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ORIGINAL ARTICLE

The effect of β-cyclodextrin on the solubility and dissolution rate of meloxicam and investigation of the driving force for complexation using molecular modeling

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Abstract The aim of this study was to investigate the effect of β-cyclodextrin (β-CD) on the solubility and dissolution rate of meloxicam. The methods that were employed to prepare meloxicam–β-cyclodextrin complexes were physical mixture, kneaded dispersion, and spray drying. Spray drying method was found to be the best to form a true inclusion complex. Complexes were characterized by thermal analysis, X-ray diffractometry (XRD), and Fourier transform infrared (FT-IR) spectroscopy. The apparent stability constant of the complex, K_c, calculated from the slope and intercept of the A_L solubility diagram was found to be 429.73, 259.96, 183.31, and 36.50 L mol^{-1} at pH 2, 3, 6.5, and 10.3, respectively. The dissolution rate of meloxicam from the complexes was higher than from meloxicam alone. Molecular modeling was also used to investigate the interaction between meloxicam and β-CD. The dominant driving force for the complexation was evidently Van der Waals force with very little electrostatic contribution.

Keywords Meloxicam · β-Cylodextrin · Inclusion complex · Dissolution · X-ray diffraction · DSC · FT-IR · Molecular modeling

Introduction

Cyclodextrins (CD) are cyclic (α-1, 4)-linked oligosaccharides of α-D-glucopyranose containing a hydrophobic central cavity and a hydrophilic outer surface. Cyclodextrins are toroidal or cone shaped with primary hydroxyl groups located on the narrow side of the torus, while secondary hydroxyl groups located on the wider edge. The most common cyclodextrins are α-CD, β-CD, and γ-CD, which consist of six, seven, eight glucopyranose units, respectively [1, 2].

The most common pharmaceutical application of cyclodextrins is to enhance drug solubility in aqueous solutions. The cyclodextrin complex of a poorly water-soluble drug is usually more hydrophilic than the free drug itself. It renders itself to wetting more easily and the drug dissolves faster and better [3–5].

Improvement of drug stability is another pharmaceutical application of cyclodextrins and it includes: heat stability, oxidation resistance, and hydrolysis resistance [2, 6–8]. Other pharmaceutical applications of cyclodextrins are improvement of bioavailability and reduction in the toxicity of some drugs; cyclodextrins are also useful in sustained release formulations [1, 9].

Meloxicam, ($C_{14}H_{13}N_3O_4S_2$, M.Wt 351.4), is 4-hydroxy-2-methyl-N-(5-methyl-1, 3-thiazol-2-yl)-2H-1, 2 benzothiazine-3-carboxamide 1,1 dioxide. Meloxicam is an enolic acid, non-steroidal anti-inflammatory drug. It is indicated for osteoarthritis and rheumatoid arthritis. Meloxicam is characterized by poor and pH dependent water-solubility [10]. The chemical structure of meloxicam is shown in Fig. 1.

Recently, several studies investigated the complexation of meloxicam with β-CD [11–15]. The majority of them studied the dissolution kinetics of meloxicam by several methods of complexation as well as characterization of the prepared complexes [11, 13–15]. Others investigated the influence of complexation with β-CD on the anti-inflammatory and ulcerogenic activity of meloxicam [12]. The objectives of this study were, firstly, to investigate the

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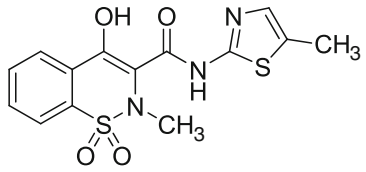

Fig. 1 Chemical structure of meloxicam

formation of inclusion complexes between β-CD and meloxicam by utilizing spray drying technique and comparing it to kneading and physical mixture in order to study the effect of β-CD on the solubility and dissolution rate of meloxicam. Secondly, to investigate the dominant driving force for the complexation process between meloxicam and β-CD using molecular modeling.

Experimental

Materials

Meloxicam, pharmaceutical grade, was kindly provided by The Jordanian Pharmaceutical Manufacturing (JPM) Co. (Jordan). β-CD was purchased from Sigma Chemical Co. (USA) and used without further treatment. All other chemicals and reagents were of analytical reagent grade and were used as supplied.

