TABLE 3: EFFECT OF LEAVES EXTRACTS ON BREAKING STRENGTH OF THE GRASS PITH INDUCED GRANULOMA STUDIES.

Group	Oral Dose (mg/kg)	Breaking strength (g)
Control	0.5 ml of 1% Gum acacia	129.8±10.9
Methanol	100	248.0±5.1*
Butanone	100	135.0±11.9
Butanol	100	210.8±6.6*
Ethanol	100	165.0±12.0
Petroleum ether	100	161.0 ±10.9

All value are mean±SE, *P<0.001 Vs Control, n = 6 (number of animals)

ing activity, there by justifying its use in the indigenous system of medicine.

ACKNOWLEDGEMENTS

We thank Dr. F. V. Manvi, Principal, K. L. E. Society's College of Pharmacy, Belgaum for providing the facilities to carry out this study. We also extend our gratitude to Late Shri A. P. Kore of R. L. Sc. Institute, Belgaum for authentication of the plant.

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A Comparative Dissolution Study of Commercial and Prepared Formulations of Celecoxib

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Accepted 29 October 2005

Revised 17 February 2005

Received 1 March 2004

Celecoxib, a COX-2 inhibitor, useful in the relief of symptoms of rheumatoid arthritis, suffers from the draw back of poor aqueous solubility, thereby giving problems during formulations and in achieving good oral bioavailability. The present paper attempts at preparing three formulations of celecoxib in conjunction with β-cyclodextrin for the purpose of solubility enhancement of the drug. The formulations were tested in different media (water, 0.1 N HCl, phosphate buffer pH 7.4). Phosphate buffer was found to be the most suitable amongst the three with good discriminating power. The formulations were compared with two marketed capsule samples of celecoxib. A marked enhancement in the dissolution of celecoxib from the laboratory made formulations was observed as compared to the marketed preparations.

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TABLE 1: PERCENT RELEASE DATA AT 60 MIN FOR DIFFERENT PREPARED FORMULATIONS OF CELECOXIB.

Dissolution Medium	Formulations of Celecoxib			
	CB-1	CB-2	CB-3	CB-4
Water	9.4 (1.65)	11.2 (1.21)	15.3 (1.11)	19.2 (1.22)
0.1 N HCl	8.2 (1.42)	8.9 (1.26)	21.3 (1.31)	24.0 (1.76)
Phosphate buffer pH 7.4	10.7 (1.38)	11.6 (0.89)	32.8 (1.28)	55.2 (1.54)

n=6, CB-1=plain drug, CB-2=physical mixture, CB-3=drug-cyclodextrin complex and CB-4=drug-cyclodextrin complex with additives.

Cyclooxygenase-2 (COX-2) inhibitors[1] constitute a new group of NSAIDs, which at recommended doses blocks prostaglandin production by COX-2, but not by Cyclooxygenase-1 (COX-1). The two recently developed and clinically available selective COX-2 inhibitors, celecoxib and rofecoxib are about 100-1000 times more selective on the COX-2 enzyme than the COX-1 isoenzyme. Celecoxib is indicated in the treatment of osteoarthritis and rheumatoid arthritis[2-4]. However, celecoxib along with the other COX-2 inhibitors shows poor aqueous solubility, which hinders its easy formulation and dissolution.

In the present study, attempts have been made to prepare three formulations of celecoxib with β-cyclodextrin, one contains physical mixture, the second contains a solid inclusion complex of celecoxib: β-cyclodextrin (1:2 M) and third contains the inclusion complex along with an additive, which enhances the dissolution, in the formulations. The release characteristics, with respect to pure drug, in these three formulations have been studied in different dissolution media. For the purpose of comparison, two marketed formulations (celic, 100 mg, Unichem and Zycle, 100mg, Zydus Cadila, India) of celecoxib were also tested along with the laboratory-made preparations.

Celecoxib was obtained as a gift sample from Lupin Laboratory Limited, Aurangabad. All other chemicals used for were of analytical grade. The formulations used for the study were: CB-1, containing celecoxib 100 mg in hard gelatin capsule size '0' and CB-2, comprising of a physical mixture of the drug and β-cyclodextrin in 1:1M ratio. The third formulation CB-3 comprised of a drug:β-cyclodextrin solid inclusion complex in the ratio of 1:2 M prepared by kneading method. The complex was prepared by weighing calculated quantity of β-cyclodextrin to which, one-third quantity of water by weight was added to make a homogenous paste. To this paste, the powder drug was added gradually and mixed continuously for 15-30 min. The paste was dried in vacuum at 40°, pulverized and finally sieved through mesh no 100.The fourth formulation CB-4, contained drug-β-cyclodextrin complex along with an additive (citric acid or sodium bicarbonate 1:2 M) in the formulation, which act as solubility enhancing agent by altering the drugs microenvironment during dissolution.

