β -Cyclodextrin Complexes of Celecoxib: Molecular-Modeling, Characterization, and Dissolution Studies

Submitted: October 6, 2003; Accepted: January 23, 2004; Published: March 5, 2004

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ABSTRACT

Celecoxib, a specific inhibitor of cyclooxygenase-2 (COX-2) is a poorly water-soluble nonsteroidal anti-inflammatory drug with relatively low bioavailability. The effect of β -cyclodextrin on the aqueous solubility and dissolution rate of celecoxib was investigated. The possibility of molecular arrangement of inclusion complexes of celecoxib and β -cyclodextrin were studied using molecular modeling and structural designing. The results offer a better correlation in terms of orientation of celecoxib inside the cyclodextrin cavity. Phase-solubility profile indicated that the solubility of celecoxib was significantly increased in the presence of β -cyclodextrin and was classified as A_L -type, indicating the 1:1 stoichiometric inclusion complexes. Solid complexes prepared by freeze drying, evaporation, and kneading methods were characterized using differential scanning calorimetry, powder x-ray diffractometry, and scanning electron microscopy. In vitro studies showed that the solubility and dissolution rate of celecoxib were significantly improved by complexation with β -cyclodextrin with respect to the drug alone. In contrast, freeze-dried complexes showed higher dissolution rate than the other complexes.

KEYWORDS: celecoxib, β -cyclodextrin, complexation, molecular-modeling, phase solubility, characterization, dissolution rate

INTRODUCTION

Celecoxib, 4-[5-(4-methylphenyl)-3-trifluoromethyl-1H-pyrazol-1-yl] benzene sulphonamide, is a 1,5-diaryl-substituted pyrazole with a pK_a of 11.1 (Figure 1). Celecoxib was the first specific inhibitor of cyclooxygenase-2 (COX-2) to be approved by the United States Food and Drug Administration (FDA), in 1998. This clinical introduction of celecoxib has been the result of the important discovery of the COX isoenzymes and the subsequent search for molecules effective in selectively inhibiting COX-2 with little or no effect on COX-1. The major clinical goal was to produce a nonsteroidal anti-inflammatory drug (NSAID) that had little or no effect on the gastrointestinal (GI) tract and kidney.¹ Celecoxib is used in the treatment of rheumatoid arthritis, osteoarthritis, and for the management of the pain of these conditions.²⁻⁴ The aqueous solubility of celecoxib is low at 3 to 7 $\mu\text{g/mL}$ when determined in vitro at pH 7 and 40°C. Since the pK_a of celecoxib is 11.1 the solubility of the drug is likely to also be low at physiological pH.⁵ The oral bioavailability of celecoxib is between 22% and 40%.⁶ Thus, it is important to enhance the solubility and dissolution rate of celecoxib to improve its overall oral bioavailability.

Figure 1. Structure of celecoxib.

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The solubility of poorly soluble drug can be altered in many ways, such as modification of drug crystal forms, addition of cosolvents, addition of surfactants, addition of cyclodextrins (CD), etc. Among the possibilities, the cyclodextrin approach is of particular interest.

Cyclodextrins are cyclic (α -1, 4)-linked oligosaccharides of α -D-glucopyranose, containing a relatively hydrophobic central cavity and hydrophilic outer surface. Owing to lack of free rotation about the bonds connecting the glucopyranose units, the cyclodextrins are not perfectly cylindrical molecules but are toroidal or cone shaped. Based on this architecture, the primary hydroxyl groups are located on the narrow side of the torus, while the secondary hydroxyl groups are located on the wider edge (Figure 2).

Figure 2. The chemical structure (A) and the toroidal shape (B) of the β -cyclodextrin molecule (7 α -1,4-linked gluco-pyranose units form a cone with a hydrophilic outer surface and a lipophilic cavity in the center).

