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ORIGINAL ARTICLE

Inclusion complexation of weakly acidic NSAID with β-cyclodextrin: selection of arginine, an amino acid, as a novel ternary component

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Abstract The purpose of the present study was to investigate the influence of an amino acid, arginine, as a ternary component on the complexation of Lornoxicam, a poorly water-soluble and weakly acidic anti-inflammatory agent, with β-cyclodextrin (β-CD). The molecular inclusion of Lornoxicam with βCD alone and in combination with ternary component was aimed at improvement in solubility and, subsequently, dissolution rate limited oral absorption. The solid complexes of Lornoxicam and β-CD with or without arginine (binary and ternary systems, respectively) were prepared as Freeze dried product in different stoichiometric ratios. The formation of inclusion complexes in solid state was confirmed by using classical instrumental techniques like IR, DSC, XRD, and in liquid state by phase solubility analysis, UV spectroscopy, HPLC and ^{1}H NMR. The in vitro dissolution and the saturation solubility of complex are determined analyzing by UV spectrophotometer. Assay and level of related substance was monitored by developed RP-HPLC method. Inclusion ternary complex of Lornoxicam with β-CD and arginine showed significant improvement in dissolution compared with uncomplexed drug and binary system. This improved physicochemical behavior of ternary complex with the novel inclusion of an arginine translated into enhanced in vitro dissolution of Lornoxicam compared with standard rapid marketed formulation.

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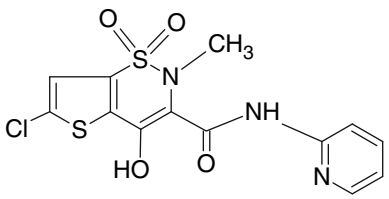
Introduction

Lornoxicam (6-chloro-4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno [2, 3-e]-1, 2-thiazine-3-carboxamide-1,1-dioxide) is a novel non-steroidal anti-inflammatory drug (NSAID) with marked analgesic properties [1, 2]. Its structural formula is shown below



Lornoxicam a novel highly selective COX-2 inhibitor is used for a variety of acute and chronic inflammatory diseases [3]. However, its very low aqueous solubility and poor dissolution in upper gastric fluid cause formulation problems and limits its therapeutic application by delaying rate of absorption and finally the onset of action [4]. Together with permeability, the solubility and/or dissolution rate of a drug are key determinants of its oral bioavailability. It is generally considered that compounds with very low aqueous solubility will show dissolution rate-limited absorption and hence poor absorption, Improvement of aqueous solubility in such a case is a valuable goal to improve therapeutic efficacy. Cyclodextrins (CDs) are commonly used in drug formulations as solubility enhancers because of their ability to form water-soluble inclusion complexes with poorly water-soluble drugs

[5–7]. Various anti-inflammatory drugs have been complexed with cyclodextrins, obtaining in this case further advantages of ternary component on complexation that may play a role in drug solubilization [8–10]. Therefore, it seemed of interest to extend our investigation to form binary and ternary systems of Lornoxicam with crystalline native β-cyclodextrin (βCD). Arginine was selected as ternary component to form a better inclusion complex.

At the alkaline pH Lornoxicam is Zwitterionic. The Zwitterionic structure of Lornoxicam in terms of molecular confirmation is planner, this flatness results intermolecular hydrogen bonding with βCD with better complexation [11]. The ternary complexes were prepared by Freeze drying method with a subsequent improvement in dissolution due to amorphization. In this study, an attempt was made to compare the similarity between in vitro dissolution profiles of Lornoxicam from complexes and standard formulation (Xefo® rapid). Dissolution profiles were compared by calculating similarity factor (f2) [12]. The influence of the ternary component on complexation and on the physico-chemical properties of the drug–CD complex was investigated in order to select the most effective system for improving Lornoxicam dissolution [11, 13].

Materials and methods

Materials

Lornoxicam gift sample provided by Sun Pharmaceutical, Vadodara, India, β-cyclodextrin (βCD, was procured from Wacker-Chemie GmbH, Germany. Arginine was purchased from SD Fine Chemicals, India. Ethanol and other solvents used were of HPLC grade; other chemicals used were of analytical grade.

