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Original research paper

Physicochemical characterization and *in vitro* dissolution behaviour of celecoxib-β-cyclodextrin inclusion complexes

VIVEK RANJAN SINHA[1]*
R. ANITHA[1]
SOMA GHOSH[2]
AMITA[1]
RACHANA KUMRIA[1]
JAYANT RAJARAM BHINGE[1]
MANOJ KUMAR[1]

[1] *University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh India*

[2] *Department of Chemistry, Panjab University, Chandigarh, India*

In this study, attempts were made to investigate the effects of β-cyclodextrin (β-CD) on the aqueous solubility and dissolution rate of celecoxib. Inclusion complexes were prepared by the kneading method and characterized by SEM, NMR, IR, DSC, and X-ray powder diffraction. Dissolution rate of the complexes was significantly greater than that of the corresponding physical mixtures and pure drug, indicating that the formation of inclusion complex increased the solubility of the poorly soluble drug celecoxib.

Keywords: celecoxib, β-cyclodextrin, inclusion complex, dissolution profile

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Cyclodextrins are chemically and physically stable molecules formed by the enzymatic modification of starch (1). They are cyclomalto oligosaccharides composed of six, seven or eight α-D-glucopyranose units (α-, β-, γ-CD, respectively). Their hollow structure enables them to host a variety of molecules (guests) partially or entirely in their hydrophobic caving. These inclusion complexes exist both in aqueous solution and in solid state. As a result of complexation of compounds by cyclodextrins, the apparent solubility of the molecule can be altered (2), stability of the compound in the presence of light and oxidizing conditions is increased (3) and volatility of compounds is decreased (4). Many scientists have studied the cyclodextrin complexes of various NSAIDs such as valdecoxib, diclofenac, piroxicam, ketoprofen, *etc.* and have showed their superiority over physical mixtures (5–8).

Celecoxib, 4-[(5-(4-methyl phenyl)-3-trifluoro methyl)-1*H*-pyrazol-1-yl] benzene sulfonamide is a non steroidal anti-inflammatory drug that is a specific inhibitor of COX-2 enzyme. Celecoxib is widely used in the treatment of rheumatoid and osteoarthritis. According to the biopharmaceutical classification system, celecoxib belongs to class II type

* Correspondence, e-mail: vr_sinha@yahoo.com

drugs. Celecoxib is poorly soluble in water (3–7 μg mL^{-1} at 40 °C and pH 7) and possesses a slow dissolution rate. Lower dissolution in the gastrointestinal fluid may constitute the rate limiting step for the absorption process (9).

The objective of the present work was to prepare and characterize the drug-CD complexes and to investigate the possibility of improving the solubility and dissolution of celecoxib by its complexation with β-cyclodextrin. The systems were prepared by the kneading method using various drug-CD molar ratios. NMR, DSC, IR, SEM, and X-ray powder diffraction were used to characterize the solid state of all binary systems. The results obtained from celecoxib-β-CD complexes and their physical mixtures were compared.

EXPERIMENTAL

Materials

Celecoxib and β-CD were obtained as gift samples from Hetero Drugs Ltd. (India), and S. A. Chemicals (India), respectively, and were used as such. All other reagents and solvents used were of analytical grade.

Preparation of solid complexes

β-CD was wetted with water in a mortar until a paste was obtained. Celecoxib was then added in divided portions and the slurry was kneaded for about 1 h. An appropriate amount of water was added in order to maintain suitable consistency. The paste was washed with diethyl ether to remove the uncomplexed drug. Further, the product was dried under vacuum at 40 °C for 48 h. Inclusion complexes of various drug-to-β-CD molar ratios were prepared: 1:1 (KC1), 1:2 (KC2), 1:3 (KC3), 2:1 (KC4) and 3:1 (KC5) and

Table I. Composition of inclusion complexes and physical mixtures

Formulation code	Molar ratio (celecoxib to β-CD)
KC1	1:1
KC2	1:2
KC3	1:3
KC4	2:1
KC5	3:1
PM1	1:1
PM2	1:2
PM3	1:3
PM4	2:1
PM5	3:1

used for further studies. Similarly, physical mixtures of various drug-to-β-CD molar ratios were prepared: 1:1 (PM1), 1:2 (PM2), 1:3 (PM3), 2:1 (PM4) and 3:1 (PM5) using a mortar and pestle. Composition of inclusion complexes and physical mixtures is listed in Table I.

NMR

^{1}H NMR spectra were obtained with a Bruker AVANCE DPX 300 spectrometer (Switzerland) in a CD_3OD/D_2O (1:1) mixture with tetramethyl silane as internal standard. Chemical shifts are given as parts per million (ppm) downfield from that of tetramethylsilane.

Thermal analysis

The DSC curves of different samples were recorded on a Mettler Toledo Star system DSC calorimeter (Switzerland), calibrated with indium, at heating rates of 10 °C min^{-1}. The thermal behaviour was studied by heating 1–7 mg of samples in aluminium pans under nitrogen gas flow (20 mL min^{-1}) over the temperature range of 0 to 450 °C.