During the past 2 decades, cyclodextrins and their derivatives have aroused considerable interest in the pharmaceutical field because of their potential to form complexes with many varieties of drug molecules.⁷ When cyclodextrins are used to solubilize water insoluble drugs, it is generally assumed that the solubilization proceeds through inclusion complex formation.⁸⁻¹¹ The hydrophobic cavity of cyclodextrins is capable of trapping a variety of molecules within to produce inclusion compounds. Numerous scientific articles describe the advantages of drugs complexed with cyclodextrins in this way: increased solubility; enhanced bioavailability; improved stability; the masking of bad taste or odor; reduced volatility; transformation of liquid or gas into solid form; reduced side effects; and the possibility of a drug release system.¹²⁻¹³

In this study, investigations were performed on the possibility of complexation of celecoxib with β -cyclodextrin for improving the solubility and dissolution rate, thereby increasing the bioavailability and therapeutic efficacy of this COX-2 inhibitor (NSAID). The complexes of cele-

coxib with β -cyclodextrin were prepared by using different methods: kneading, evaporation, and freeze drying at stoichiometric ratios.¹² Selective physicochemical determinations based on differential scanning calorimetry (DSC), powder x-ray diffractometry (PXRD), and scanning electron microscopy (SEM) were used to characterize the complexes. In-vitro aqueous solubility and dissolution rate profiles of the complexes were performed.

MATERIALS AND METHODS

Materials

Celecoxib was a generous gift from Dr. Reddy's Laboratories Ltd (Hyderabad, India). β -cyclodextrin was purchased from Sigma Chemical Co (St Louis, MO); both were used as received with no further purification. All other reagents and chemicals were of analytical grade.

Molecular-Modeling Studies

Molecular mechanics and dynamics calculations were performed with the Insight II/Discover program (Molecular Simulations Inc, San Diego, CA) using consistent valence force field (CVFF) on an SGI Octane platform (Silicon Graphics Inc, Mountain View, CA). The structure of β -cyclodextrin was taken from the Cambridge Structural Database (Reference code PIJGIY).¹⁴ The β -cyclodextrin dimer was constructed according to the experimental procedure of Bonnet et al.¹⁵ The celecoxib molecule was drawn using the builder program of Insight II. The structure was then energy minimized with several algorithms (at first, steepest descent, followed by conjugate gradient to refine the structure) until the derivative was less than 0.01 kcal mol⁻¹. The Electrostatic Potential (ESP) changes were extracted using AM₁ calculations.

Docking Studies

To fit the celecoxib into the cavity of CD, Monte Carlo docking simulations were performed with the refined structures. Several initial configurations were tried. Each cycle began with a random change of up to 5 degrees of freedom among them. If the energy of the resulting host-guest system was within 1000 kcal/mol from the previous accepted structure, the system was subjected to 100 interactions of conjugate gradient energy minimization. The nonbonded interactions were calculated by cell-multipole method,¹⁶ and the dielectric constant was set to 1.

One of the low-energy structures of the docking simulations of each host-guest complex was subjected to molecular-dynamics (MD) simulation. MD simulations were performed in vacuo. The MD calculations were done using the velocity verlet algorithm¹⁷ at constant volume with the cell-multipole method for the calculation of nonbonded interactions. The initial atomic velocities were assigned from a Gaussian distribution corresponding to a temperature of 298 K. The system was equilibrated for 100 ps and the production run was done for 250 ps with a time step of 1 fs. Intermediate structures were saved every 100 fs for analysis. Solvent and counter-ion effects were simulated using a distance-dependent dielectric constant with $E = \epsilon_{rij}$, where $\epsilon = 3.5$ during Molecular-Mechanics (MM) stages and 1 during MD stage.

Phase-Solubility Study

The phase-solubility technique permits the evaluation of the affinity between β -cyclodextrin and celecoxib in water. Phase-solubility studies were performed according to the method reported by Higuchi and Connors.¹⁸ Celecoxib, in amounts that exceeded its solubility, was taken into vials to which were added 15 mL of distilled water (pH 6.8) containing various concentrations of β -cyclodextrin (3-15 mM). These flasks were sealed and shaken at 20°C for 5 days. This amount of time is considered sufficient to reach equilibrium. Subsequently, the aliquots were withdrawn, using a syringe, at 1-hour intervals, and samples were filtered immediately through a 0.45- μ nylon disc filter and appropriately diluted. A portion of the sample was analyzed by UV spectrophotometer (SPECTRAmax PLUS, Molecular Devices, Sunnyvale, CA) at 254 nm against blanks prepared in the same concentration of β -cyclodextrin in water so as to cancel any absorbance that may be exhibited by the β -cyclodextrins. Shaking was continued until 3 consecutive estimations were equivalent. The solubility experiments were conducted in triplicate.