Phase solubility studies and saturation solubility

The phase solubility experiment was performed by the method reported by Higuchi and Connors [14]. In brief, an excess amount of Lornoxicam in purified water and in simulated gastric fluid pH 1.2 containing various concentrations of βCD (0–10 mM) was shaken for 24 h at 37 °C on a shaker rotating at 200 rpm (Orbital Shaker Incubator). The equilibrated aliquots were filtered through 0.22-μm PVDF filter (Millipore, India) followed by dilution and analyzed spectrophotometrically at 376 nm (Jasco V-530 UV/Vis Spectrophotometer). The stability constant K_s for 1:1 Lornoxicam-βCD were calculated, using the equation:

$$K_s(1:1) = \text{Slope}/S_o(1 - \text{slope})$$

where S_o is the solubility of the Lornoxicam in the absence of βCD [14]. Saturation Solubility of Lornoxicam and solid complex is carried out in water, pH 1.2 and pH 6.8 buffers.

Chromatographic system and separation

Chromatographic system consists of Jasco HPLC system comprising PU-2080 plus 515 pump, injector, and MD-2015 plus PDA were used for analysis. A reversed-phase Lichrospher C18 column (Column Engineering, USA), 250 mm × 4.6 mm, particle size 5 μ were used for separation. Chromatographic separation involves isocratic elution with mobile phase (Sodium acetate (0.025 M): Methanol (1:1, v/v) and 0.05% triethylamine). The flow rate was 1 mL/min. Samples of 20 μL were injected into the column and the detector was set at 284 nm [15].

Preparation of solid complexes

The solid complexes of Lornoxicam and βCD with or without arginine were prepared by the following techniques. The stoichiometric ratio of binary system was kept as 1:1 and 1:2, whereas that of ternary systems was kept as 1:2:1.

Physical mixture

The physical mixtures were prepared by gently mixing Lornoxicam, βCD, and arginine. These mixtures were passed through an (85#) sieve prior to use. A similar experiment was performed without arginine.

Freeze drying

Solid-state Lornoxicam ternary complexes with βCD and arginine in 1:2:1 M ratio was prepared. Lornoxicam, βCD was accurately weighed and dissolved in distilled water (10 mL). To this aqueous solution further, weight quantity of arginine was added to dissolve the Lornoxicam. The whole solution was stirred on magnetic stirrer for 1 h. The resulting solution was the freeze dried. The dried powder was passed through sieve (85#) and stored in a dessicator until further evaluation.

Drug content and impurity analysis

The samples of complexes were assayed for Lornoxicam content by dissolving a specific amount of the complexes in methanol and 1.5% sodium acetate solution (1:1) and analyzing for the Lornoxicam content and Impurity analysis by HPLC.

Characterization of the complex

UV spectroscopy and high performance liquid chromatography

In solution state complex formation is characterized by UV spectrophotometer [16] and High Performance Liquid Chromatography [17]. For UV characterization drug concentration is keep constant (2×10^{-6} M) and scan between 200 and 400 nm same concentration of solution is prepared by increasing βCD concentration 5, 10, 15 mM and scan between 200 and 400 nm. For HPLC characterization mobile phase is prepared as describe earlier and to the mobile phase increasing concentration of βCD solution is added 0.2, 0.5, 1, 1.5 mM, and retention behavior of Lornoxicam is observed.

Differential scanning calorimetry

Thermal characteristics of native Lornoxicam and its complexes were analyzed under dry nitrogen purge (20 mL/min) at a heating rate of 10 °C/min using a Differential Scanning Calorimeter (Perkin Elmer, Pyris-6 DSC, USA).

Powder X-ray diffractometry

Powder X-ray diffraction patterns of native Lornoxicam and its solid complexes were recorded using Phillips P Analytical X'Pert PRO powder X-ray diffractometer using Ni-filtered, Cu K_α radiation, a voltage of 40 kV and a current of 30 mA. The scanning rate employed was 1°/min and samples were analyzed between 2θ angles of over 10–40°.

Fourier transforms infrared (FTIR) spectroscopic analysis

FTIR spectra of native Lornoxicam and its solid complexes were recorded on a FTIR-5300 Spectrophotometer (Jasco, Japan) by KBr disk method using Hydrostatic press to from a compact disc of samples. The scanning range was 4,000–400 cm^{-1}.

^{1}H-NMR spectroscopy

The ^{1}H-NMR spectra of Lornoxicam, βCD and the solid complex prepared by freeze drying method were recorded using Ultrashield 700 Plus Bruker (500 MHz) Fourier Transform Nuclear Magnetic Resonance (FTNMR) instrument at 298 K. The spectra of all the above mentioned drug, carriers and selective dispersions was recorded in Deuterated Water (D_2O) solvent systems.