Instrumentation

Nicolet Avatar Fourier transform infrared spectrometer using Nicolet ez-omnic software for data analysis (360 FT-IR, Nicolet Instrument Corp., USA). Shimadzu DSC-50 differential scanning calorimeter (Shimadzu, Japan) equipped with a computerized data station. Centra 5 UV-visible spectrophotometer (GBC Scientific Equipment, Australia). Hanna pH-meter, HI 8519 N (Hanna Instruments, UK). Philips X-ray diffractometer, PW 1729 equipped with X-ray generator (Philips, The Netherlands). Buchi 190 mini spray dryer (Buchi, Germany).

Phase solubility

Solubility measurements were carried out according to the method of Higuchi and Connors [11]. Excess amounts of meloxicam, exceeding its solubility, were weighed and placed in vials to which 20 mL of phosphate buffer (0.05 mol L^{-1}, ionic strength 0.2 mol L^{-1}) was added containing various concentrations of β-CD (in the range of 0–18 mmol L^{-1}). The vials were placed in a shaking water bath at 37 °C for 20 h. Then samples were taken from the vials and filtered using membrane filters (0.45 μm, Millipore, USA). Samples were appropriately diluted and analyzed for the content of meloxicam by UV-spectroscopy at $\lambda = 362$ nm. The solubility studies were carried out at pH 2, 3, 6.5, and 10.3. The apparent stability constant of the complex, K_c, was calculated from the straight line of the phase solubility diagram according to the following equation:

$$K_c = \text{slope}/[S_o(1 - \text{slope})]$$

where S_o is the solubility of pure drug (meloxicam) without cyclodextrin and slope is the slope of the line obtained from the phase solubility diagram [16, 17].

Preparation of physical mixture

Meloxicam and β-CD were added together in the molar ratio 1:1. The two substances were thoroughly mixed using the geometric dilution technique.

Preparation and analysis of meloxicam-β-CD complexes

Kneading: A mixture of ethanol (96%) and water (volume ratio 1:1) was added to the physical mixture of meloxicam and β-CD until a paste was formed. The paste was kneaded thoroughly and placed in a vacuum oven at room temperature over night. The product was pulverized and stored in a dessicator over silica gel until used.

Spray drying: Solution of meloxicam and β-CD was prepared by dissolving equal molar amounts of the two compounds in 200 mL borate buffer of pH 10. Then the drug was precipitated by lowering the pH of the solution to 2.8 by adding 0.2 mol L^{-1} HCl. The objective of precipitation was to produce smaller particles of meloxicam and thus more soluble drug. Finally, the pH of the solution was raised to pH 7.4 by adding 0.2 mol L^{-1} NaOH. The solution was dried by mini spray dryer. Inlet and outlet temperatures were 134 and 84 °C, respectively.

Ten milligram of the product prepared by each method were dissolved in 100 mL of methanol. The amount of meloxicam included by each method was determined spectrometrically as stated above.

Characterization of meloxicam–β-CD complexes

Differential scanning calorimetry (DSC): The equipment was calibrated using indium. Meloxicam, β-CD, and meloxicam–β-CD complexes were heated at 10 °C min^{-1} in capped aluminum pans under nitrogen atmosphere. The instrument automatically calculated the melting points of the samples.

Fourier transform infrared spectroscopy (FT-IR): FT-IR spectra of meloxicam, β-CD, and inclusion complexes were performed using the KBr disc method.

X-ray diffraction: X-ray diffraction patterns were recorded for meloxicam, β-CD, kneaded product and spray dried product at 35 KV over a 2θ range of 2–80 at a scanning speed of 0.02 s/2θ ($\lambda = 1.54186$ Å).

Intrinsic dissolution

In vitro drug dissolution rate studies were carried out from constant surface area discs. Samples of meloxicam, physical mixtures and the prepared inclusion complexes were compressed using a hydraulic press (Specac, UK) under a compression force of 43 kN cm^{-2}. The compressed disc was placed in a plexiglass holder and mounted in a water jacketed dissolution vessel equipped with a synchronous motor operated at 100 rpm where one face of the disc was exposed to 500 mL of phosphate buffer of pH 6.7 and maintained at 37 °C. Every 10 min intervals, 5 mL aliquot samples were withdrawn from the dissolution medium and immediately replaced with the same volume of buffer. The samples were filtered using membrane filters, suitably diluted if necessary, and assayed spectrometrically for meloxicam. Dissolution runs for all samples were carried out in triplicate and the mean value was calculated.

