulations. Therefore, it was concluded that with proper design and approach, good formulations of rofecoxib could be developed which can give satisfactory *in vitro* and *in vivo* performance.

Cyclooxygenase-2 (COX-2) inhibitors constitute a new group of NSAIDs, which at recommended doses block the prostaglandin production by COX-2, but not by COX-1. The recently developed and clinically available selective COX-2 inhibitor, rofecoxib, is about 100-1000 times more selective on the COX-2 than on the COX-1 isoform. It is indicated for the treatment of symptoms and signs of osteoarthritis. The major clinical interest of this drug has been related to the lower incidence of gastric bleeding and other gastro-toxic effects than the non-selective NSAIDs[1-8]. Rofecoxib is chemically, 4-[4-(methylsulfonyl) phenyl]-3-phenyl-2-(5H)-furanone. It is off-white to slight yellowish powder. It is sparingly soluble in acetone, slightly soluble in ethanol and insoluble in water[9].

The present study attempts to highlight the importance of proper formulation development for rofecoxib. Dissolution behavior of five marketed preparations of rofecoxib was investigated. Two formulations of rofecoxib were prepared in the laboratory using β-cyclodextrin with/without additives and the dissolution performance of these two formulations were compared to those of the marketed preparations. The dissolution medium was also optimized for the study.

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MATERIALS AND METHODS

Rofecoxib was obtained as a gift sample from Dr. Reddy's Laboratories, Hyderabad and β-cyclodextrin was obtained from Cavitron, USA. Methanol, hydrochloric acid and sodium hydroxide were obtained from Merck, Mumbai. Di-sodium hydrogen phosphate and potassium hydrogen phosphate were procured from Qualigens, Mumbai. All other chemicals used were of analytical grade. The five marketed formulations taken up in the present investigation were, Dolib (M1, Panacea), Rofib (M2, Aristo Pharmaceuticals), Flexib (M3, Alkem) Certane, (M4, Rallies) and Rofaday (M5, Lupin Laboritories). Each tablet contained 25 mg of rofecoxib.

Preparation of formulation 1 (RB-1):

RB-1 comprising of drug:β-cyclodextrin complex in the ratio of 1:2 was prepared using the kneading method. Weighed quantity of β-cyclodextrin was taken to which one third quantity of water was added to make a homogenous paste, to which the drug was gradually added and mixed continuously for 30 min. The preparation was dried at 45°

for 24 h, pulverized and finally sieved through mesh no. 100.

Preparation of formulation 2 (RB-2):

This formulation contained drug:β-cyclodextrin complex in the ratio of 1:2, along with solubility enhancing additive like citric acid. The presence of citric acid in the formulation appears to modify the dissolution behavior of the drug by altering its surrounding microenvironment. The resulting formulations were then subjected to differential scanning calorimetric (DSC) studies, for confirmation of complex formation and then filled in hard gelatin capsules of size '0' containing drug equivalent to 25 mg. These were further taken for dissolution studies.

Dissolution study:

A single point dissolution study (percent drug dissolved at 60 min) was performed for all the formulations using a 6-station USP XXI/XXII-Dissolution Test Apparatus (Model-Electrolab, TDT-06P, Germany) with a paddle stirrer. The conditions employed were 900 ml dissolution medium (0.1 N HCl/water/phosphate buffer pH 7.4), one capsule or tablet containing drug equivalent to 25 mg, a speed of 50 rpm and a temperature of 37±0.50. Samples were withdrawn at 60 min and filtered through Whatman paper No 41, diluted suitably and assayed for drug content spectrophotometrically. Each dissolution value reported was a mean of six readings taken. The results of dissolution for both commercial as well as test formulations are shown in Tables 1 and 2, respectively.

Estimation of rofecoxib:

Standard curve for the drug in different media was prepared by measuring absorbance at 276 nm. In each case the assay method was calibrated for linearity, accuracy, precision and Beer's Law limit. The values are depicted in Table 3.

Dissolution medium optimization:

For poorly water soluble drugs, proper design of the dissolution medium is essential as these drugs attain saturation solubility conditions quickly in the dissolution media which may affect the release behavior of the drug leading

TABLE 1: DISSOLUTION OF THE COMMERCIAL FORMULATIONS IN DIFFERENT MEDIA.