The apparent stability constant (K_c) according the hypothesis of 1:1 stoichiometric ratio of complexes was calculated from the phase-solubility diagrams using the following equation.¹⁸

$$K_{1:1} = \frac{\text{Slope}}{S_0(1 - \text{slope})} \quad (1)$$

The slope is obtained from the initial straight-line portion of the plot of celecoxib concentration against β -cyclodextrin concentration, and S_0 is the equilibrium solubility of celecoxib in water.

Preparation of Solid Complexes

The preparation of solid complexes of celecoxib and β -cyclodextrin were performed by different techniques, which are described below in detail. Based on the results of the molecular-modeling studies, the molar ratio was kept at 1:2 (celecoxib: β -cyclodextrin) in all the cases, since it forms a more stable complex (the energy obtained is -57.9 kcal/mol).

Physical Mixture

Physical mixtures were prepared by homogeneous blending of previously sieved and weighed celecoxib and β -cyclodextrin in a mortar.

Kneading Method

β -cyclodextrin (2 mM) and distilled water (1.7 mL) were mixed together in a mortar so as to obtain a homogeneous paste. Celecoxib (1 mM) was then added slowly; while grinding, a small quantity of ammonium hydroxide (0.5 mL of 35% NH_4OH) was added to assist the dissolution of celecoxib. The mixture was then ground for 1 hour. During this process, an appropriate quantity of water was added to the mixture in order to maintain a suitable consistency. The paste was dried in oven at 40°C for 24 hours. The dried complex was pulverized into a fine powder.

Freeze-Drying Method

The required 1:2 stoichiometric quantity of celecoxib (1 M) was added to an aqueous solution of β -cyclodextrin (2 M) while mixing with a magnetic stirrer. After 24 hours of agitation, the resulting solution was frozen by keeping it in a repository at -60°C and was lyophilized in a freeze-dryer (HETO, Allerød, Denmark) for 24 hours.

Evaporation Method

After dissolution of β -cyclodextrin in water, the 1:2 molar proportion of celecoxib was added. This suspension was further kept under stirring for 24 hours. The obtained clear solution was evaporated under vacuum at a temperature of 45°C and 100 rpm in a rotary evaporator (Heidolph, Laborata 4000 Rotavac, Schwabach, Germany). The solid residue was further dried completely at 40°C for 48 hours.

Powder X-Ray Diffractometry

The powder x-ray diffraction patterns were recorded using a Siemens Kristalloflex D-5000 diffractometer (Siemens, Munich, Germany), with Cu as anode material and crystal graphite monochromator, operated at a voltage of 40 Kv and a current of 30 mA. The samples were analyzed in the 2θ angle range of 2° to 65° and the process parameters were set as follows: step size of 0.045° (2θ), scan step time of 0.5 seconds, and time of acquisition of 2 hours.

Differential Scanning Calorimetry

The DSC measurements were performed using a Mettler Toledo DSC 821° DSC module controlled by STAR° software (Mettler-Toledo GmbH, Switzerland). All accurately weighed samples (1 mg of celecoxib or its equivalent) were placed in sealed aluminum pans, before heating under nitrogen flow (20 mL/min) at a scanning rate of 10°C min⁻¹, over the temperature range of 30°C to 220°C. An empty aluminum pan was used as reference.

Scanning Electron Microscopy

The surface morphology of the raw materials and of the binary systems was examined by means of Hitachi S-520 SEM (Tokyo, Japan). The powders were precisely fixed on an aluminum stub using double-sided adhesive tape and then were made electrically conductive by coating in a vacuum with a thin layer of gold (~300 Å), for 30 seconds and at 30 W. The pictures were taken at an excitation voltage of 10 KV and a magnification of ×750 or ×500.