X-ray diffractometry

Powder X-ray diffraction patterns were recorded using a Philips PW 1729 X-ray generator (Holland) with Ni filtered Cu Kα radiation as source. It operated at a voltage of 35 kV and a current of 20 mA. The samples were analyzed in the 2θ angle range of 2–40°.

IR spectroscopy

The samples were previously ground and mixed thoroughly with potassium bromide. The KBr disks were prepared by compressing the powders in a hydraulic press (7×10^4 kPa). The scanning range was from 4500–400 cm^{-1}. IR spectra were obtained using a 360 Perkin Elmer IR spectrometer (USA).

Electron microscopy

The external morphology of the samples was examined under a JSM 6100 JEOL scanning electron microscope (Japan). The samples were previously fixed on a brass stub using double-sided adhesive tape and were then made electrically conductive by coating with a thin layer of gold and palladium alloy (180–200 Å) using a fine coat ion sputter (JEOL, fine coat ion sputter JFC-1100). The pictures were taken at an excitation voltage of 20 kV and magnification in the range of 250 to 2000 X.

Dissolution studies

Dissolution was performed using a USP dissolution test apparatus (type 2) (10). Dissolution medium consisted of 900 mL of phosphate buffer pH 7.2 containing surfactant (polysorbate 80). The surfactant was added to provide sink conditions. Powdered samples containing 5 mg of celecoxib or its equivalent in complexed or physically mixed form with β-CD were used. The stirring speed was 50 rpm and the temperature was

maintained at 37 ± 0.5 °C. Ten millilitre aliquots of dissolution media were withdrawn at various time intervals and replaced by 10 mL of fresh dissolution medium. The collected samples were filtered through a 0.22 μm membrane filter (Sartorius cellulose nitrate filter, Germany) and analyzed spectrophotometrically at 249 nm.

Data analysis of mean percent release values were performed using the oneway analysis of variance (ANOVA) with Tukey's test for multiple comparisons.

RESULTS AND DISCUSSION

NMR

Proton magnetic resonance spectroscopy was carried out for celecoxib-CD inclusion complexes in order to gain an insight into the inclusion mode of the complex. The chemical shifts of CDs in the presence of celecoxib are summarized in Table II. Major changes in the chemical shift values were observed in the CD region (3.6–3.8 ppm), which provided information about the guest molecule inclusion. Appreciable shift occurred in H(5) proton and H(3) proton in kneaded complexes KC1, KC2, KC4, which correlate the interaction of the drug and H(3)/H(5) protons of β-CD. Similar results were reported by many authors (11–12).

A typical structural inference is that if only the H(3) proton undergoes a shift in the presence of substrate, then the cavity penetration is shallow whereas if also H(5) shifts, then the penetration is deep (13). The H(3) and H(5) protons located inside the cavity and the H(6) proton located on the cavity rim at the narrow end of the molecule have shifted appreciably. Therefore, it can be inferred in the present study that the drug penetrates deeply into the CD cavity.

Table II. Chemical shifts (ppm) for the protons of β-CD in free state and in kneaded complexes

Proton	$\delta_{\beta\text{-CD}}$ (free)	δ_{KC1}	$\Delta\delta_1{}^*$	δ_{KC2}	$\Delta\delta_2{}^*$	δ_{KC4}	$\Delta\delta_4{}^*$	δ_{KC5}	$\Delta\delta_5{}^*$
H-1	4.96 (doublet)	5.01	0.05	5.01	0.05	–	–	4.95	–0.01
H-2	3.54 (doublet of doublet)	3.59	0.05	3.59	0.05	3.56	0.02	3.50	–0.04
H-3	3.84 (doublet)	3.91	0.07	3.91	0.07	3.90	0.06	3.88	0.04
H-4	3.49 (multiplet)	3.53	0.04	3.53	0.04	3.51	0.02	3.47	–0.02
H-5	3.67 (doublet)	3.76	0.09	3.76	0.09	3.74	0.07	3.73	0.06
H-6	3.79 (multiplet)	3.87	0.08	3.87	0.08	3.84	0.05	3.84	0.05

$\Delta\delta^* = \delta_{complex} - \delta_{\beta\text{-CD(free)}}$

In the ^{1}H NMR spectra of KC1, KC2 and KC4 complexes, all CD protons were deshielded indicating that the celecoxib molecule created magnetic anisotropic effects in the interior of the cavity due to weak interactions (van der Waal's forces) with the internal hydrogen atoms [H(3) and H(5)]. Many authors reported similar observations. Lesser shift values were observed in the case of the KC5 complex. Change in the splitting pattern (Fig. 1) also indicates the inclusion complex formation. In the case of free β-CD the H(5) proton (3.67 ppm) was well resolved from H(6) and H(3) protons, which was very conspicuous (Fig. 1a), while it was introduced in the H(6) proton area in the case of inclusion complexes KC1, KC2, KC4 (Figs. 1b, 1c and 1d). The KC5 complex showed resolution between H(6) and H(5) protons (Fig. 1e). The splitting pattern of KC5 was towards free β-CD.