Marketed Formulations	0.1 N HCL	Phosphate buffer (pH 7.4)	Water%
	Release at 60 min	% Release at 60 min	% Release at 60 min
M1	27.9±0.676	8.0±0.950	12.2±0.984
M2	12.2±0.164	5.1±0.278	10.9±0.572
M3	24.0±0.754	8.9±0.120	16.0±0.468
M4	20.6±0.032	11.4±0.206	16.3±0.557
M5	27.4±0.627	9.0±0.567	20.6±0.761

All values are expressed as mean ±standard deviation of a sample size of 6. M1 represents Dolib (Panacea Biotech Ltd.), M2 indicates Rofib (Aristro Pharmaceuticals) M3 is Flexib (Alkem Laboratories Ltd.) M4 refers to Certane (Rallis India Ltd.) and M5 denotes Roladay (Lupin Laboratories Ltd.)

TABLE 2: DISSOLUTION OF LABORATORY-MADE TEST FORMULATIONS IN DIFFERENT MEDIA.

Formulations	Pure Drug	RB-1	RB-2
	% Release at 60 min	Release at 60 min	% Release at 60 min
Water	39.4±2.03	42.8±1.05	52.2±1.21
0.1 N HCl	38.7±0.99	52.4±1.32	60.1±1.45
Phosphate Buffer (pH 7.4)	12.6±1.02	22.0±0.87	50.7±1.15

All values are expressed as mean ±standard deviation of a sample size of 6. RB1is the formulation containing drug:β-cyclodextrin inclusion complex (1:2), RB2 is the formulation containing drug:β-cyclodextrin inclusion complex (1:2) and a dissolution enhancing agent.

to poor release behavior resulting in poor *in vitro-in vivo* correlation (IVIVC). This may also hinder the ability of the dissolution medium to properly discriminate amongst the different formulations[10,11]. It has been observed that the addition of surfactant had significantly enhanced the dissolution behavior of several drugs and provided good IVIVC correlations[12]. Therefore, with this rationale, 0.5% sodium lauryl sulphate (SLS) was added as surfactant in each medium to help in the dissolution. The results are shown in Table 4.

RESULTS AND DISCUSSION

The solubility of Rofecoxib was found to be as follows: 17.7 mg/l in water 65.7 mg/l in 0.1 N HCl and 18.4 mg/l in phosphate buffer pH 7.4. The drug was found to exhibit better solubility in acidic media, which may be attributed to the slightly basic nature of the drug. The DSC thermogram of rofecoxib exhibited an endothermic peak at 208° corresponding to its melting point. B-CD alone showed a broad endothermic representing a loss of water molecule, a dehydration process. The thermogram of physical mixture and complexes are different from the pure drug, thereby giving clear evidence for the formations of complexes as shown in fig. 1.

The results of dissolution of all the marketed formulations show that the dissolution is very poor and does not exceed 12% in phosphate buffer (pH 7.4), 20% in Water and 28% in 0.1N HCl in any case respectively. This data indicates the necessity for proper formulation development of Rofecoxib for better performance.

The results of dissolution of test formulations in comparison with the pure drug are shown in Table 2. It was observed that the formulations RB-1and RB-2 showed marked