Dissolution Rate Studies

The dissolution behaviors of the celecoxib-β-cyclodextrin complexes were compared with those of pure celecoxib and physical mixture. The dissolution rate studies were performed according to the *United States Pharmacopeia (USP)* XXII rotating basket method (SR8 PLUS model, Hanson Research, Chatsworth, CA). The samples, corresponding to 50 mg of celecoxib, were placed into hard gelatin capsules. The dissolution medium was 900 mL of 0.1 N HCl without enzymes (pH 1.2). The stirring speed was 100 rpm, and the temperature was maintained at 37°C ± 1°C. The samples (3 mL) were withdrawn at various time intervals using a syringe, filtered through 0.45 μ nylon disc filter, and analyzed by UV spectrophotometer at 254 nm. The dissolution profiles were evaluated on the basis

of dissolution efficiency (DE) parameter at 15 and 60 minutes and the dissolved percentage (DP) at 15 and 60 minutes.¹⁹ Data variations were analyzed statistically using an analysis of variance (ANOVA) procedure, and significance was tested at *P* values of .05.

$$DE = \frac{\int_0^t y \cdot dt}{y_{100} \cdot t} \cdot 100\% \quad (\text{Khan KA, 1975})^{20} \quad (2)$$

RESULTS AND DISCUSSION

Molecular-Modeling Studies

Figures 3 and 4 show the structures obtained by molecular modeling according to the methods described in the experimental section. The Monte Carlo (MC) simulations showed a general tendency of inclusion complex formation and lowering interaction energy. The interaction energy was defined as the difference between the sum of the energy of individual host and guest molecule and the energy of the inclusion complex. The calculated energy value is -45.4 kcal/mol for structure 1 (Figure 3), when celecoxib is docked through the head region of the β-cyclodextrin (ie, through the narrow rim [primary hydroxyl groups]). The energy value is -48.2 kcal/mol when celecoxib is introduced through the tail region of the β-cyclodextrin (ie, by the wider rim [secondary hydroxyl groups]). The low energy confirmation of the β-cyclodextrin dimer-celecoxib complex was found at -61.68 kcal/mol, indicating that the inclusion complex formation of the β-cyclodextrin dimer with celecoxib (Figure 4) was energetically more favorable than that of β-cyclodextrin. In the β-cyclodextrin dimer, the guest molecule was fully embedded in the cavity, whereas in β-cyclodextrin, a part of the celecoxib was exposed out of the host.

The general features of the MD trajectories were very similar to those from MC docking simulations. Figures 5A and 5B show overlap of snapshots from MD trajectories of 10 minimum energy structures. The calculations converge well with maximum violation of 0.42 Å° and the Root Mean Square Deviation (RMSD) backbone of 0.95 Å° for β-cyclodextrin and 0.87 Å° for β-cyclodextrin dimer. It can be seen from the Figures 5A and 5B that β-cyclodextrin dimer bound celecoxib more tightly than β-cyclodextrin. The interaction energy for the lowest energy structure showed good agreement with the MC docking simulations. The interaction energies were -57.9 kcal/mol for β-cyclodextrin dimer, -36.5 kcal/mol for structure 1 and -37.2 kcal/mol for structure 2. These results indicate the relative energetic stability of the β-cyclodextrin dimer-celecoxib complex compared

with β -cyclodextrin-celecoxib as in the case of MC docking simulations. A possible molecular arrangement for the inclusion compound is that the molecule celecoxib is buried in the cavity of the β -cyclodextrin dimer in a configuration in which half the molecule is lying in one monomer and other half is lying in the other monomer. It is being held in position due to the formation of hydrogen bonds between the hydroxyl groups of the β -cyclodextrin and the fluorine and nitrogen atoms of the celecoxib. The contribution due to the electrostatic interactions is very small (ie, -0.45 kcal/mol).

Figure 3. Celecoxib docked into the β -cyclodextrin monomer through the head (primary hydroxyl groups) region (ball and sticks indicate celecoxib).

Phase-Solubility Study

The phase-solubility diagram for the complex formation between celecoxib and β -cyclodextrin is presented in Figure 6. This plot shows that the aqueous solubility of the drug increases linearly as a function of β -cyclodextrin concentration. It is clearly observed that the solubility diagram of celecoxib in the presence of β -cyclodextrin can be classified as the A_L type.¹⁸ The linear host-guest correlation with slope of less than 1 suggested the formation of a 1:1 (celecoxib- β -cyclodextrin)

complex with respect to β -cyclodextrin concentrations. The apparent stability constant, K_c , obtained from the slope of the linear phase solubility diagram was found to be 214.9 M^{-1} , which indicates that the celecoxib- β -cyclodextrin complexes at 1:1 ratios are adequately stable.

Figure 4. Celecoxib docked into the β -cyclodextrin dimer (ball and sticks indicate celecoxib).