Molecular modeling

Structures of the drug and β-CD were separately optimized in vacuum using the molecular mechanics (MM^{+}) force field (Hyperchem Version 6, Hypercube, Canada). Interaction energies against distance were computed for the drug approaching from either of its longitudinal side groups to access the β-CD cavity. The complex binding energy ($E_{binding}$) was plotted against the distance (x) for each longitudinal approach to indicate the energy minima where (x) is the distance for the approach of meloxicam along the symmetric x-axis of the β-CD cavity. The binding energies ($E_{binding}$) with their electrostatic and Van der Waals contributions were also computed. Interaction energies were computed for the drug approaching from triazole group to access the most probable optimal configurations for the complex formed. Moreover, approaches through the narrow and wide rims of β-CD were also investigated.

Results and discussion

Phase solubility

Figure 2 shows the phase solubility diagram for meloxicam with increasing the concentrations of β-CD at pH 2, 3, 6.5, and 10.3. These diagrams indicate that the solubility of meloxicam increased linearly with increasing the concentration of β-CD at all pH values of the experiment with slopes <1. Consequently, the diagrams can be classified as A_L type, and the stoichiometry of binding between meloxicam and β-CD is 1:1 at all pH values investigated [17, 18]. In general, in an A type profile, the apparent solubility of the substrate increases as a function of increasing CD concentration. A type profiles are classified into A_L, A_P, and A_N profiles. In particular, an A_L profile indicates a linear increase in the solubility of the substrate as a function of CD concentration while A_P profile shows a positive deviation and A_N profile shows a negative deviation from linearity [19]. Since the slopes of the straight lines of the diagrams at different pH values were <1, it was assumed that the observed increase in solubility was due to the formation of a complex with a 1:1 stoichiometry.

The apparent stability constants, K_c, of meloxicam complexes calculated from the slopes of the phase solubility diagrams were 429.73, 259.95, 183.31, and 36.50 L mol^{-1} at pH values 2, 3, 6.5, and 10.3, respectively. These results indicated that the unionized form of the drug interacts more strongly with β-CD compared to the ionized form. This is expected since K_c decreased when the pH was raised.

Characterization of meloxicam–β-CD complexes

DSC, FT-IR and X-ray data were recorded for meloxicam, β-CD, physical mixture, kneaded dispersion, and spray dried complex. Figure 3 shows an endothermic peak for meloxicam at 255.44 °C and a broad endothermic rise for β-CD between 69.96 and 138.57 °C and a peak at 118.45 °C. The thermogram of the physical mixture and the kneaded dispersion are approximately the superposition of the patterns of the raw materials. The characteristic endothermic peak of meloxicam at 255.44 °C was not observed for the spray dried complex. The disappearance of the endothermic peak can be attributed to the inclusion of meloxicam in the β-CD cavity which provided an evidence that the complex prepared by spray drying is a true inclusion complex. However, the peaks at 128.97 and 142.06 °C in the DSC thermogram of the spray dried product may be attributed to the presence of additives that were used during the preparation of the product.

Figure 4 shows the N–H stretching band of the FT-IR spectra of meloxicam, β-CD, physical mixture, kneaded dispersion, and spray dried complex. The spectra of the inclusion complexes were superimposed to the spectra of pure meloxicam and β-CD, with the exception of N–H stretching band at 3,291 cm^{-1}. N–H stretching disappeared in the spray dried complex and it was displaced by an intense broad peak. This observation might be due to the formation of hydrogen bonds between the N–H of meloxicam molecules and the hydroxyl groups of β-CD molecules.

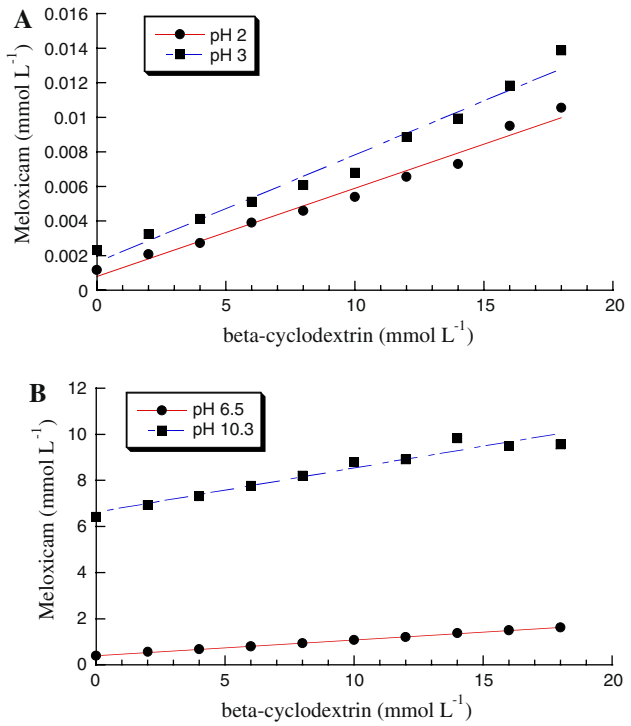

Fig. 2 Phase solubility diagram of meloxicam as a function of β-CD concentration at 37 °C at: **a** pH 2 and 3, **b** pH 6.5 and 10.3