In vitro dissolution studies

The in vitro dissolution studies of physical mixtures and solid complexes and Xefo® rapid tablet were carried out by using USP type II apparatus (Electrolab, India). Sample equivalent to 8 mg of Lornoxicam was taken in 900 mL of stimulated gastric fluid without enzyme pH 1.2 maintained at 37 ± 0.2 °C and stirred at 100 rpm. Samples were withdrawn at 5, 10, 15, 30 and 60-min interval, filtered through Whatman filter paper, and analyzed for Lornoxicam spectrophotometrically at 378 nm [18].

Results and discussion

Phase solubility studies and saturation solubility

Phase solubility analysis has been among the preliminary requirements towards the optimization of the development into inclusion complexes of the drugs as it permits the evaluation of the affinity between βCD and drug molecule in water [14]. The phase solubility curve of Lornoxicam in the

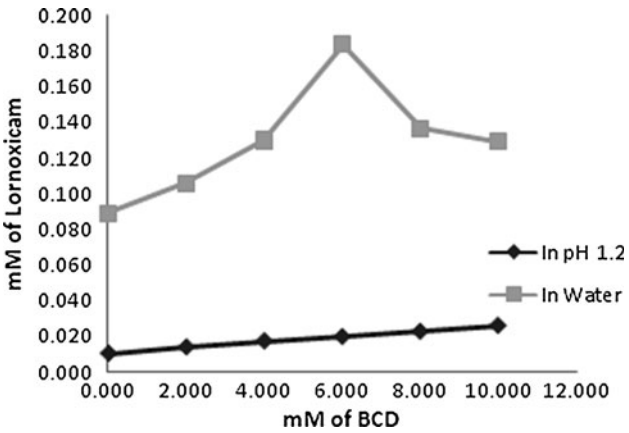


Fig. 1 Phase solubility diagram of Lornoxicam–cyclodextrin system. Each point is the mean (±SD) of three determinations

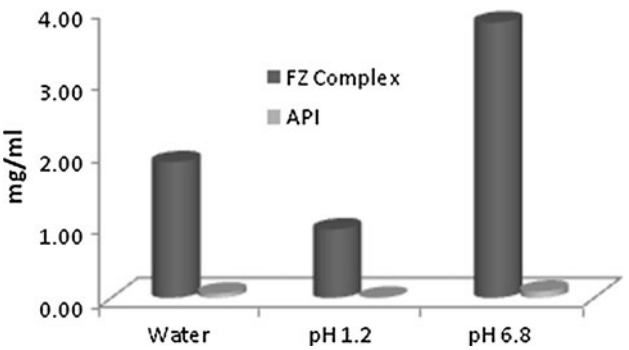


Fig. 2 Saturation solubility of Lornoxicam Lornoxicam–cyclodextrin ternary complex

Table 1 Analysis of Lornoxicam and impurities in Lornoxicam solid complex

Sample	Assay (%)	Imp A	Imp B	Imp C	Imp D	Individual unknown (%)	Total impurities (%)
Solid complex	97.69	0.0079	ND	ND	0.0048	0.0711	0.085

ND not detected

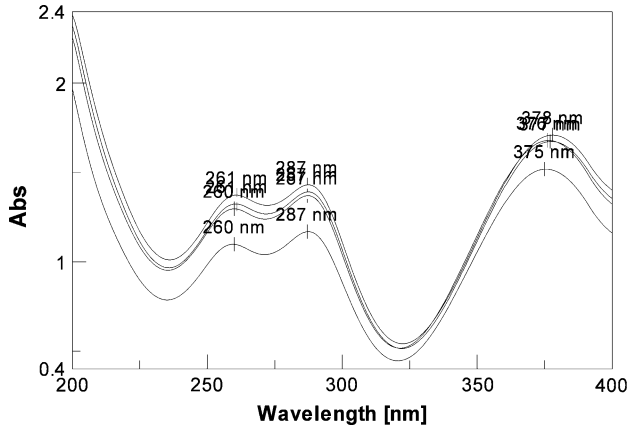


Fig. 3 Absorption spectra of Lornoxicam with increasing concentration of βCD

presence of βCD is shown in Fig. 1. The curve in simulated gastric fluid pH 1.2 indicated a linear increase in solubility of Lornoxicam with an increase in concentrations of βCD. However the curve in water shows negative deviation indicating the limited solubility of complex due to precipitation. Increasing amounts of βCD increased the amount of Lornoxicam going into simulated gastric fluid pH 1.2 improving the aqueous solubility of Lornoxicam upper gastric fluid. The stability constants (K_s) for the complexes at 37 °C, assuming a 1:1 stoichiometry, calculated from the slope of phase solubility diagram were 100 M^{-1} for βCD-Lornoxicam in simulated gastric fluid pH 1.2 and assuming a 1:2 stoichiometry in water was 229 M^{-1} which indicated a suitable and stable complex formation. Saturation solubility of solid complex as compared to Lornoxicam in water, pH 1.2 and pH 6.8 buffers shows many folds increment of solubility as shown in Fig. 2.