Powder X-Ray Diffraction

The PXRD patterns for the celecoxib, celecoxib- β -cyclodextrin physical mixture, and the corresponding β -cyclodextrin complexes are presented in Figure 7. As a consequence of the coincidence of diffraction peaks between celecoxib and β -cyclodextrin, we have selected as characteristic peaks of celecoxib those situated at 6° and 32° (2θ), for confirmation of the nature of celecoxib for these studies. The presence of several different peaks in the celecoxib diffraction pattern indicates that the drug is in crystalline form. The diffraction patterns of the physical mixture and kneaded systems show simply the sum of each component, indicating the presence of celecoxib in the crystalline state. In contrast, the freeze-dried system exhibits considerable diminution of the diffraction peaks, suggesting that it is less crystalline than the physical mixture, kneaded, and evaporated systems. The reduction in crystallinity attributed to the freeze-drying treatment is clearly evident for pure β -cyclodextrin, while celecoxib does not show this effect. These results suggest that celecoxib and β -cyclodextrin form an inclusion complex in the solid state, demonstrating that a new solid phase is formed in the freeze-dried product. It may be concluded that as the heights of the diffraction peaks

were reduced, the degree of crystallinity was reduced in the case of solid inclusion complexes. The results also suggest a partial inclusion at 1:2 M ratio in solid state.

Figure 5. The overlap of snapshots during the MD simulations on the initial conformation (A) β -cyclodextrin-celecoxib complex (B) β -cyclodextrin dimer-celecoxib complex.

Differential Scanning Calorimetry

The DSC thermograms for the celecoxib, celecoxib- β -cyclodextrin physical mixture and the corresponding β -cyclodextrin complexes assayed are represented in Figure 8. As shown in the figure, celecoxib exhibits a characteristic endothermic fusion peak at 162.46°C; hence no polymorphs of celecoxib could be found. Fur-

thermore, β -cyclodextrin shows a broad endothermic effect at 118.34°C. The DSC thermograms for the celecoxib- β -cyclodextrin systems show the persistence of the endothermic peak of celecoxib for the physical mixture and the kneaded product. For the freeze-dried and evaporated system, this peak is very small; this result can be explained on the basis of a major interaction between the drug and cyclodextrin. Furthermore, the characteristic endothermic effect of β -cyclodextrin is slightly shifted to higher temperatures for the freeze-dried and evaporated systems, indicating that celecoxib has complexed with β -cyclodextrin. In fact, even though not unambiguously attributable to inclusion complexation, this phenomenon is indicative of a stronger interaction between celecoxib and β -cyclodextrin in the solid state.²¹

Figure 6. Phase-solubility pattern of celecoxib- β -cyclodextrin system in water (mean $\pm$ SD; $n = 3$).

Figure 7. X-ray diffractograms of celecoxib (A); β -cyclodextrin (B); celecoxib: β -cyclodextrin physical mixture (C); celecoxib: β -cyclodextrin kneaded (D); freeze-dried (E); and evaporated (F) system.

Figure 8. DSC thermograms of celecoxib (A); β -cyclodextrin (B); celecoxib: β -cyclodextrin physical mixture (C); celecoxib: β -cyclodextrin freeze-dried (D); kneaded (E); and evaporated (F) system.

Scanning Electron Microscopy

The SEM of celecoxib, celecoxib: β -cyclodextrin systems are shown in Figure 9. Celecoxib has appeared as irregular-shaped crystals, and β -cyclodextrin has presented a parallelogram shape. Celecoxib: β -cyclodextrin physical mixture and the corresponding kneaded product were constituted by relative bulky particles (β -cyclodextrin), with other small ones (celecoxib) adhered on its surface. The comparable morphology of these systems with pure components could reveal that apparently no celecoxib: β -cyclodextrin interaction has taken place in the solid state, although the number of celecoxib particles that adhered on β -cyclodextrin surface was greater in the kneading system. In the evaporated and freeze-dried products, the original morphology of the raw materials disappeared, and it was not possible to differentiate the 2 components. The evaporated and freeze-dried samples appeared as agglomerates. The drastic change of the particles' shape and aspect in the evaporated and freeze-dried samples was indicative of the presence of a new solid phase, leading us to estimate the existence of a single phase, thus corroborating the PXRD observations.

Figure 9. Scanning electron photomicrographs of celecoxib (A); β -cyclodextrin (B); celecoxib: β -cyclodextrin physical mixture (C); celecoxib: β -cyclodextrin kneaded (D); freeze-dried (E); and evaporated (F) system.