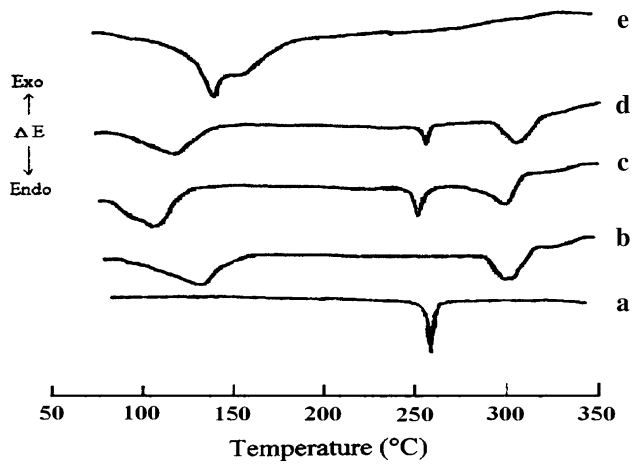

Fig. 3 DSC thermograms of: (a) meloxicam, (b) β-CD, (c) physical mixture, (d) kneaded dispersion, and (e) spray dried complex

The X-ray diffraction patterns are illustrated in Fig. 5. Physical mixture and kneaded dispersion were superimposed of each component with lower intensity. Kneaded dispersion showed peaks with lower intensity than those of the physical mixture. Peaks of pure meloxicam and β-CD disappeared in the spectrum of spray dried complex. Peaks observed in the diffraction pattern of the spray dried complex could be attributed to the additives such as boric

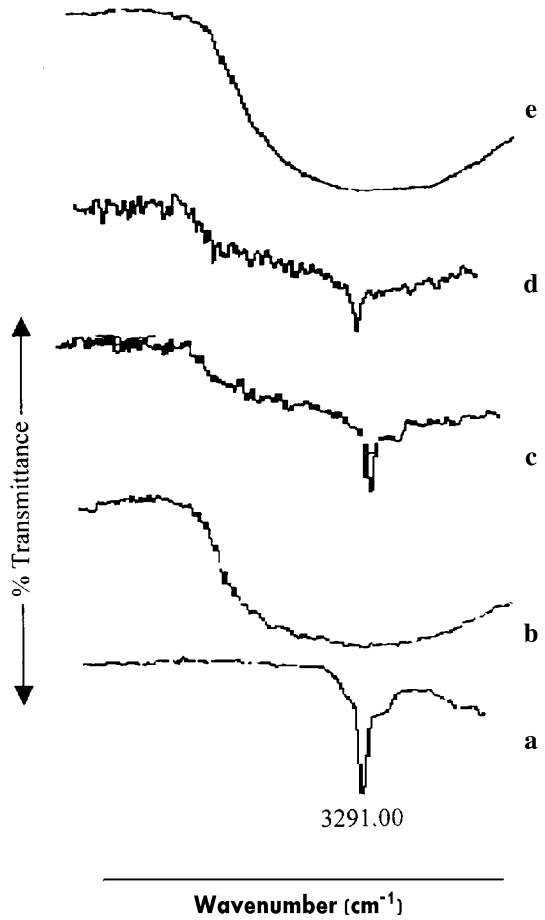

Fig. 4 NH stretching bands in FT-IR spectra of: (a) meloxicam, (b) β-CD, (c) physical mixture, (d) kneaded dispersion, and (e) spray dried complex

acid and potassium chloride that were used during the preparation of the product. X-ray diffraction pattern of the spray dried complex indicated that spray drying method was the most effective method for complex formation among the methods used in this study.

Intrinsic dissolution

Figure 6 shows the dissolution profiles of pure meloxicam and physical mixture from constant surface area. The dissolution rates of these two materials were represented by the slopes of the dissolution profiles. Slopes were found to be 0.0116, and 0.0193 μg mL^{-1} min^{-1} for pure meloxicam and physical mixture, respectively. In case of kneaded dispersion and spray dried complex, the intrinsic dissolution could not be performed. That was due to the high dissolution rate of these two products where their discs dissolved immediately when they were exposed to the dissolution medium.