Drug content and impurity analysis

The drug and impurity content of the solid complex (Table 1) were found out to be within range, which indicate content uniformity of Lornoxicam in its complex form.

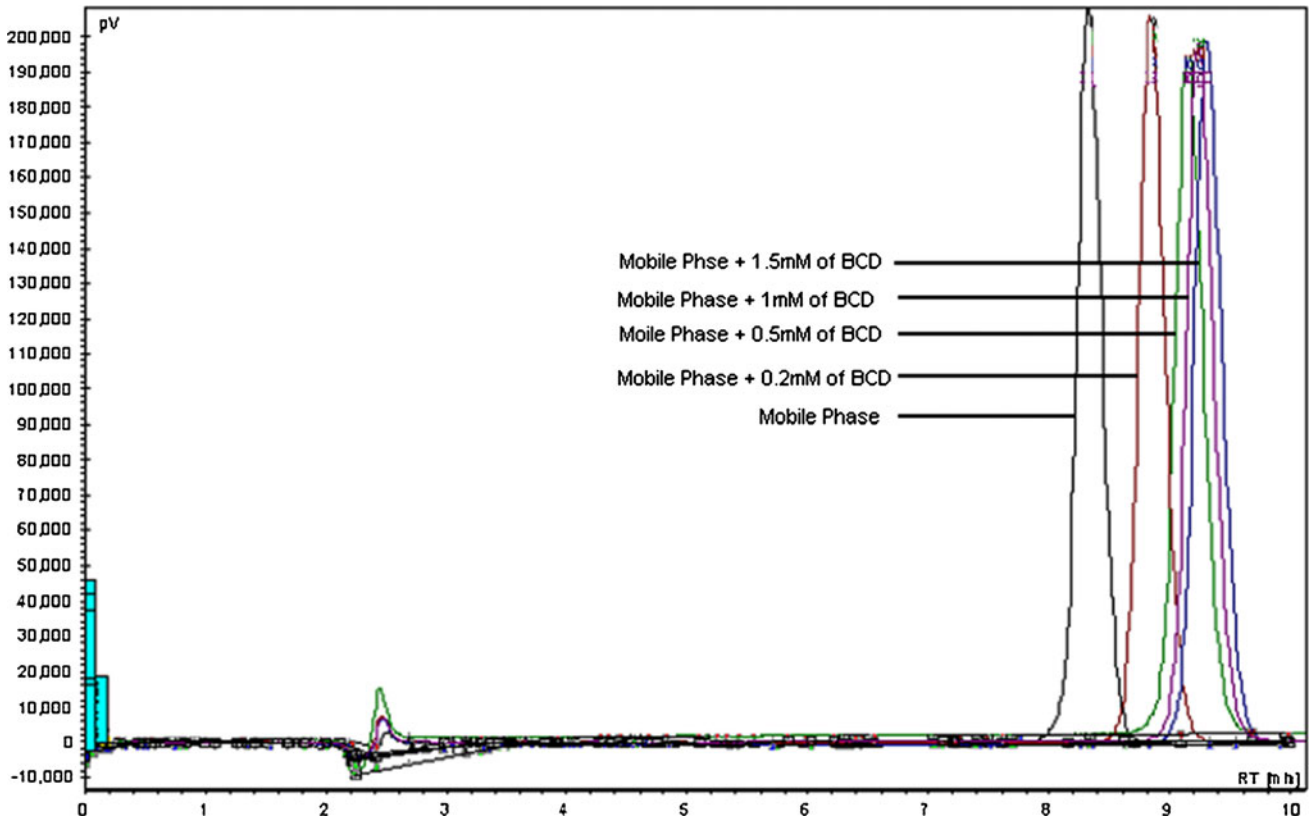


Fig. 4 HPLC chromatogram of Lornoxicam with increasing concentration of βCD in mobile phase

Characterization of solid complexes

UV spectroscopy and high performance liquid chromatography

In UV characterization as the concentration of βCD s increased the λ_{max} of Lornoxicam at 375 nm is shifted by 1 nm suggest the possible interaction of aromatic portion of Lornoxicam in solution state with βCD as shown in Fig. 3. However in case of drug High Performance Liquid Chromatography as the βCD Concentration in mobile phase is increased the retention time of Lornoxicam is get increased as as shown in Fig. 4 because Lornoxicam form complex with βCD as it comes contact with βCD which alter its partition between mobile phase and stationary phase [16, 17].

