

ENHANCEMENT OF LORNOXICAM SOLUBILITY BY INCLUSION COMPLEXATION WITH CYCLODEXTRIN: PREPARATION AND CHARACTERIZATION

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ABSTRACT

Objective: Lornoxicam is a potent anti-inflammatory drug which has analgesic and antipyretic properties. It is water-insoluble powder. The inclusion complexes of lornoxicam (LOR) with β -cyclodextrin (β CD) and 2-hydroxypropyl- β -cyclodextrin (HPCD) were prepared and characterised in order to improve the solubility of the drug and enhance its bioavailability.

Methods: Complexes were prepared by physical mixing and freeze-drying in three different drug/polymer ratios (1:1, 1:2 and 3:2). The solid complexes were characterised through differential scanning calorimetry (DSC), scanning electron microscopy (SEM), X-ray diffraction, nuclear magnetic resonance (NMR) spectroscopy, and Fourier transformed infrared (FTIR) spectroscopy.

Results: The data showed that LOR may be complexed with cyclodextrin (CD) forming soluble complexes. The lyophilized 1:2 LOR/HPCD complex is the most soluble.

Conclusion: Solubility increases with lyophilization than with physical mixing and by the use of HPCD than β CD in complexation.

Keywords: Lornoxicam, Cyclodextrin, Lyophilization, Physical mixing, Inclusion complex

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INTRODUCTION

Lornoxicam (chlo-rtenoxicam) is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam class with analgesic, anti-inflammatory and antipyretic properties. It is available in oral and parenteral formulations. LOR is used for the treatment of various types of pain, especially those resulting from inflammatory diseases of the joints, osteoarthritis, and rheumatoid arthritis [1]. The physicochemical characteristics of these molecules vary greatly depending upon the environment [2]. LOR is a yellow insoluble powder. Supra-molecules are ordered molecular aggregates associated with two or more molecules, ions or coordination compounds through intermolecular interaction, which has particular functions. Examples of host molecules in supra-molecular chemistry include crown ethers, cryptates, calixarenes, and cyclodextrins. CDs are cyclic oligosaccharides with several d-glucopyranoses linked by α -1, 4-glycosidic bonds [3]. α -, β - and γ -CD are the most common CDs, which have six, seven and eight glucose units, respectively [4]. Due to lack of free rotation of the bonds connecting the glucopyranose units, the CDs have a toroid or cone shape, where the primary hydroxyl groups are located on the narrow side of the torus while the secondary hydroxyl groups are located on the wider edge. This arrangement provides the formation of an internal hydrophobic cavity and a hydrophilic external surface. The lipophilic cavity provides a microenvironment into which appropriately sized non-polar moieties can enter to form inclusion complex [5]. CDs are capable of forming inclusion complexes with many drugs by taking up a whole drug molecule, or a part of it, into the cavity of the CD molecule. Drug CDs complexes can improve the clinical usage of drugs by increasing their aqueous solubility, dissolution rate, and pharmaceutical availability [6, 7]. CDs can also act as penetration enhancers by increasing drug availability at the surface of the biological barrier [8, 9]. CDs are able to improve the solubility of a lot of drugs, such as phenytoin [10], acyclovir [11], glyburide [12], celecoxib [13], bromazepam [14] and resveratrol [15]. In our study, we evaluated the complexation of LOR with β CD and HPCD prepared by two different methods in different molar ratios and were then *in vitro* characterised to investigate more soluble LOR complexes with higher bioavailability.

MATERIALS AND METHODS

Chemicals

LOR as a gift from EPCI (pharmaceutical company), β CD and HPCD were purchased from SIGMA-ALDRICH. All chemicals are of analytical grade.

Methods

Preparation of LOR inclusion complexes

LOR complexes with β CD and HPCD in three different molar ratios were prepared using two different techniques (table 1);

- Physical mixing: physical mixtures were prepared by homogeneous blending of previously weighed LOR and CD in a mortar for 30 min.
- Freeze-drying: freeze-dried products were prepared by dissolving the different molar ratios (mentioned above) in suitable volumes of 50% methanol in water. The solutions were shaken for 24 h at 25 °C, frozen at -20 °C and lyophilized in a freeze dryer (Edwards EF4 Modulyo freeze dryer, UK) for 48 h.