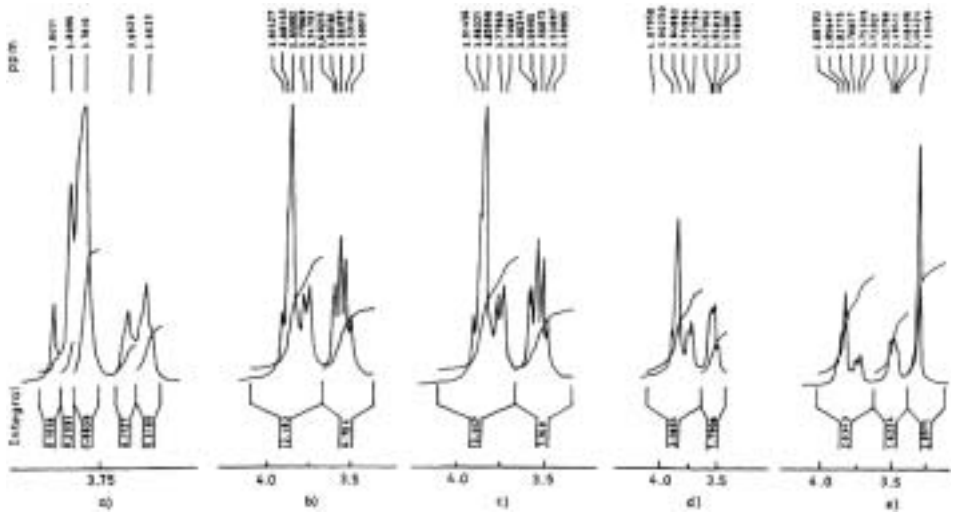

Fig. 1. Splitting pattern of H(3) and H(5) protons: a) free β-CD, b) KC1, c) KC2, d) KC4 and e) KC5.

Change in the chemical shift values of celecoxib in the presence of β-CD is depicted in Table III. Small changes in chemical shifts (~0.002–0.04 ppm) were observed. Maximum shift was observed in the aromatic protons containing – SO_2NH_2 group. The H-1a protons of celecoxib had a shift value of 0.01–0.02 ppm and H-1b protons had a chemical shift value of ~0.032–0.037 ppm in kneaded complexes KC1, KC2 and KC4. This observation indicates that the polar group might participate in the weak interaction with H(3) and H(5) protons of β-CD due to hydrogen bonding or van der Waals forces. Chemical shifts were also observed in the case of 5a–5b protons (0.010–0.019 ppm) and methyl protons (~0.002–0.0088 ppm) of celecoxib, suggesting that the *p*-tolyl part of celecoxib could be accommodated into the hydrophobic cavity of β-CD. In the case of KC5, the shift values of celecoxib were almost comparable to that of free drug. The above observations suggest the existence of inclusion complex formation in the case of kneaded complexes KC1, KC2 and KC4. Lesser interaction was observed in the case of the KC5 complex.

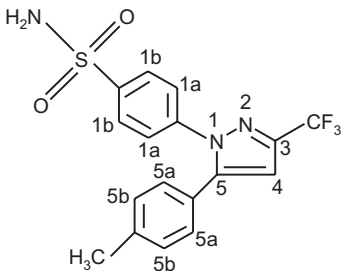

Table III. Chemical shifts (ppm) for the protons of celecoxib in free state and in kneaded complexes

Celecoxib proton	$\delta_{celecoxib(free)}$	δ_{KC1}	$\Delta\delta_1$*	δ_{KC2}	$\Delta\delta_2$*	δ_{KC4}	$\Delta\delta_4$*	δ_{KC5}	$\Delta\delta_5$*
CH_3	2.3469 (singlet)	2.3498	0.0029	2.3498	0.002	2.3557	0.0088	2.3471	0.002
H-1a	7.4863 (doublet)	7.4987	0.0124	7.4987	0.0124	7.5046	0.0182	7.4881	0.0018
H-1b	7.9295 (doublet)	7.9623	0.0373	7.9623	0.0328	7.9614	0.0319	7.9282	–0.0013
H-5a, H-5b	7.1772 (doublet of doublet)	7.1896	0.0107	7.1896	0.0123	7.1965	0.0193	7.1831	0.0059
H-4	6.9051 (singlet)	6.9098	0.004	6.9097	0.004	6.9474	0.0423	6.9104	0.0088

$\Delta\delta^* = \delta_{complex} - \delta_{celecoxib\ (free)}$

Thermal analysis

When guest molecules are included in the CD cavity, their melting, boiling and sublimation points usually shift to a different temperature or disappear within the temperature range at which the CD is decomposed (14). DSC thermograms of pure celecoxib and β-CD, physical mixtures and the corresponding inclusion complexes are shown in Fig. 2. DSC thermogram of celecoxib (Fig. 2a) exhibited a sharp endothermic peak at 163 °C corresponding to its melting point (157–163 °C). Scan of β-CD (Fig. 2b) showed a very broad endothermic peak in the range of 100–142 °C due to the elimination of crystallization water, which was in agreement with the findings of various authors (15). The endothermic peak of the drug was retained at 163 °C in all physical mixtures (Figs. 2c and 2d) in the case of PM1 and PM2, respectively, attributing to the presence of less or no interaction between the pure components in the physical mixture.