Dissolution Rate Studies

The dissolution profiles of celecoxib alone, physical mixture, and the celecoxib- β -cyclodextrin complexes are reported in Figure 10. The release rate profiles were drawn as the percentage of drug dissolved vs time. Ac-

Table 1. Dissolution Efficiency (DE) and Dissolution Percentage (DP) Values at 15 and 30 Minutes From Celecoxib, Celecoxib- β -Cyclodextrin Physical Mixture and the Corresponding Celecoxib- β -Cyclodextrin Complexes*

Systems	Elaboration Method	DE ₁₅	DP ₁₅	DE ₆₀	DP ₆₀
Celecoxib	Freeze-dried	0.0796 $\pm$ 0.9	24.029 $\pm$ 0.6	0.2345 $\pm$ 0.7	31.026 $\pm$ 0.5
Celecoxib - β -Cyclodextrin	Evaporation	0.2869 $\pm$ 1.2	80.442 $\pm$ 1.2	0.8436 $\pm$ 1.3	90.407 $\pm$ 1.4
	Kneading	0.2143 $\pm$ 1.1	72.045 $\pm$ 0.7	0.7984 $\pm$ 0.7	77.469 $\pm$ 0.8
	Physical mixture	0.1976 $\pm$ 0.4	56.872 $\pm$ 1.1	0.6421 $\pm$ 0.4	66.974 $\pm$ 0.6
		0.1432 $\pm$ 0.2	40.145 $\pm$ 0.8	0.4518 $\pm$ 1.8	44.229 $\pm$ 1.2

*DE indicates dissolution efficiency; DP, dissolution percentage. All values are expressed as mean $\pm$ SD (n = 3).

According to these results, the inclusion complexes released up to 80% of the drug in 15 minutes, and up to 85% after 30 minutes; whereas celecoxib pure drug exhibited the release of ~24% after 15 minutes and not more than 31% after 60 to 120 minutes. These quantities contrast with the markedly 3-fold increase in the release of freeze-dried product.

Figure 10. Dissolution rate profiles of celecoxib, celecoxib- β -cyclodextrin physical mixture and the corresponding β -cyclodextrin complexes (mean $\pm$ SD; n = 3).

It is also evident that the freeze-dried, evaporated, and kneaded systems exhibit higher dissolution rates than the physical mixture and the pure drug (Table 1). The extent of the enhancement of the dissolution rate was found to be dependent on the preparation method, since the freeze-dried and evaporated products exhibited the highest dissolution rates. This enhancement has been attributed in all these cases both to the formation of an inclusion complex in the solid state and to the reduction of the crystallinity of the products, as confirmed by PXRD studies. The dissolution rate increase reached for the physical and kneaded mixtures is only due to the wetting effect of the β -cyclodextrin; in fact, this effect is more evident for the kneaded product, where the mixing process between the 2 components is more intensive. The

effect of complexation with β -cyclodextrin on the solubility of celecoxib can be explained in terms of the reduction in the crystallinity of the drug caused by the freeze-drying process and the inclusion into the hydrophobic cavity of the β -cyclodextrin.²²⁻²⁴

The complexes prepared by kneading technique offer a dissolution rate of approximately 70% in 60-minutes, which may be of particular interest for industrial scale preparations because of the low cost and the simple process, which involves less energy, time, and equipment.

CONCLUSION

The aqueous solubility and dissolution rate of celecoxib can be increased by inclusion complexation with β -cyclodextrin. Molecular-modeling studies support the formation of stable molecular inclusion complexation of celecoxib with β -cyclodextrin dimer. Phase-solubility profile indicated that the solubility of celecoxib and apparent stability constant was significantly increased in the presence of β -cyclodextrin dimer. Results obtained by different characterization techniques clearly indicate that the freeze-drying method leads to formation of solid-state complexes between celecoxib and β -cyclodextrin. The complexation of celecoxib with β -cyclodextrin lends an ample credence for better therapeutic efficacy.

ACKNOWLEDGEMENTS

The authors wish to thank Dr K. V. Raghavan, Director, Indian Institute of Chemical Technology Hyderabad, India, for providing necessary facilities. One of the authors, M.N. Reddy, is thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for the award of the Senior Research Fellowship.

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