fluorescence intensity diminished gradually. The optimized method was validated in terms of accuracy, precision, linearity, limit of detection and limit of quantification. The results are summarized in Table 2. The proposed method was successfully applied for the determination of atenolol in pharmaceutical dosage forms.

The analysis results of marketed formulations (tablets) are in good agreement with the labeled claim. The reproducibility, repeatability and accuracy of these methods were found to be good, which is evidenced by low standard deviation. The percent recovery obtained was 99.2-100.3 indicates non-interference from the common excipients and colour used in the formulations. Thus the developed spectrofluorimetric method was simple, sensitive, accurate, precise and reproducible and can be successfully applied for the routine estimation of atenolol in bulk and pharmaceutical dosage forms.

REFERENCES

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Inclusion Complexation of Rofecoxib with Dimethyl β-Cyclodextrin

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An attempt has been made to enhance solubility and dissolution of rofecoxib by complexation using dimethyl β-cyclodextrin. Complexes were prepared by physical mixture, kneading and spray drying methods. The prepared complexes were evaluated by Fourier transform infra-red spectroscopy, X-ray diffraction, differential scanning calorimetry and scanning electron microscopy. Release profile of the drug from the complexes were studied in pH 1.2 and pH 7.4 and it was found that the marketed preparation showed lesser release characteristics as compared to the complex prepared by kneading method.

Cyclodextrins are cyclic maltooligosaccharides, which have been extensively used to increase aqueous solubility of poorly soluble drugs. Amongst the existing cyclodextrins, β-cyclodextrin (β-CD) has been used extensively to modify the physico-chemical properties. Rofecoxib is a selective cox-2 inhibitor, which is used in the treatment of osteoarthritis and rheumatoid arthritis. This drug is practically insoluble in water and has a longer onset of action. Since it is used in the treatment of osteoarthritis, its prolonged use is associated with incidence of side effects that include GI perforations, ulcerations and bleeding. Therefore, an attempt has been made to improve the aqueous solubility of rofecoxib by complexing it with dimethyl β-cyclodextrin (DIMEB), thus enhancing its dissolution rate, thereby showing a faster onset of action and less GI mucosal toxicity.

Rofecoxib and DIMEB were obtained as a gift sample
from Ranbaxy Pharmaceuticals Ltd., Delhi, and Cyclo Labs, Budapest, respectively. All other reagents and chemicals were of analytical reagent grade. The solubility studies were performed by adding an excess amount of rofecoxib to the aqueous solution of DIMEB (mw: 1331) at various concentrations (2-10 mM/ml). The contents were stirred for 72 h at 30±1°. After equilibrium, the samples were filtered and absorbance read at 261 nm.

The inclusion complex was prepared in the molar ratio of 1:1. Physical mixture (PM) was prepared by triturating together the powders for 30 min in a clean, dry pestle and mortar. The kneaded dispersion (KN) was prepared by wetting the powders with dichloromethane. It was kneaded to get a paste like consistency and stirring continued till it starts peeling off from the walls of the mortar. It was then dried in a hot air oven at 60° for 20 min. The spray dried (SD) product was prepared by spray drying a solution of rofecoxib and DIMEB in dichloromethane. The inlet temperature of the spray dryer was 33-34°, the outlet temperature was 32.8°, the feed pump efficiency was 15-17% and atomization pressure was 1.8kg/cm². Dichloromethane was taken, as the solvent as both the drug and DIMEB was completely soluble in it. The solid obtained was sieved through 85 mesh BS.

DSC of the samples was carried out using Perkin Elmer Pyris 6 system at a scanning range of 50-400°/30°/min. XRD of the samples was performed using high power X-ray diffractometer RU-200B from M/s Rigaku, Japan. The scanning speed was 5° min. The FT-IR spectra of samples were recorded on FT-IR Magma IR 750 by Nicolet series III instrument using the KBr disc technique. Scanning was done from 4000 to 500 cm⁻¹. SEM of samples was performed using Joel scanning microscope JSM-840 with a 10 KV acceleration voltage.

Dissolution studies were conducted for pure rofecoxib, rofecoxib marketed formulation (Rofexax, Ranbaxy Pharmaceuticals Ltd) and for inclusion complex using USP SRS paddle type apparatus at 37±1° at 100 rpm. The dissolution medium used was 900 ml of simulated gastric fluid without pepsin (pH 1.2) and phosphate buffer (pH 7.4) containing 0.5% w/v sodium lauryl sulfate. The drug and the inclusion complex were filled in hard gelatin capsule shell so as to contain 12.5 mg rofecoxib/capsule. At various time intervals, 5 ml sample was withdrawn and replaced with fresh dissolution medium. The absorbance of filtered sample was read at 261 nm. Experiment was performed in triplicate.

The phase solubility diagram for rofecoxib-DIMEB system in water can be characterized as A₁ type phase solubility curve, which suggests that the molar ratio of the complex is 1:1 (fig.1). The stability constant was found to be 191.11 M⁻¹.