DSC thermogram of KC1 displayed an endothermic peak at 150 °C (Fig. 2e). The endothermic peak of celecoxib (163 °C) was absent in this case, which may be ascribed to the formation of inclusion complexes. Various authors observed similar results (16). The

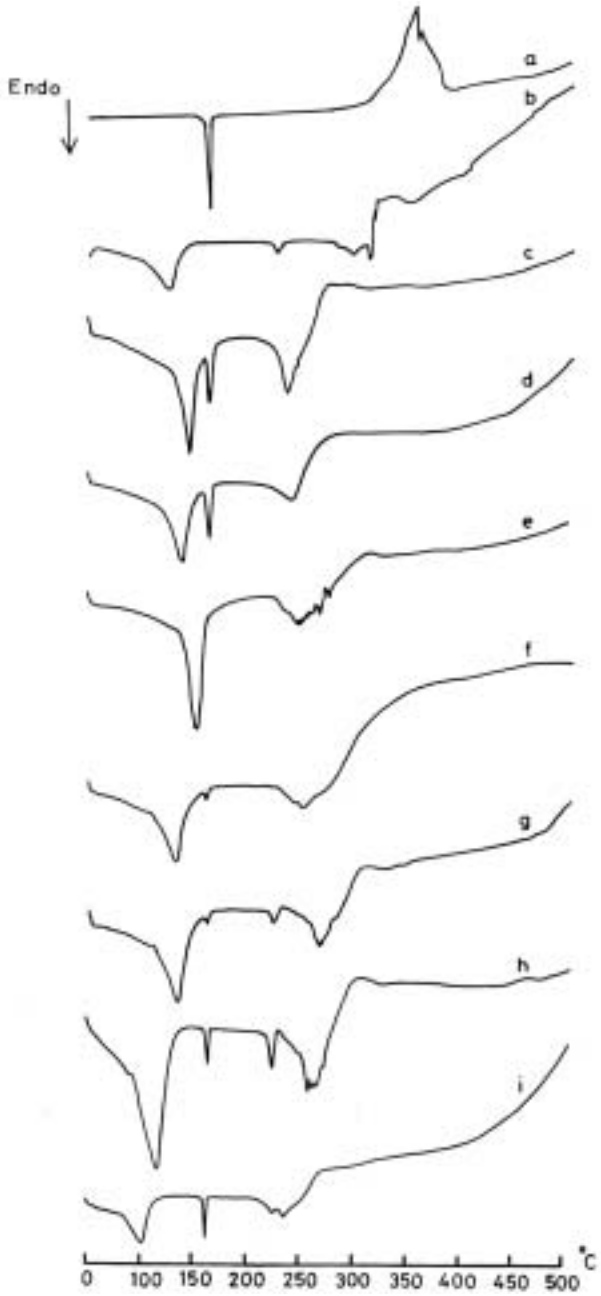

Fig. 2. DSC thermograms of: a) celecoxib, b) β-CD, c) PM1, d) PM2, e) KC1, f) KC2, g) KC3, h) KC4 and i) KC5.

peak at 163 °C can still reflect the presence of free drug in the case of KC2, KC3, KC4 and KC5 complexes (Figs. 2f and 2i). The presence of drug peak indicated that celecoxib was dispersed in the free state between inclusion complexes.

X-ray diffraction

Powder XRD was used to measure the crystallinity of the formed complexes. The peak position (angle of diffraction) is an indication of crystal structure and peak heights are measures of sample crystallinity in a diffractogram (17). Formation of an amorphous state proves that the drug was dispersed in molecular state with CD (18). Various authors have reported the formation of a diffuse diffraction pattern, appearance of new peaks and disappearance of characteristic peaks of the guest as evidences for formation of inclusion complexes of the drug with CD (19). The powder X-ray diffraction patterns of pure celecoxib, β-CD and their physical mixtures and inclusion complexes are represented in Fig. 3. Most of the principal peaks of celecoxib and β-CD were present in the diffraction patterns of physical mixtures (Fig. 3). This indicated that there was no interaction between the pure components in physical mixtures.

The kneaded complexes showed crystalline peaks suggesting the formation of a crystalline inclusion compound. However, the complexes showed a different diffraction pattern from that of pure celecoxib and β-CD, for example, the characteristic peaks of celecoxib at 14.8, 16.0, 21.6, 22.3, 23.5 and 25.4° disappeared in KC1 (Fig. 3). These observations are attributed to an interaction between celecoxib and β-CD, showing the presence of a new solid phase where possible formation of an inclusion complex may be considered.

IR

Supporting evidence for complexation of the guest molecule with β-CD can be obtained by IR spectroscopy. Upon complexation, a significant shift in the characteristic peaks of the guest molecule, either to higher or lower frequency, was observed by some authors (20, 21). Disappearance and broadening of the peaks of the guest also proves interaction between the drug and β-CD molecules (18).

IR spectrum of celecoxib showed medium absorption bands at 3160 and 3260 cm^{-1}, which were assigned to the drug –NH symmetric and asymmetric stretching vibrations, respectively. The other characteristic bands may be attributed to the following group vibrations: 1150 and 1340 cm^{-1} (S=O symmetric and asymmetric stretching, respectively), 1560 cm^{-1} (NH bend), and 780 cm^{-1} (aromatic –CH bend).