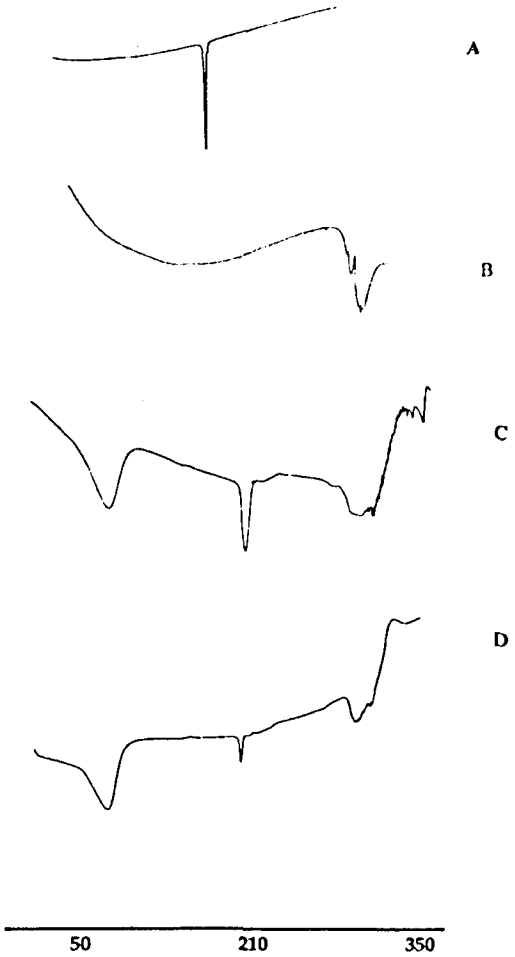

Fig 1: DSC Thermograms of rofecoxib β-cyclodextrin.

DSC thermograms of pure rofecoxib (A), β-cyclodextrin, (B), a physical mixture of rofecoxib and β-cyclodextrin (C) and a 1:2 complex of rofecoxib and β-cyclodextrin.

TABLE 3: ANALYTICAL METHOD PARAMETERS FOR ROFECOXIB IN DIFFERENT MEDIA.

Parameters	Water	0.1N HCl	Phosphate Buffer pH 7.4
Beer's Law Limit	5-50 μg/ml	5-50 μg/ml	5-50 μg/ml
Imax	268 nm	269 nm	276 nm
Molar Absorptivities	$1.023X10^{-5}$	$1.27 X10^{-5}$	$1.34X10^{-5}$
Sandell's Sensitivity	$3.165X10^{5}$	$2.541X10^{5}$	$2.416X10^{5}$
Slope	0.0415	0.1967	0.2058
Intercept	0.0016	-0.1718	-0.1803
Correlation coefficient	0.9996	0.9993	0.9991

All parameters were determined after performing the assay in triplicate

TABLE 4: OPTIMIZATION OF DISS OLUTION MEDIUM WITH 0.5% SLS.

Media	Pure Drug	RB1	RB2	M1	M2
	% Release at 60 min	% Release at 60 min	% Release at 60 min	Release at % 60 min	% Release at 60 min
Water+0.5% SLS	50.9±1.19	85.3±3.50	87.3±1.63	24.4±1.45	22.7±1.20
0.1 N HCl +0.5% SLS	75.2±1.77	75.3±1.52	92.9±2.05	42.3±2.65	23.6±1.63
Phosphate Buffer (pH 7.4) + 0.5% SLS	34.5±1.71	72.9±2.55	83.3±2.15	20.2±1.40	18.6±1.53

All values are expressed as mean ±standard deviation of a sample size of 6.

enhancement in dissolution (1.5 to 2 fold increase) in 0.1 N HCl and (2 to 4-fold increase) in phosphate buffer when compared to the pure drug. It is a well-established fact that complexation of poorly soluble drugs with β-cyclodextrins helps to improve their solubility and dissolution rate[13]. Amongst the two formulations, RB-2 showed a still better increase in dissolution as compared to RB-1. This is probably because in RB-2 there is incorporation of an extra additive citric acid in the formulation, which provided an acidic microenvironment around the drug, which led to enhance drug dissolution.

It can be seen from Table 4 that the presence of SLS in the concentration of 0.5% dramatically improved the drug dissolution in all the three media. The percent (%) drug release is almost comparable in water and phosphate buffer both containing 0.5% SLS. However, because of higher solubility of drug in water containing SLS, the variations in dissolution character of the different formulations is nullified to some extent. Therefore, phosphate buffer containing SLS (0.5%) can serve as a good dissolution medium for testing of rofecoxib formulations. To confirm the utility of this media, two commercial formulations M1 and M2 were also tested in this media. The results show good variation in dissolution behavior of the formulations-both commercial and laboratory made. The observed difference may be attributed to formulation variables Therefore, it may be inferred that dissolution medium optimization can help in modifying drug release behavior thereby making it possible to achieve good *in vitro-in vivo* correlation (IVIVC) and may also help in discriminating among the drug release from different formulations[13].

It may be concluded based on the results obtained in the present study that with a proper design and approach, rofecoxib formulations that exhibit superior performance compared to currently available commercial formulations may be developed which may help to improve patient compliance and market penetration.

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