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Fast Dissolving Rofecoxib Tablets

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Inclusion complex of rofecoxib, an NSAID with β -cyclodextrin using ball milling technique has been prepared and evaluated using DSC. The fast dissolving tablet composition with 25 mg equivalent rofecoxib showed complete release of rofecoxib in 12 min as compared to 20% drug release from the conventional release marketed tablets during the same period. The stability studies conducted as per ICH guidelines at 40° and 75% RH showed insignificant loss in drug content at the end of six months.

Pain is an unpleasant sensation and demands instant relief. Pharmacologic management has been the main stay of treatment for many pain syndromes. A major group of drugs used in pain management are nonsteroidal antiinflammatory drugs (NSAIDs), which also have analgesic and antipyretic associated activities. These NSAIDs relieve pain by cyclooxygenase (prostaglandin synthetase) inhibition¹.

The rapid relief of pain sensation would depend on rapidity of absorption of NSAID, which, in turn, is governed by its dissolution rate. The drug delivery system involving fast dissolving dosage forms are well established in the management of pain therapy (e.g. nimesulide, piroxicam). Several methods have been reported for preparing fast dissolving dosage forms². These necessarily use drug in water-soluble form. The water-insoluble drugs need manipulation to make them water-soluble. Among different approaches for solubilization³⁻⁵, formation of inclusion complexes with non-toxic excipients such as cyclodextrins (CDs) is the most common approach used in practice⁶⁻⁸. This paper reports the preparation of β -CD complex of rofecoxib, a water-insoluble

drug and its incorporation in a fast dissolving tablet dosage form.

Rofecoxib was obtained from Virdev Chemicals, β -CD was obtained from Cerestar, USA, PVP-K30 and Kollidon CL (Crospovidone) were obtained from BASF Corp., Germany, Avicel pH 102 (MCC) and Nymcel ZSX (Croscarmellose sodium) were obtained from FMC Corp., USA, Hyswell (Sodium starch glycolate) was obtained from Maruti Chemicals and Aerosil (200#) was obtained from Degussa Corp., Germany. Lactose, talc and starch used in the investigation were of IP grade. Conventional release marketed rofecoxib tablets representing 25 mg drug per tablet were obtained for comparison purposes. All these above chemicals were used as received. All other reagents and chemicals employed were of AR/GR grade or of the highest purity.

Rofecoxib and β -CD in molar ratios of 1:1, 2:3 and 1:2 were blended in a cone blender for 5 min (batch size 2.5 kg), wetted with adequate amount of water to achieve paste consistency and milled in a porcelain ball-mill (capacity 5.0 kg; 12 balls with diameter of 1.5 cm) for 36 h. The paste was dried in an oven at 45°, and sifted through 120# sieve. The

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dried powders were evaluated using spectrofluorimetry and DSC to determine the extent of drug complexation. An optimum drug- β -CD ratio indicating the highest degree of complexation (fig.1) was ascertained.

Tablets of rofecoxib- β -CD complex (in the molar ratio of 2:3) were prepared by wet granulation using 160.5 mg of dried complex powder (representing 25 mg of rofecoxib), lactose 40mg, Avicel pH102 50 mg, Kollidon CL 7.0 mg, Nymcel ZSX 19.7 mg, Hyswell 15 mg, talc 0.1 mg, Aerosil 0.6 mg, PVP-K30 10 mg and 10% starch paste 60 mg. The average weight per tablet was 309 mg. All the excipients previously sifted through 120# screen were mixed with the dried complex powder and granulated with starch paste using standard procedure. The granules dried in a fluid bed dryer were finally passed through 24# superimposed on 40# and compressed on a 10-station rotary tablet press using 10.5 mm standard concave punch set. Using the above formulation (except 10% starch paste), the tablets with an average weight of 303 mg were prepared by direct compression of the drug-complex and excipients mix. The tablets were packaged in a blister pack.