Differential scanning calorimetry

Thermal behavior of Lornoxicam and its solid complexes along with its individual components are shown in Fig. 5. As depicted in Fig. 5, Lornoxicam showed a sharp exotherm at 235 °C. whereas βCD showed a broad endotherm from 65 to 100 °C, which could be attributed to the loss of moisture. Being highly crystalline, arginine showed a sharp melting peak at 221 °C. Thermograms of the solid complex prepared by physical mixture showed a exothermic peak at 219 °C which could be correspondingly attributed to the melting of arginine and Lornoxicam. Lower shift in exothermic peak of Lornoxicam is attributed to the presence of ternary mixture, as the melting point of a material is known to shift to the lower scale in the presence of other substances [19]. On the contrary, the thermograms of solid complexes prepared by Freeze Dry Method are different from that of physical mixture and pure components. The melting of both Lornoxicam and arginine were found missing, which gives a clear premise that there is formation of solid ternary complexes.

Powder X-ray diffractometry

The PXRD patterns of native Lornoxicam and solid complexes prepared by Freeze Dry Method (Freeze Dry product) along with its individual components are presented in

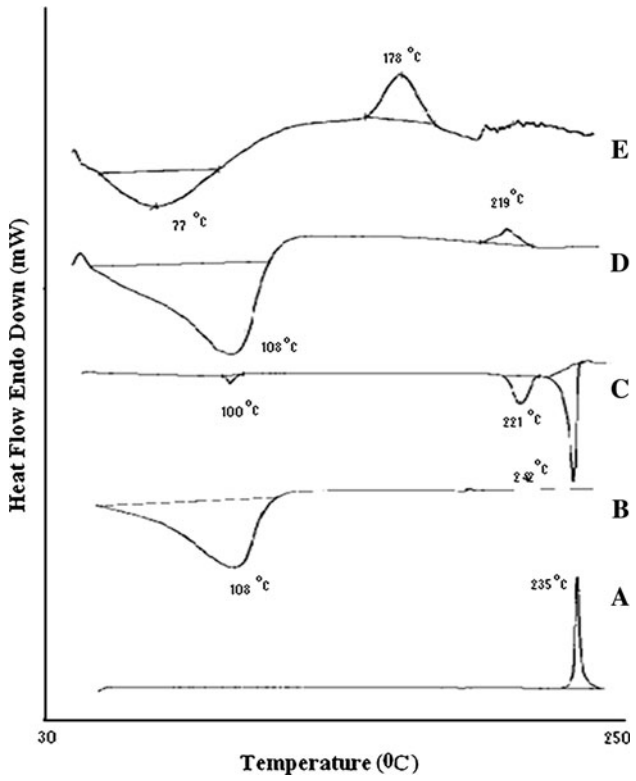


Fig. 5 DSC curves of Lornoxicam (*a*), β-cyclodextrin (*b*), arginine (*c*), equimolar ternary physical mixture (*d*), solid freeze dried complex (*e*)

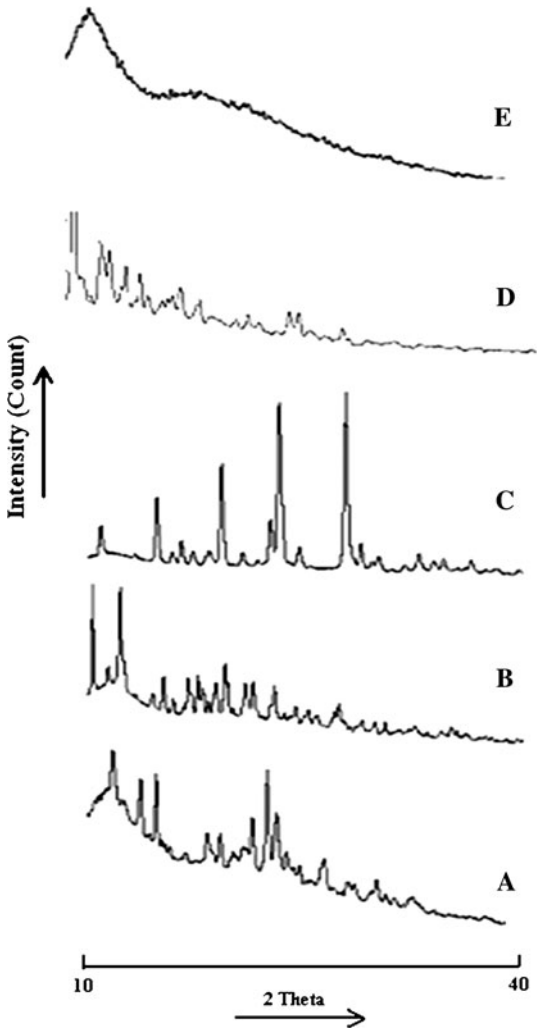


Fig. 6 XRD spectra of plain Lornoxicam (*a*) β-cyclodextrin (*b*), arginine (*c*), equimolar ternary physical mixture (*d*), solid freeze dried complex (*e*)