IR spectrum of β-CD showed a broad absorption band at 3340 cm^{-1} due to the –OH stretching. IR spectrum of the physical mixture PM1 retained the characteristic –NH absorption band. There was no shift in the S=O stretching vibration of celecoxib at 1340 cm^{-1}. These observations led to the conclusion that there was less interaction between celecoxib and β-CD in the physical mixture. The characteristic –NH stretching bands of celecoxib at 3160 cm^{-1} and 3260 cm^{-1} were masked in cases of all kneaded complexes. The stretching band of S=O group at 1340 cm^{-1} shifted to lower frequencies (1320 cm^{-1}) in the case of kneaded complexes KC1 and KC2. The S=O stretching band became broadened in KC3 and KC4 complexes, whereas it remained unchanged in KC5 complexes. The observed shifts in the case of KC1 and KC2 complexes may be attributed to the

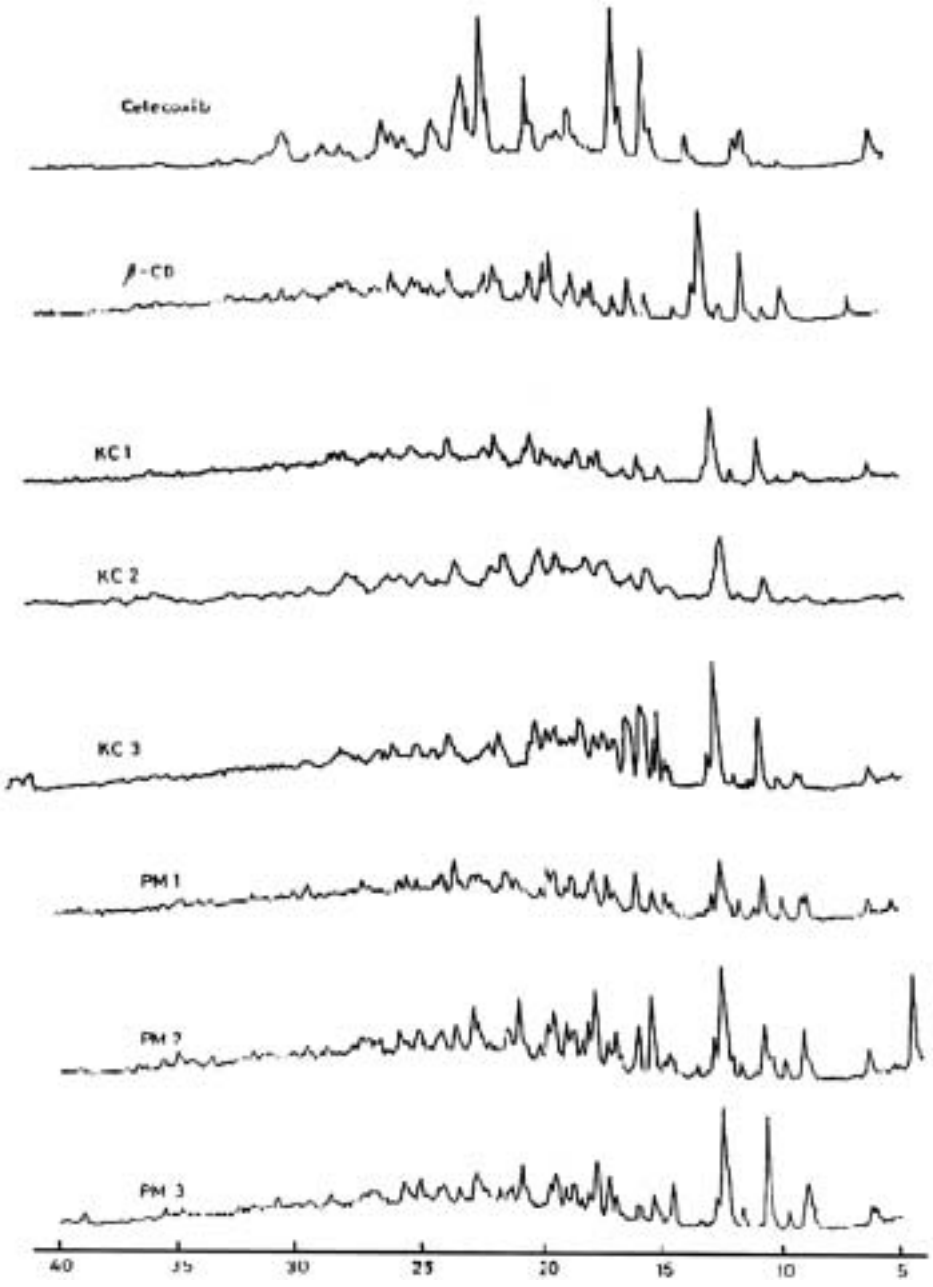

Fig. 3. Powder X-ray diffraction patterns of celecoxib, β-CD kneaded complexes and physical mixtures.

breakdown of the intermolecular hydrogen bonds of the crystals (22) and formation of a monomeric drug dispersion as a consequence of the interaction with CDs, which could result in inclusion of the drug in the hydrophobic cavity of the carrier (23). The broadening of S=O stretching at 1340 cm^{-1} in cases of KC3 and KC4 and masking of –NH stretching band in KC5 may suggest the existence of some interaction between the drug and β-CD.