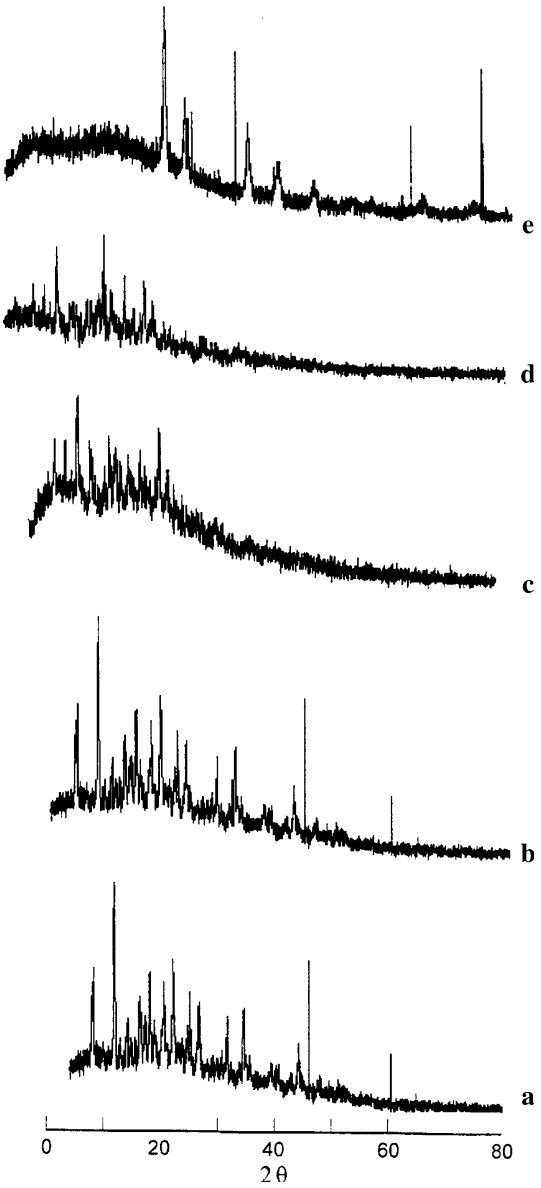

Fig. 5 X-ray diffraction patterns of: (a) meloxicam, (b) β-CD, (c) physical mixture, (d) kneaded dispersion, and (e) spray dried complex

Molecular modeling

Interaction energies were computed for the drug approaching from triazole group to access the most probable optimal configurations for the complex formed. Moreover, approaches through the narrow and wide rims of β-CD were also investigated.

The binding energy (E_{binding}) was plotted against x for each approach to highlight the most probable configurations as shown in Fig. 7. The corresponding binding energies with their electrostatic and Van der Waals contributions were also computed. The results are listed in

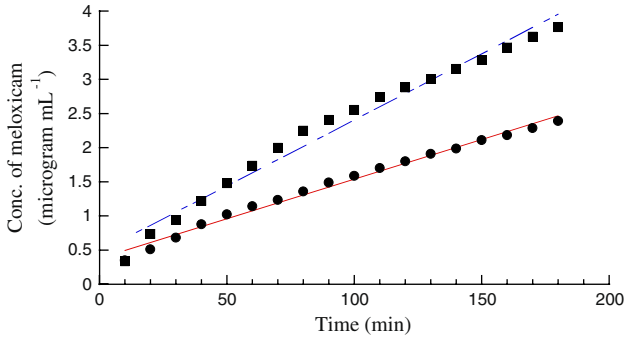

Fig. 6 Intrinsic dissolution profiles of pure meloxicam and physical mixture in phosphate buffer of pH 6.7: pure meloxicam (●), and physical mixture (■)

Table 1, which clearly show that the complex formed from meloxicam passing from the triazole side through the wide rim of the each approach to highlight the most probable configurations β-CD cavity produces the most stable 1:1 complex configuration. Figure 8 illustrates the side views of the most probable configurations for the complexes of meloxicam and β-CD at different distances. Figure 8a depicts the optimal 1:1 complex configuration thus obtained, which shows the inclusion of carboxamide and partial benzothiazine moieties. The benzene and triazole moieties are oriented outside the wide and narrow rims of β-CD. Although the formation of other complex configurations appears possible, they apparently form with a lower probability. The dominant driving force for complexation process between meloxicam and β-CD is evidently Van der Waals with very little electrostatic contribution as indicated in Table 1 (Fig. 8).