The tablets were evaluated for their characteristics such as physical appearance, weight variation, hardness, friability and disintegration time employing standard procedures^{9,10}.

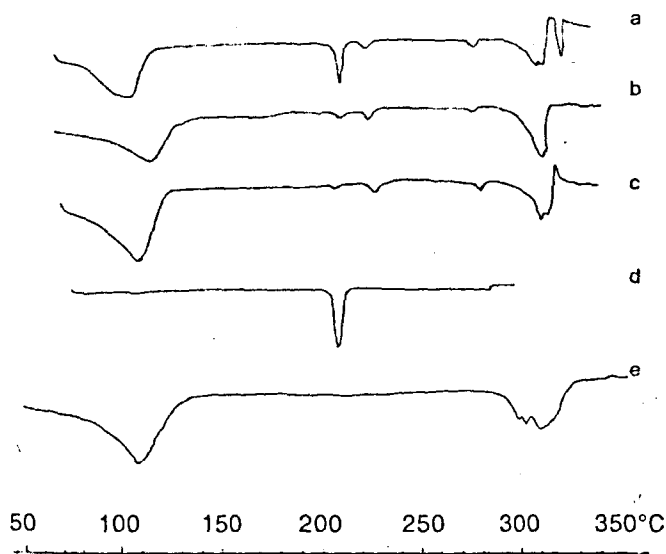


Fig. 1: DSC thermograms of rofecoxib- β -CD system. 'a', 'b' and 'c' indicate thermograms of ball-milled samples prepared in ratio of 1:1, 2:3 and 1:2 respectively; 'd' represents pure rofecoxib and 'e' represents thermogram of pure β -CD.

The tablets after activation at 366 nm for 22 min were assayed in a spectrofluorimeter (Jasco Japan, Model: FP-760) [(λ_{ex} =261 nm; λ_{em} =381 nm) for rofecoxib and (λ_{ex} =265 nm; λ_{em} =406 nm) for rofecoxib as β -CD complex].

The *in vitro* dissolution studies were conducted at 37.5° (\pm 1°) in 900 ml each of distilled water and 0.1 N HCl using a validated USP XXIII, 6-station, dissolution tester (Electrolab, India) with paddle rotating at 100 rpm. Ten ml aliquots were withdrawn after 3, 6, 9, 12, 15, 18, 21, 25, 30 and 60 min for analysis. For comparison purposes, dissolution rate of conventional rofecoxib tablets available in the market was determined. The dissolution profiles of the fast dissolving and conventional release market tablets are shown in figs. 2 and 3. Accelerated stability studies at 40° \pm 2° and 75% \pm 5% RH for a period of six months (as per the