Characterization of the prepared inclusion complexes

Solubility study

A solubility study [7] was carried out by adding excess amounts of prepared mixtures to a suitable volume of aqueous media and stirred for 24 h at 25 °C. The dispersion was then filtered through 0.45 μ disc filter and the solutions were assayed spectrophotometrically using UV spectrophotometer (Spectro 22 Digital labo Med, USA) at 381 nm for determination of the amount of LOR dissolved. Each molar ratio was done in triplicate.

Differential scanning calorimetry (DSC)

DSC thermograms were obtained with a Shimadzu DSC-60 calorimeter (Shimadzu Co., Kyoto, Japan) under a dynamic nitrogen atmosphere at a heating rate of 10 °C. Min⁻¹. Samples were accurately weighted and submitted to heat scanning from 25 °C to

350 °C in a sealed aluminum pan. An empty sealed aluminum pan was used as a reference.

Scanning electron microscopy (SEM)

The morphology of the inclusion complexes was investigated using SEM (Jeol JSM 6510 microscope, Japan) at a voltage of 20 kV. The samples were previously mounted on aluminum stubs using double-sided adhesive tape and vacuum-coated with a thin layer of gold.

X-ray diffraction

X-ray diffraction patterns were obtained on Empyrean diffract meter (PANalytical B. V, Netherlands) with Cu K α radiation, the voltage of 40 kV and current of 30 mA with a scan time of 0.5 seconds.

Nuclear magnetic resonance spectroscopy

NMR spectra were recorded to investigate the chemical structure of the complexes using (Bruker DRX400-AVANCE) spectrometer operating at 400 MHz, equipped with a 5 mm inverse probe with the z-gradient coil. DMSO-d₆ (isotopic purity at least 99.5%) was used as a solvent and tetramethylsilane (TMS) as an internal standard. One-dimensional ¹H NMR spectra were acquired under standard conditions. All experiments were recorded at 300 K.

Fourier transform infrared (FT-IR)

FT-IR spectra were recorded on a Perkin-Elmer Model 1600 apparatus using KBr discs, samples corresponding to 2.0 mg of LOR/CD mixtures were compressed and tested in the range of 4000–400 cm⁻¹.

Statistical analysis

All measurements in the study were carried out in triplicate and the reported data were expressed as the mean values \pm standard deviation. One-way analysis of variance followed by the Turkey–Kramer multiple comparisons test using GraphPad prism software v.5 was used to determine the statistical significance of the differences in solubility and crystallinity. All P-values were two-tailed, and differences were considered significant when the P-value was less than 0.05 [16]. Statistical analysis of the data obtained was performed with computer software [17].

RESULTS AND DISCUSSION

In cyclodextrin chemistry, inclusion complexation is accomplished by the intermolecular interaction between CD and guest molecule,

which leads to the penetration of guest molecule partially or completely into the cavity of the CD. Contrarily, if some guest molecules only reside in the packing interstice of CD, an encapsulation interaction occurs [18]. Complexation between CD and organic compounds with low polarity was studied for decades [19, 20]. Past research indicated that the process of inclusion complexation between CD and guest is driven by electrostatic forces, van der Waals forces, hydrophobic interactions, hydrogen bonding and release of conformational strain [21, 22]. The driving forces always coexist or have a synergistic effect. The relative strength of each force is usually related to certain factors like the size of the CD cavity and the nature of modified groups of CD. The shape, volume, polarity, number and character of substituting groups of guest, as well as reaction medium, temperature and ionic strength, will affect the form and relative strength of these forces [23, 24].

Solubility studies

The results of solubility studies were given in table 1. The solubility of LOR/CD complexes was significantly ($P < 0.05$) higher than that reported for pure LOR which was 1.2 mg/100 ml [25]. The solubility of the formulated complexes was entirely affected by the Drug: CD ratio. It was found that the 1:2 ratio achieved the highest amount dissolved regardless to the type of CD used which may be attributed to the high complexation efficiency in 1:2 complex. There was a significant difference in solubility between 1:2 and 3:2 complexes. However, no significant difference in solubility between 1:1 and 1:2 complexes was observed. The solubility of HPCD complexes was more than that of β CD complexes. This is because the solubilizing effect of CD derivatives is in the following order: HPCD > β CD [26]. HPCD has higher water solubility and safety compared to other CDs [27]. Regarding the effect of the preparation method, statistical analysis of data revealed that there was no significant impact from using either the freeze-drying or physical mixing on the solubility of the prepared complexes ($p < 0.05$).