Fig. 6. The diffractograms of Lornoxicam and arginine exhibited a series of intense peaks, which are indicative of their crystalline character. The PXRD of βCD showed broad intense peaks, indicating presence of crystalline state. An X-ray diffraction pattern of physical mixture was constituted by some of the characteristic peaks of Lornoxicam, indicating an absence of stoichiometric complexation. Freeze dried solid complexes, on the other hand, indicated a significant reduction in peak intensity (amorphonization), thus confirming the ternary complex corroborating the DSC observations.

Fourier transforms infrared (FT-IR) spectroscopic analysis

Fourier transform infrared spectroscopy (FT-IR) has been used to assess the interaction between CD and guest molecules in the solid state. The chemical interaction between the drug and the carrier often leads to identifiable changes in the infrared (IR) profile of complexes [20]. In case of any interactions, the principal peaks pertaining to the various functional groups present in the guest molecule may be affected. IR spectral studies may also be indicative of hydrogen bonding phenomenon that may be occurring between guest and host. The principal peaks corresponded to the structural features of Lornoxicam are found due to O–H stretching at 3,400 cm^{-1}, N–H stretching at 3,090, aromatic C–H stretching at 2,927 cm^{-1} and –CCl stretching at 766 cm^{-1}. The FT-IR spectrums of the β-CD are characterized by intense bands at 3,300–3,500 cm^{-1} due to O–H stretching vibrations. The vibration of the –CH and CH_2 groups appears in the 2,800–3,000 cm^{-1} region. In case of arginine shows NH stretching at 3,179 cm^{-1} and –CO stretching at 1,022 cm^{-1}. Any sign of interaction would be reflected by changes in the characteristic peaks of Lornoxicam, depending on the extent of interaction. In IR study solid complex and physical mixture showed combination of the peaks of PE and carrier. The overlays of IR spectra are presented in Fig. 7. The principal peaks corresponding to the Lornoxicam were affected. Lornoxicam crystals show a characteristic absorption band at 3400, 3090 cm^{-1}, assigned to O–H and N–H stretching. The FT-IR spectra of ternary solid complex were compared to the physical mixtures and Lornoxicam. In all the case of the characteristic-stretching band of lornoxicam disappeared along with reduced intensity of the other band. Changes in the characteristic bands of Lornoxicam confirm the existence of the complex as a new compound with different spectroscopic bands. All other signals appear to be affected from the observation of IR overlay. Thus from the IR studies it can be concluded that aromatic functional group of Lornoxicam interact with O–H group of Cyclodextrin through hydrogen bonding.