A single point dissolution test (release at 60 min) was performed for all the formulations under study using USPXXI/XXII, 6 station dissolution test apparatus (Model: Electro lab, TDT-06P) with a paddle stirrer. The conditions employed were, 900 ml dissolution medium (0.1 N HCl/ water/phosphate buffer, pH 7.4), one capsule containing one of the prepared formulation equivalent to 100 mg of drug, a speed of 50 rpm and temperature of 37±0.5°.

The samples withdrawn were filtered using a Whatman paper No. 41 and assayed for drug content spectrophotometrically by measuring the drug absorbance at 252 nm. The solubility of celecoxib is very poor in all the three media 15.13 mg/l in water, 12.88 mg/l in 0.1N HCl and 47.15 mg/l in phosphate buffer pH 7.4.

The results of dissolution of all the laboratory-made formulations are tabulated in Table 1. It can be seen that all the three prepared formulations CB-2, CB-3 and CB-4 showed a marked enhancement (about five folds) in the dissolution of celecoxib as compared to CB-1, which contained pure drug. The improvement of dissolution was found to be in the order CB-1<CB-2<CB-3<CB-4. The drug:β-cyclodextrin complex, CB-3 showed three fold increase in the dissolution as compared to the physical mixture CB-2 (1.5 fold) due to better interaction of the drug with β-cyclodextrin complex prepared by the kneading method. CB-4 is found to be still better than CB-3 because of the incorporation of solubility enhancing additives, which provide a slightly alkaline microenvironment to celecoxib, thereby enhancing the dissolution further (five fold increase).

TABLE 2: DISSOLUTION PROFILE OF DIFFERENT FORMULATIONS OF CELECOXIB IN PHOSPHATE MEDIUM PH 7.4

Formulations	% Release of drug						Rate constant $K_1 min^{-1} \times 10^{-3}$	DE_{15} (%)
	5	10	15	30	45	60		
M1	2.3(0.88)	3.7(1.62)	4.2(1.42)	4.3(1.35)	4.4(1.48)	4.5(1.52)	3.7	2.8
M2	2.4(1.21)	4.0(1.83)	4.6(1.72)	4.9(1.17)	5.2(1.67)	5.3(1.47)	4.2	2.9
CB-1	1.1(1.36)	2.8(1.49)	4.2(1.93)	6.3(1.61)	8.9(1.82)	10.7(1.85)	2.8	3.1
CB-2	2.7(2.04)	4.8(1.55)	6.3(1.68)	8.5(1.31)	10.9(1.46)	11.6(1.92)	4.8	8.6
CB-3	12.3(1.22)	17.8(1.57)	21.6(1.43)	24.3(1.03)	29.5(1.41)	32.8(1.53)	17.7	12.7
CB-4	17.4(1.72)	25.8(1.54)	34.5(1.37)	42.0(1.45)	50.4(1.25)	55.2(1.51)	25.9	19.2

n=6, K_1=dissolution rate constant, M1=marketed sample 1, M2=marketed sample 2, CB-1=capsule containing plain drug, CB-2= capsule containing physical mixture, CB-3= capsule containing drug-cyclodextrin inclusion complex, CB-4=capsule containing drug-cyclodextrin inclusion complex and sodium bicarbonate, DE_{15} (%)=dissolution efficiency of percent drug release, compared at 15 min.

Since all the formulations showed best release in phosphate buffer media, therefore this medium was chosen for further study-comparison of drug release rate with commercial formulations M_1 and M_2. The results are given in Table 2. Here again, we observed the superior performance of the laboratory-made formulations as compared to the commercial ones. The test formulations CB-2, CB-3 and CB-4 gave faster and higher dissolution of celecoxib than M_1 and M_2. A similar order, as before was followed here: CB-4>CB-3>CB-2>CB-1. The present study serves to highlight the need for proper formulation development of poorly-water soluble drugs such as celecoxib. With proper design, the formulation can be optimized for good performance both *in vitro* and *in vivo*.

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Spectrophotometric Estimation of Etoricoxib in Bulk Drug and Dosage Forms

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Accepted 29 October 2005

Revised 18 February 2005

Received 4 January 2005

Simple UV and first derivative spectrophotometric methods have been developed for the determination of etoricoxib in bulk drug and its pharmaceutical formulations. In simple UV spectrum of etoricoxib in 0.1 N sodium hydroxide, it exhibits absorption maxima (λ_{max}) at 284 nm where as in first derivative spectrum it shows maxima at 301.0 nm and minima at 266.8 nm. Both the methods were found to be simple, economical, accurate, reproducible and can be adopted in routine analysis of etoricoxib in bulk drug and its pharmaceutical formulations.

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