Lipophilic compounds like LOR bound non-covalently to the hydrophobic cavity of the CD molecule to form inclusion complexes which in turn altered the aqueous solubility of the drug [28]. Inclusion systems occur when some of the guests have been incorporated in the sandwich structure formed by intermolecular hydrogen bonds between two CD molecules [29] or stay completely out of the cavity [30]. Further evidence of the complex formation was obtained by differential scanning calorimetry, X-ray diffractometry and by FTIR spectroscopy.

Table 1: Formulation codes and solubility of the prepared mixtures

Formulation code	pm11b	pm12b	pm32b	pm11h	pm12h	pm32h	fd11b	fd12b	fd32b	fd11h	fd12h	fd32h
Preparation method	physical mixing						freeze-drying					
Polymer type	β CD	β CD	β CD	HPCD	HPCD	HPCD	β CD	β CD	β CD	HPCD	HPCD	HPCD
Ratio (drug/CD)	1:1	1:2	3:2	1:1	1:2	3:2	1:1	1:2	3:2	1:1	1:2	3:2
Solubility (mg/100 ml) ^a	4.53 \pm 0.27	5.04 \pm 0.52	4.19 \pm 0.1	4.71 \pm 0.35	5.58 \pm 0.279	4.16 \pm 0.208	5.14 \pm 0.42	5.61 \pm 0.66	4.51 \pm 0.11	5.62 \pm 0.66	6.21 \pm 0.96	4.64 \pm 0.17

^amean \pm SD, n = 3, pm11b means 1:1 Lornoxicam: β -cyclodextrin physical mixture, pm12b means 1:2 Lornoxicam: β -cyclodextrin physical mixture, pm32b means 3:2 Lornoxicam: β -cyclodextrin physical mixture, pm11h means 1:1 Lornoxicam: hydroxyl propyl β -cyclodextrin physical mixture, pm12h means Lornoxicam: hydroxyl propyl β -cyclodextrin physical mixture, pm32h means 3:2 Lornoxicam: hydroxyl propyl β -cyclodextrin physical mixture, fd11b means 1:1 Lornoxicam: β -cyclodextrin freeze-dried mixture, fd12b means 1:2 Lornoxicam: β -cyclodextrin freeze-dried mixture, fd32b means 3:2 Lornoxicam: β -cyclodextrin freeze-dried mixture, fd11h means 1:1 Lornoxicam: hydroxyl propyl β -cyclodextrin freeze-dried mixture, fd12h means 1:2 Lornoxicam: hydroxyl propyl β -cyclodextrin freeze-dried mixture, and fd32h means 3:2 Lornoxicam: hydroxyl propyl β -cyclodextrin freeze-dried mixture.

Differential scanning calorimetry (DSC)

Thermal analysis is conducted to evaluate the possible physical and chemical changes that might happen in heated samples. DSC thermograms are shown in fig. 1. LOR exhibited two characteristic endothermic peaks at 220 °C and 260.9°C indicating a cubic crystal polymorph form [31]. β CD presents broad endothermic peaks at 108

°C and 318.5°C. HPCD presents endothermic peaks at 92.88 °C and 295.4 °C. The thermal behavior of HPCD exhibited no phenomena in any temperature intervals. In all of the prepared complexes, there is slight dislocation of the peaks indicating the possibility of complex formation. Similar results were observed in complexation between β CD and carbamazepine [32]. But in freeze-dried mixtures, the dislocation of peaks is more than that of physical mixtures. Also, the intensity of peaks

in freeze-dried mixtures is more reduced than in physical mixtures. The decrease in intensity of the peak in the thermogram of the freeze-dried complexes could be attributed to the inclusion of LOR in CD molecule [33]. The change in peaks may be related to a physical interaction between LOR and CD indicating the formation of an amorphous system. In the freeze-dried complex, LOR was dispersed in the amorphous host and altered its crystallisation. Similar results were obtained in complexation between β CD and piroxicam [34]. In fig. 1D, 1G, 1J and 1M, endothermic peaks were more reduced in HPCD 1:1 complex than β CD

1:1 complex indicating more inclusion of LOR in HPCD. The intensity of the peaks was more reduced in 1:2 complexes than 1:1 complexes indicating more effective inclusion as shown in fig. 1E, 1H, 1K and 1N. Similar results were observed in 1:2 inclusion complex between of β CD with iodide ion [35] as well as the complex of hexakis (3-O-acetyl-2, 6-di-O-methyl)- α -CD with butyl acetate [28]. The intensity of the peaks in 3:2 complex was not reduced much (fig. 1F, 1I, 1L and 1O) indicating less effective inclusion as appeared in the complex of β CD with 1,10 phenanthroline [36].