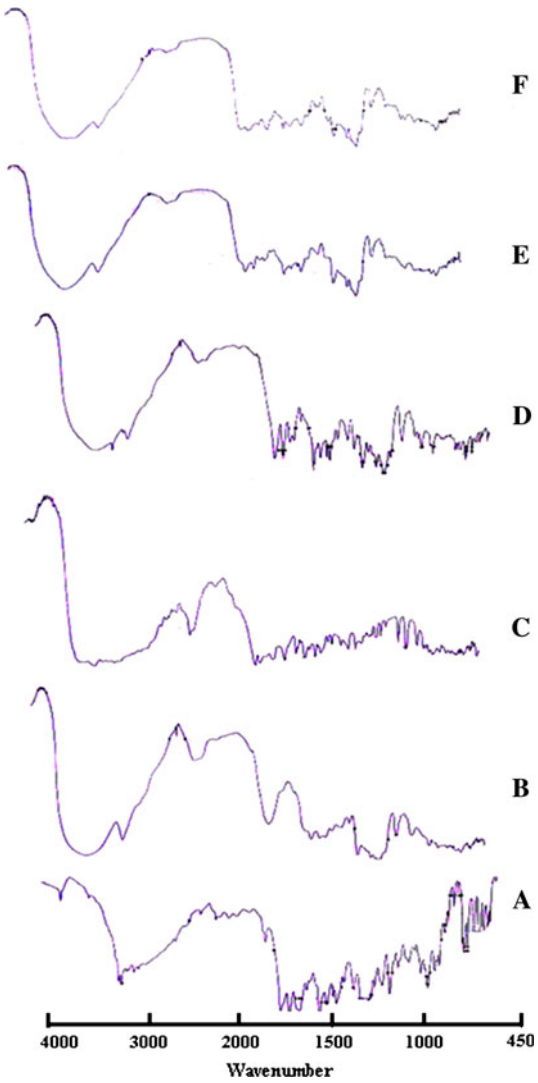


Fig. 7 Infra red spectra of plain Lornoxicam (*a*) β-cyclodextrin (*b*), arginine (*c*), equimolar binary physical mixture (*d*), equimolar ternary physical mixture (*e*), solid freeze dried complex (*f*)

Nuclear magnetic resonance (NMR) spectroscopic

The chemical shift changes in the ^{1}H-NMR spectra have been used to monitor the complex formation process, since if a guest is incorporated into the cyclodextrin cavity, the hydrogen atoms located in the interior of the Cyclodextrin cavity (H-3 and H-5) will be considerably shielded by the guest molecule causing a significant up field shift whereas the protons on the exterior surface of the torus (H-1, H-2, H-4 and H-6) will either be unaffected or experience a marginal shift. Alternately if association takes place at the exterior of the torus (surface interaction) H-1, H-2, H-4 and H-6 shall be strongly shielded. The different protons of Lornoxicam have been labeled as shown in Fig. 8 [21]. The ^{1}H NMR spectrum of βCD in D2O consists of six protons