SEM

The scanning electron microphotographs of β-CD, pure celecoxib, celecoxib-β-CD physical mixtures and inclusion complexes are given in Fig. 4. The microphotograph of β-CD appeared as three-dimensional parallelogram-shaped particles. Celecoxib appeared as irregular and three-dimensional particles. The physical mixture clearly depicted the crystalline structure of both celecoxib and β-CD. The SEM of kneaded complexes (KC1 and KC2) is shown in Fig. 4. Whereas the physical mixture (PM1) showed the crystalline structure of celecoxib and β-CD, the features of both crystals in the kneaded complex were not easily detectable. The kneaded complex showed adherence of drug particles to β-CD. This observation suggested the existence of interaction between celecoxib and β-CD.

Dissolution studies

The dissolution profiles of celecoxib and celecoxib-β-CD binary systems are illustrated in Figs. 5a and 5b. The reported values are the arithmetic mean of three measurements. The results of dissolution rate studies expressed by $t_{50\%}$ are collected in Table IV.

One-way analysis of variance (ANOVA) showed that the increase in dissolution rate was significant ($p < 0.001$) with all kneaded complexes (KC1–KC5) and their respective physical mixtures (PM1–PM5) as compared to pure celecoxib. All pair-wise multiple com-

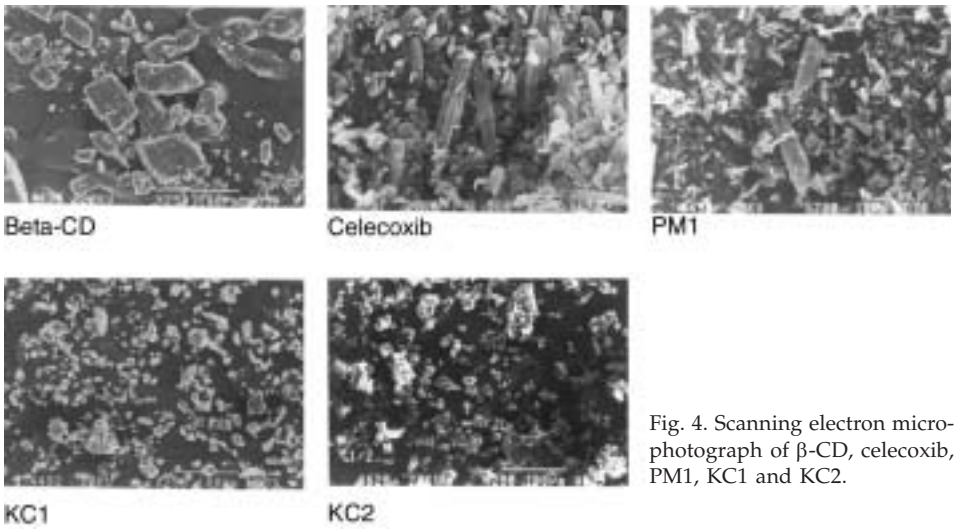

Fig. 4. Scanning electron microphotograph of β-CD, celecoxib, PM1, KC1 and KC2.

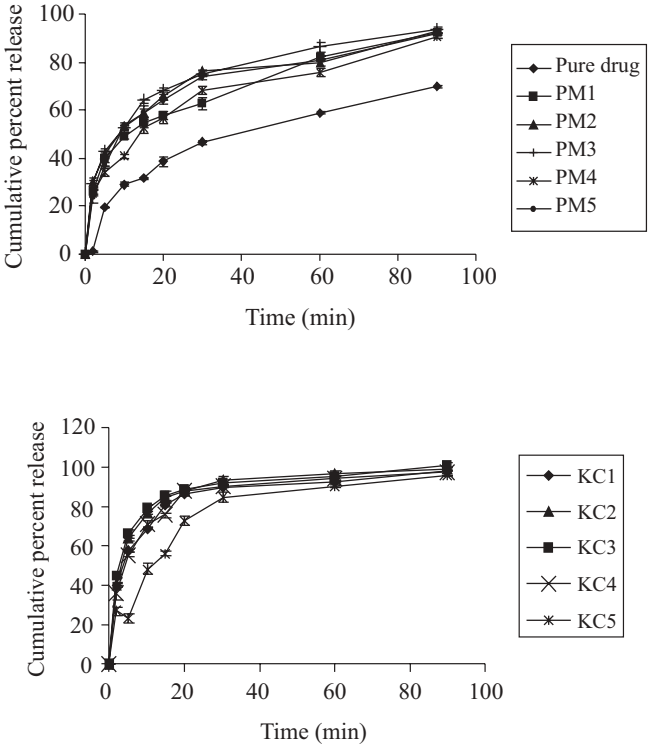

Fig. 5. Cumulative percent release *vs.* time profile of: a) pure drug and physical mixtures and b) kneaded complexes (mean ± SD, n = 3).

parison analyses (Tukey's test) illustrated that the kneaded complexes (KC1–KC5) also produced a statistically significant ($p < 0.05$) increase in the dissolution rates as compared to their respective physical mixtures.