Conclusions

The aim of this study was to improve the solubility and dissolution rate of meloxicam by complexation with β-CD utilizing the spray drying technique. It can be concluded that complexation with β-CD is an effective method to achieve the aim of the study. The extent of complexation was found to be affected by pH value. The spray dried complex showed the strongest interaction and the physical mixture showed the weakest interaction.

The dissolution rate of meloxicam can be improved in the presence of β-CD. Kneaded dispersion and spray dried complex showed an immediate dissolution. Spray drying was found to be an effective method to prepare inclusion complex for meloxicam and β-CD.

In this study we have investigated the utility of the spray drying technique in the preparation of such a complex. In addition, we have also investigated the dominant driving

Table 1 Molecular modeling of interaction energies corresponding to optimal configurations of meloxicam/β-CD inclusion complexes (1:1)

Approach/moieties included	1:1 Complex			
	Distance (Å)	$E_{binding}$ (kcal mol^{-1})	E_{vdw} (kcal mol^{-1})	$E_{electrostatic}$ (kcal mol^{-1})
Triazole WR/carboxamide and partial benzothiazine	0	−32.25	−29.31	−2.94
Triazole WR/partial benzothiazine	7	−26.13	−22.67	−3.46
Triazole NR/triazole and carboxamide	1	−28.90	−24.71	−4.19
Triazole NR/total benzothiazine	11	−29.37	−25.63	−3.74

WR wide rim of β-CD, *NR* narrow rim of β-CD

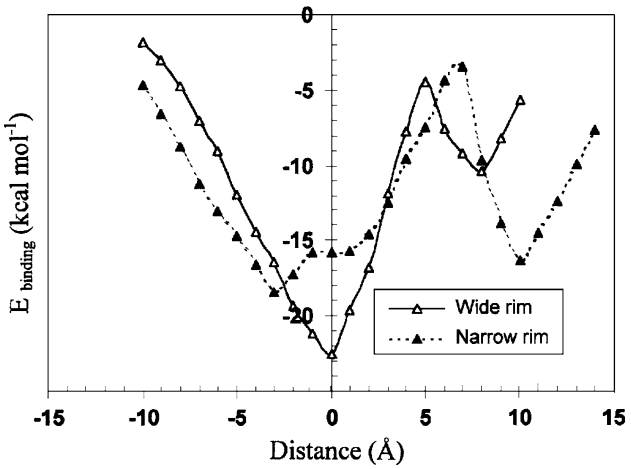

Fig. 7 A plot of the $E_{binding}$ against distance (Å) in vacuum for the triazole approaching through the wide and narrow rims of β-CD for the 1:1 complex of meloxicam and β-CD

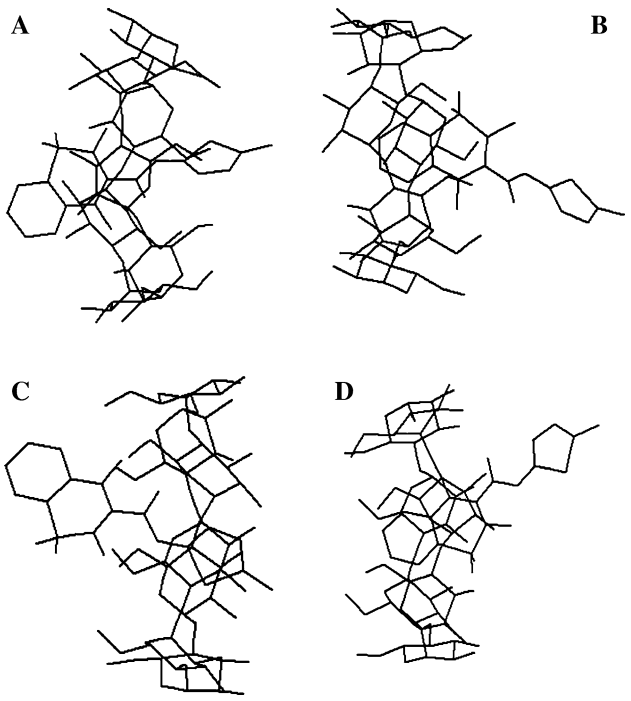

Fig. 8 Side views of the most probable meloxicam/β-CD configurations obtained for the 1:1 complexes at different distances: **a** 0 Å (WR), **b** 7 Å (WR), **c** 1 Å (NR) and **d** 11 Å (NR)

force for the complexation process between meloxicam and β-CD using molecular modeling.

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