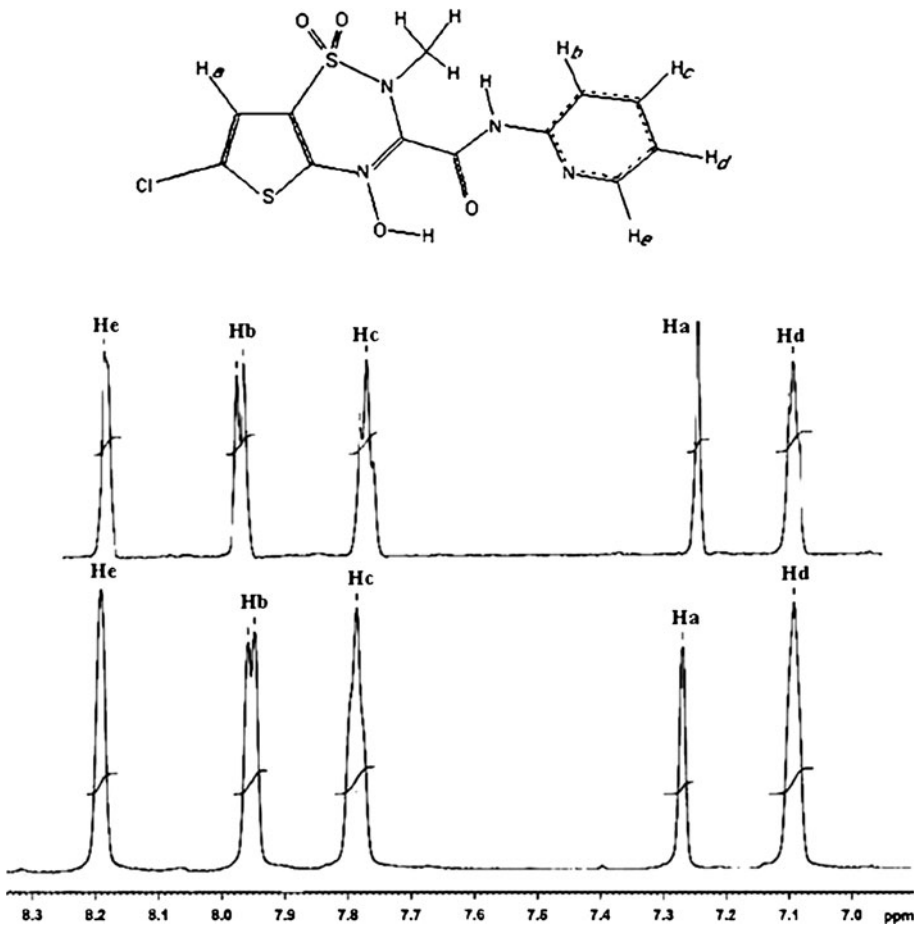


Fig. 8 ^{1}H NMR spectra of free Lornoxicam and ternary solid complex

the H-3 triplet at δ 3.913, a strong unresolved broad peak consisting of H-5 and H-6 at δ 3.822 and δ 3.808, H-4 triplet appears at δ 3.540. It is well known that the H-3 and H-5 protons are located in the interior of the βCD cavity and it is therefore, likely that the inclusion of Lornoxicam with βCD will specifically affect the chemical shifts of these two protons. The complexation of Lornoxicam with βCD causes upfield shifts of βCD spectrum, however the up field shifts is not the same for all protons. The ^{1}H NMR spectrum of βCD complex shows H-3 signal of pure βCD is shifted and most likely merged with that of the unresolved peak of H-5 and H-6 protons [22, 23]. H-3 signal shows strong upfield shifts of about δ −0.003 ppm. Since H-3 is located in the interior of the cavity, we suggest that H-5 signal shows upfield shifts because both are located inside the cavity. The upfield shifts observed for H-3 and H-5 protons confirms the inclusion inside the cavity. Further confirmation is obtained by following the changes in the chemical shifts of aromatic proton of Lornoxicam [20]. The ^{1}H NMR spectrum for aromatic proton of Lornoxicam is shown in Fig. 8 and we focused only on aromatic protons of Lornoxicam i.e. H_a, H_b, H_c, H_d and H_e. The formation of complex of Lornoxicam with βCD shows the downfield shifts of H_b, H_c, H_d and H_e corresponding to pyridine ring of Lornoxicam as in Table 2. The observed upfield shifts H-3 and H-5 protons of βCD in Table 3, coupled with downfield shifts for aromatic protons observed for Lornoxicam lead to conclusion of interaction of pyridine moiety of Lornoxicam with βCD.

Dissolution studies

Dissolution profiles of Physical mixture, solid complex and Xefo® rapid tablet are shown in Fig. 9. Dissolution studies

Table 2 Chemical shifts (ppm) for the protons of Lornoxicam in the free state and in the inclusion complex

^{1}H of Lornoxicam	δ Free	δ Complex	δ Complex − δ free
H_d	7.093	7.106	+0.013
		7.103	
H_a	7.270	7.259	−0.011
H_c	7.787	7.803	+0.016
		7.793	
H_b	7.949	7.989	+0.040
	7.959	8.001	+0.042
H_e	8.192	8.213	+0.021

Table 3 Chemical shifts (ppm) for the protons of βCD in the free state and in the inclusion complex

^{1}H of of βCD	δ Free	δ Complex	δ Complex − δ free
H-3	3.913	3.910	−0.003
H-4	3.534	3.540	+0.006
H-5	3.822	3.835	+0.013
H-6	3.808	3.816	+0.008

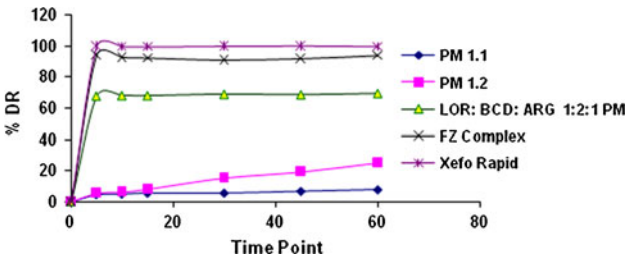


Fig. 9 Dissolution profiles Lornoxicam and complexes in stimulated gastric fluid pH 1.2

of binary physical mixture in simulated gastric fluid did not showed any significant improvement in dissolution. Lornoxicam-βCD ternary physical mixture showed significant improvement in dissolution, >60% in 10 min but slight reprecipitation of Lornoxicam was observed. However the dissolution profile of solid complex is comparatively similar to Xefo® rapid tablet which may be because of more inclusion and amorphization. As shown in the Fig. 9, the dissolution profiles of solid complexes of Lornoxicam with βCD in the presence of arginine showed improved dissolution rate. Ternary complex (Lornoxicam-βCD-Arginine) showed >95% dissolution after 20 min, and no precipitation could be observed which is comparatively similar with standard formulation with F2 value more than 50.

Conclusion

This study demonstrated the possibility of significantly improving the dissolution rate-limited bioavailability of weakly acidic molecules by using base as a suitable ternary component. The importance of proper selection and optimization of most suitable component to adequately improve solubility, complexation efficiency, and stability under various physiological pH conditions, has been addressed by using arginine-Lornoxicam-βCD ternary complex. Arginine as a ternary component seems to be contributing by a combination of multiple factors and probably offers ideal interaction with Lornoxicam, including specific hydrogen bonding and/or spatial alignment with the host.

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