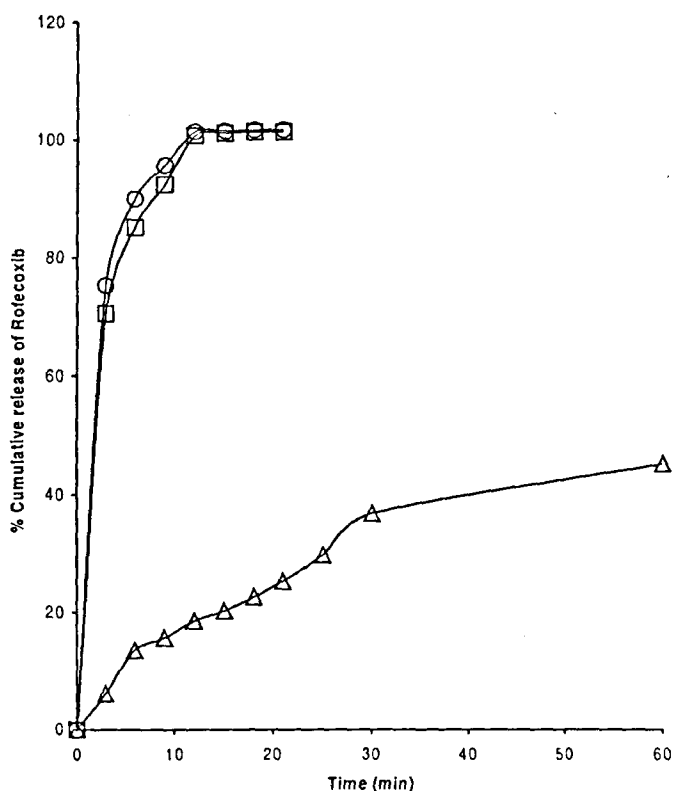


Fig. 2: Dissolution profiles of fast dissolving rofecoxib- β -CD complex tablets.

Conventional release rofecoxib tablets from market (- Δ -), rofecoxib- β -CD tablets prepared by wet granulation (- \circ -) and rofecoxib- β -CD tablets prepared by direct compression (- \square -) using 900 ml of distilled water as medium and with rofecoxib content of each tablet at 25 mg.

ICH guidelines, www.ichguidelines.com) were carried out on the above tablets.

Ground mixtures of β -CD with drugs have been reported for preparation of inclusion complexes with enhanced solubility¹¹⁻¹³. Hence, ball-milling technique was employed for complex formation, as the method is cost effective and suitable for scaling up from pilot to production scale. In preliminary studies, complexation of drug with β -CD in the ratio of (2:3) was carried out for a period of 60 h. Progress of complexation was observed with samples being withdrawn at every 4 h interval and evaluating them through DSC and spectrofluorimetry. The results indicated the optimum time of ball milling for complex formation to be 36 h. Hence, process time during ball milling was kept for 36 h. The DSC studies revealed that (i) rofecoxib has an endotherm at 207-211°; (ii) β -CD has an endotherm around 100-120° (probably due to loss of water molecules) followed by degradation around 300°. In the dried powdered samples with ratio of 2:3, the endotherm at 211° representing rofecoxib almost disappeared with an appearance of new endotherms at 225° and 282° representing rofecoxib- β -CD complex. Formation

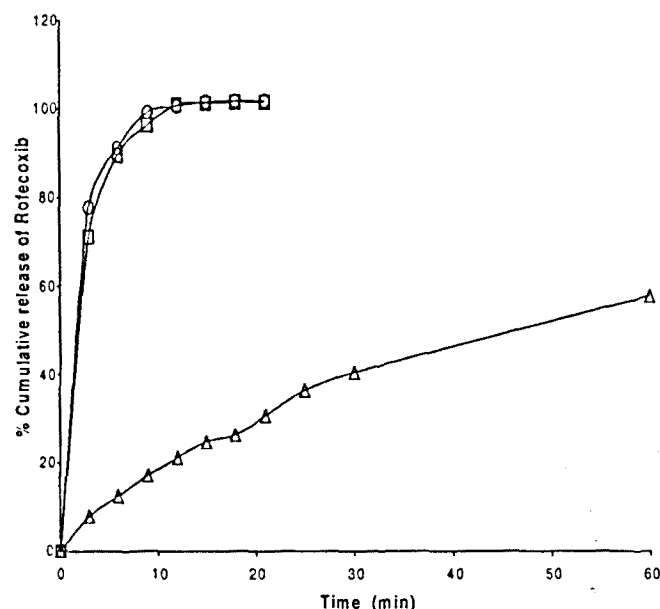


Figure 3: Dissolution profiles of fast dissolving rofecoxib- β -CD complex tablets.

Conventional release rofecoxib tablets from market (- Δ -), rofecoxib- β -CD tablets prepared by wet granulation (-O-) and rofecoxib- β -CD tablets prepared by direct compression (- \square -) using 900 ml of distilled water as medium and with rofecoxib content of each tablet at 25 mg.

of complex between rofecoxib and β -CD was confirmed by shifts in the fluorescence spectrum of complex (λ_{ex} =265 nm; λ_{em} =406 nm) compared to spectrum for pure rofecoxib (λ_{ex} =261 nm; λ_{em} =381 nm) post activation at 366 nm for 22 min. This material was taken up for further studies.