![Fig. 1: Phase solubility diagram](image)

**Effect of increase in concentration of DIMEB on the solubility of rofecoxib**

The DSC graph for pure rofecoxib shows a sharp endotherm near 210° which is indicative of its melting temperature followed by an exotherm which signifies that after melting, rofecoxib decomposes (fig.2). The thermograms of PM (1:1, drug-DIMEB) are a combination of peaks of DIMEB and rofecoxib. In the thermograms for the KN mixture (1:1) the intensity of the endotherm at 210° (which corresponds to the melting temperature of rofecoxib) diminishes in inten-

![Fig. 2: Differential scanning thermograms of prepared complexes](image)

**Differential scanning thermograms of rofecoxib (A); DIMEB (B); and complexes prepared by Physical mixture (C); Kneading (D) and Spray Drying (E) methods.**
sity and also a slight shifting of the drug melting peak from its original position of 210° to 215° is seen indicating complex formation. In the SD complex the endothermic peak of the drug at 210° has shifted to 195°, indicating that the drug has been engulfed in the cyclodextrin cavity.

The X-ray diffraction pattern of the pure drug shows peaks that are sharp and intense signifying its crystalline nature. Peaks for PM (1:1) show diffused peaks with low intensity. In KN technique (1:1) there is absence of intense peaks of rofecoxib, signifying amorphous nature of the complex. In SD complex, peaks of rofecoxib are less intense in nature, suggesting amorphization of rofecoxib. FT-IR spectra of rofecoxib shows a distinct peak at 1737 cm⁻¹ (for 5 membered lactone ring), 1640 cm⁻¹ (unsaturation), 1500, 970 and 820 cm⁻¹ (for aromatic nucleus). The IR spectrum of DiMEB shows the presence of hydroxyl group at 3280 cm⁻¹ and C-H stretching vibration at 2927 cm⁻¹. The PM and KN mixture (1:1) showed peaks corresponding to both rofecoxib and DiMEB. IR spectra of SD dispersion (1:1) show the presence of bands for hydroxyl group at 3207 cm⁻¹, C-H stretching vibration at 2927 cm⁻¹ and lactone group at 1716 cm⁻¹. However, there has been a shift in the absorption band of lactone group to lower frequency suggesting the interaction of the carbonyl group of rofecoxib with DiMEB.

The SEM technique was also used to assess the degree of complexation. Although this technique is not conclusive for assessing the existence of a true inclusion compound in the solid state, it can be of some utility to prove the

**Fig. 4:** Dissolution profiles of rofecoxib and its complexes with DiMEB in simulated gastric fluid without pepsin (pH 1.2).

The *in vitro* dissolution rate profiles of pure rofecoxib drug powder (●), rofebox (□) and complexes with Dimethyl β-cyclodextrin prepared by physical mixture (●); kneading (●) and spray drying (●) methods.

**Fig. 5:** Dissolution profiles of rofecoxib and its complexes with DiMEB in phosphate buffer (pH 7.4).

The *in vitro* dissolution rate profiles of pure rofecoxib drug powder (●), rofebox (□) and complexes with Dimethyl β-cyclodextrin prepared by physical mixture (●); kneading (●) and spray drying (●) methods.
homogeneity of the solid phases. Pure rofecoxib is characterized by the presence of crystalline particles of regular size. Pure DIMEB also appears as crystalline particles without any definite shape. The photomicrographs of PM of rofecoxib-DIMEB system shows the crystalline structure. The features of both crystals in the KD were not easily detectable. Furthermore, the micrograph of the SD system showed an amorphous product with the presence of small size particles tending to aggregation. (SEM photomicrographs not shown)

The dissolution profile of the inclusion complexes prepared by different methods is shown in fig. 4 and 5. It can be seen that after 5 min only 9.8% of the pure drug and is dissolved, and even after 120 min only 54.3% of the drug goes into solution whereas in case of rofecoxib-DIMEB inclusion complex prepared by KN and SD method, 69.2% and 50.8% drug was released within 5 min and almost complete release (99.3% and 96.4%, respectively) was seen after 45 min in pH 1.2. The release of the drug from the marketed formulation was 49.3% after 5 min and 79% after 120 min. In phosphate buffer (pH 7.4) 8.5% of pure rofecoxib was released after 5 min and at the end of 2 hours 55.6% drug went into the solution whereas in case of rofecoxib-DIMEB inclusion complex prepared by KN and SD method 91.4% and 76.9% of the drug was released after 5 min and almost complete release was observed at 45 min. In case of the marketed formulation, the percentage release was 52.7% after 5 min. and 88.5% after 120 min. It can be concluded that an inclusion complex of rofecoxib with DIMEB could be prepared successfully by kneading method in a molar ratio of 1:1 and this was confirmed by solubility studies, DSC, XRD, FT-IR and SEM. Dissolution studies of the KD complex exhibited almost complete in vitro dissolution profile.

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Spectrophotometric Estimation of Repaglinide in Bulk Drug and Tablet Formulations

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Ion-pair extractive spectrophotometric method was developed for the estimation of repaglinide. This method is based on the formation of a yellow colored ion-pair complex with bromothymol blue in presence of acid phthalate buffer (pH 2.4). This complex was then extracted with chloroform. The color of resulting solution was determined at $\lambda_{\text{max}}$ 438 nm. The calibration curve was found to be linear in the range of 5 to 25 $\mu$g/ml. The recovery study values ranges from 98 to 100%

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