The $t_{50\%}$ of kneaded complexes (KC1-KC4) was < 3.5 min while it was 10.4 min for KC5. The values of $t_{50\%}$ of all kneaded complexes were much lower than for celecoxib alone ($t_{50\%}$ = 34.6 min) while physical mixtures had values between 8.4 and 15 min (Table III). The mean percent release of drug from the kneaded complexes KC1, KC2, KC3, KC4, KC5 at 30 min was 1.9, 2.0, 2.0, 1.9, and 1.8 fold higher compared to pure celecoxib. The physical mixtures PM1, PM2, PM3, PM4, PM5 also increased the mean percent release of drug 1.3, 1.6, 1.7, 1.5, 1.6 fold, respectively. The increase in the dissolution rate of celecoxib physically mixed with β-CD was possibly a result of local solubilization operating in the microenvironment or the hydrodynamic layer surrounding the drug particles (24). This action may result in an *in situ* inclusion process, which increases the amount of dissolved drug.

The dissolution of celecoxib from the celecoxib powder alone was incomplete even after 90 min (70%), the kneaded complexes displayed better dissolution properties, 89.8,

Table IV. $t_{50\%}$ *of pure celecoxib, inclusion complexes and physical mixtures*

Formulation	$t_{50\%}$ (min)
Celecoxib	34.6
KC1	2.7
KC2	2.0
KC3	1.4
KC4	3.5
KC5	10.4
PM1	12.1
PM2	9.0
PM3	8.4
PM4	14.5
PM5	11.3

93.4, 91.6, 90.4 and 84.9% of drug released within 30 min from KC1, KC2, KC3, KC4, KC5 complexes, respectively (Fig. 5b). The significant improvement in dissolution characteristics of the complexes was justified by the concurrence of several factors, *viz.*, increased particle wettability, reduction of crystallinity of the product (25). The surfactant-like properties of CD were postulated in some cases to explain the higher dissolution rate of the complexes. CD can reduce the interfacial tension between the solid particles of celecoxib and the dissolution medium, leading to a higher rate of dissolution. The improvement in dissolution rate of celecoxib from CD complexes was in agreement with the results obtained from phase solubility analysis (26).

CONCLUSIONS

As a result of this study, it may be concluded that celecoxib-β-CD inclusion complexation led to improvement of drug solubility and dissolution rate, which suggests that the celecoxib-β-CD complex may have greater utility in the fast dissolving dosage forms, with possible enhancement of oral bioavailability.

REFERENCES

1. V. Stella and R. Rajewski, Cyclodextrins: Their future in drug formulation and delivery, *Pharm. Res.* **14** (1997) 556–567.
2. A. Latrofa, G. Trapani, M. Franco, M. Serra, M. Muggironi, F. P. Fanizzi, A. Cutrignelli and G. Liso, Complexation of phenytoin with some hydrophilic cyclodextrins effect on aqueous solubility, dissolution rate and anticonvulsant activity in mice, *Eur. J. Pharm. Biopharm.* **52** (2001) 65– 73.