The tablets prepared were biconvex, off-white in color, and had smooth texture without any cracks with hardness in the range of 3.6-4.2 kg/cm² and friability in the range of 0.35-0.40%. Although drug- β -CD complex is soluble in water, the tablet must fast disintegrate to liberate the water-soluble complex, which dissolves making the drug available for absorption. From our trials it was observed that combination of three disintegration gave the desired rapid disintegration. As a result, the tablet disintegration times were in the range of 30-40 s indicating that the tablets would immediately disintegrate on coming in contact with saliva and when swallowed with water would disperse rapidly in the stomach. The weight variation observed was less than 2% with assay of 101.5 \pm 1%. The dissolution studies indicated that the formulations prepared either by wet granulation or by direct compression method showed complete release of the drug within 12 min in both the media. The market sample showed 20 \pm 2% drug release at the end of 12 min. Between the two methods employed, the difference in dissolution time was insignificant giving flexibility of processing. At the end of the stability studies, reduction in the drug concentration in the tablets was between 1 to 1.5% with no changes in physical appearance, average weight and hardness of the tablets.

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Assay of Lacidipine in Tablets by Extraction Spectrophotometry

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Three simple spectrophotometric methods for the analysis of lacidipine in pure form or in tablets have been developed based on the formation of chloroform soluble ion associates under specific experimental conditions. Three acidic dyes, tropaeolin 000 (method A), bromocresol green (method B) and azocarmine G (method C) were utilized. The extracts of ion associates exhibited absorption maxima at 420, 500 and 540 nm for methods A, B and C, respectively. Good agreement with Beer's law was found in the range of 10–60 µg/ml (method A), 10–60 µg/ml (method B) and 10–70 µg/ml (method C). These methods are simple, precise and accurate with excellent recovery of 98–102% and also do not require any separation of soluble excipients in tablets. The results obtained are reproducible with coefficient of variation of less than 1.0%.

Lacidipine (LCD), 4-[2-(3-(1,1-dimethyl ethoxy)-3-oxo-1-propenyl phenyl)]-1,4-dihydro-2,6-dimethyl-3,5-pyridine dicarboxylic acid diethyl ester is a dihydropyridine derivative useful in the treatment of hypertension. Lacidipine is official in Martindale Extra Pharmacopoeia¹. Literature cites only High Performance Liquid Chromatographic methods²⁻⁵ and a spectrophotometric method⁶ for its estimation in dosage forms. The reported spectrophotometric method is based on oxidative coupling reaction of the drug with 3-methyl-2-benzothiazolinone hydrazone (MBTH). This method suffers from low sensitivity and low *I*_{max}. The method involves the use of MBTH, which is an expensive reagent. Moreover, the analytically useful functional groups in LCD like ester group and vinyl imino group has not been fully exploited for the development of new analytical useful methods. Hence the need for a fast, low cost and selective meth-

ods are obvious especially for routine quality control analysis of pharmaceutical products containing LCD. As the extraction spectrophotometric procedures are popular for their sensitivity and selectivity in the assay of drugs^{7,8}, this technique was therefore utilized in the present work for the estimation of LCD. The present paper describes three simple extraction spectrophotometric methods for the determination of LCD, based on its tendency to form chloroform extractable ion-association complexes with acidic dyes belonging to different chemical classes viz., tropaeolin 000 (TP 000, Mono azo), bromocresol green (BCG, triphenyl methane) and azocarmine G (AG, azine) under specified experimental conditions by exploiting the basic nature of the drug molecule.

An Elico SL 171 spectrophotometer with 1 cm matched quartz cells was used in the present study. All reagents used were of analytical grade and solutions were prepared in distilled water. Aqueous solutions of TP 000 (0.02%), BCG

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