3. C. W. Park, S. J. Kim, S. J. Park, J. H. Kim, J. K. Kim, G. B. Park, J. O. Kim and Y. I. Ha, Inclusion complexes of conjugated linoleic acid (CLA) with cyclodextrins, *J. Agric. Food Chem.* **50** (2002) 2977–2983.
4. Z. Cai, L. Wu, G. Zhong and S. Gao, Effects of inclusion of Citri reticulatae volatile oil by beta-cyclodextrin, *Zhongguo Zhongyao Zazhi* **20** (1995) 603-604; *ref. Chem. Abst*. **124** (1996) 241719a.
5. M. Jug, M. Becirevic-Lacan, A. Kwokal and B. Cetina-Cizmek, Influence of cyclodextrin complexation on piroxicam gel formulations, *Acta Pharm.* **55** (2005) 223–236.
6. M. L. Manca, M. Zaru, G. Ennas, D. Valenti, C. Sinico, G. Loy and A. M. Fadda, Diclofenac-beta-cyclodextrin binary systems: physicochemical characterization and in vitro dissolution and diffusion studies, *AAPS Pharm. Sci. Tech.* **6** (2005) E464–472.
7. K. Rajendrakumar, S. Madhusudan and T. Pralhad, Cyclodextrin complexes of valdecoxib: properties and anti-inflammatory activity in rat, *Eur. J. Pharm. Biopharm.* **60** (2005) 39–46.
8. W. L. Lu, Q. Zhang, L. Zheng, H. Wang, R. Y. Li, L. F. Zhang, W. B. Shen and X. D. Tu, Antipyretic, analgesic and anti-inflammatory activities of ketoprofen beta-cyclodextrin inclusion complexes in animals, *Biol. Pharm. Bull.* **27** (2004) 1515–1520.
9. S. K. Paulson, M. B. Vaughn, S. M. Jessen, Y. Lawal, C. J. Gresk, B. Yan, T. Maziasz, C. S. Cook and A. Karim, Pharmacokinetics of celecoxib after oral administration in dogs and human: Effect of food and site of absorption, *J. Pharmacol. Exp. Ther.* **297** (2001) 638–645.
10. *USP 27/NF 22*, The USP Convention, Rockville 2004, pp. 2303–2304.
11. G. Trapani, A. Latrofa, M. Franco, M. R. Pantaleo, E. Sanna, F. Masso, F. Tuveri and G. Liso, Complexation of zolpidem with 2-hydropropyl-β-methyl-β- and 2-hydroxypropyl-γ-cyclodextrins: Effect on aqueous solubility, dissolution rate and ataxic activity in rat, *J. Pharm. Sci.* **89** (2000) 1443–1451.
12. L. S. Koester, S. S. Guterres, M. Le Roch, V. L. Eifler-Lima, J. A. Zuanazzi and V. L. Bassani, Ofloxacin/beta-cyclodextrin complexation, *Drug Dev. Ind. Pharm.* **27** (2001) 533–540.
13. K. A. Connors, The stability of cyclodextrin complexes in solution, *Chem. Rev.* **97** (1997) 1325–1357.
14. H. Cabral Marques, J. Hadgraft and J. Kellaway, Studies of cyclodextrin inclusion complexes. I. The salbutamol-cyclodextrin complex as studied by phase solubility and DSC, *Int. J. Pharm.* **63** (1990) 259–266.
15. P. Mura, M. T. Faucci and P. L. Parrini, Effect of grinding with microcrystalline cellulose and cyclodextrins on the ketoprofen physicochemical properties, *Drug Dev. Ind. Pharm.* **27** (2001) 119–128.
16. P. Mura, E. Adragna, A. M. Rabasco, J. R. Moyano, J. I. Perez-Martinez, M. J. Arias and J. M. Gines, Influence of the preparation method on the physicochemical properties of binary systems of econazole with cyclodextrin, *Int. J. Pharm.* **193** (1999) 85–95.
17. M. D. Veiga, P. J. Diaz and F. Ahsan, Interactions of griseofulvin with cyclodextrins in solid binary systems, *J. Pharm. Sci.* **87** (1998) 891–900.
18. M. Guyot, F. Fawaz, J. Bildet, F. Bonini and A. M. Lagueny, Physicochemical characterization and dissolution of norfloxacin/CD inclusion compounds and PEG solid dispersions, *Int. J. Pharm.* **123** (1995) 53–63.
19. C. M. Fernandes, M. T. Vieira and F. J. B. Veiga, Physicochemical characterization and in vitro dissolution behaviour of nicardipine-cyclodextrin inclusion compounds, *Eur. J. Pharm. Sci.* **15** (2002) 79–88.
20. P. Mura, G. P. Bettinetti, A. Manderiol, M. T. Faucci, G. Bramanti and M. Sorrenti, Interaction of ketoprofen and ibuprofen with β-cyclodextrin in solution and solid states, *Int. J. Pharm.* **166** (1998) 189–203.

21. C. A. Ventura, S. Trendi, G. Puglisi, E. Bousquet and L. Panza, Improvement of water solubility and dissolution rate of ursodeoxycholic acid and cheno deoxycholic acid by complexation with natural and modified beta-cyclodextrin, *Int. J. Pharm.* **149** (1997) 1–13.
22. P. Briard and J. C. Rossi, Ketoprofen, *Acta Crystallogr. Cryst. Struct. Commun.* **46** (1990) 1036–1038.
23. Y. Nakai, K. Yamamoto, K. Terada and H. J. Horibe, Interaction of tri-*O*-methyl-β-cyclodextrin with drugs, *J. Incl. Phenom. Mol. Recognit. Chem.* **2** (1984) 523–531.
24. M. Becirevic-Lacan, J. Filipovic-Grcic, N. Skalko and J. Jalsenjak, Dissolution characteristics of nifedipine complexes with β-cyclodextrins, *Drug Dev. Ind. Pharm.* **22** (1996) 1213–1236.
25. S. Ismail, Interaction of anticonvulsant drugs with alpha and beta-cyclodextrins. I. Methsumide, *STP Pharm. Sci.* **1** (1991) 321–325.
26. V. R. Sinha, R. Anitha, S. Ghosh and R. Kumria, Complexation of celecoxib with beta-cyclodextrin: characterization of the interaction in solution and in solid state, *J. Pharm. Sci.* **94** (2005) 676–687.

SAŽETAK

Fizičkokemijska karakterizacija inkluzijskih kompleksa celekoksiba s β-ciklodekstrinom i oslobađanje celekoksiba *in vitro*

VIVEK RANJAN SINHA, R. ANITHA, SOMA GHOSH, AMITA, RACHANA KUMRIA, JAYANT RAJARAM BHINGE i MANOJ KUMAR

U radu je ispitivan utjecaj β-ciklodekstrina (β-CD) na vodotopljivost i oslobađanje celekoksiba iz inkluzijskih kompleksa. Kompleksi su priređeni metodom gnječenja i karakterizirani pomoću SEM, NMR, IR, DSC i difrakcijom rentgenskim zračenjem. Oslobađanje iz kompleksa bilo je značajno bolje nego iz fizičke smjese što ukazuje da je stvaranje inkluzijskog kompleksa povećalo topljivost teško topljivog celekoksiba.

Ključne riječi: celekoksib, β-ciklodekstrin, inkluzijski kompleks, profil oslobađanja

University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India

Department of Chemistry, Panjab University, Chandigarh, India