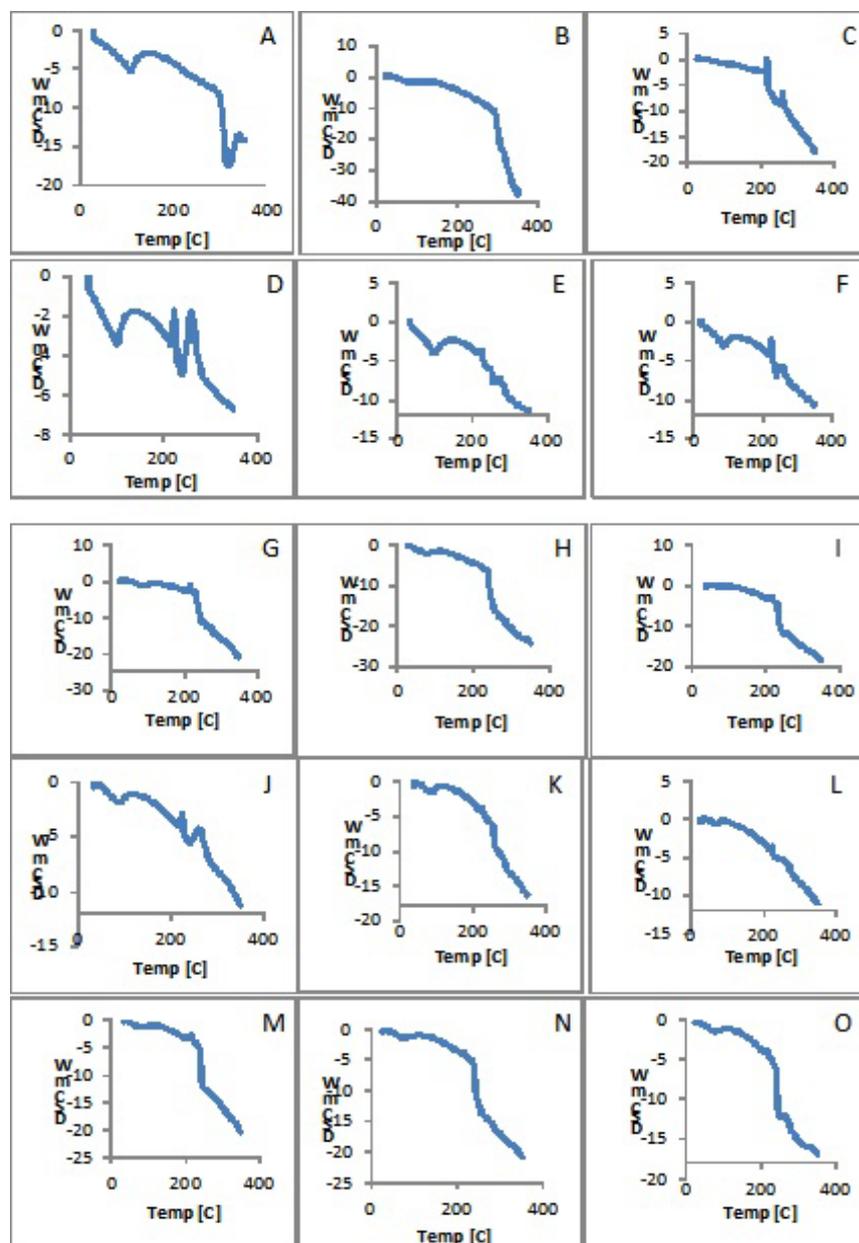


Fig. 1: Showing DSC for of (A) β CD, (B) HPCD, (C) LOR, (D) pm11b, (E) pm12b, (F) pm32b, (G) pm11h, (H) pm12h, (I) pm32h, (J) fd11b, (K) fd12b, (L) fd32b, (M) fd11h, (N) fd12h, (O) fd32h

Scanning electron microscopy (SEM)

The photomicrographs obtained for the prepared LOR-CD solid complexes were presented in fig. 2. β CD and HPCD revealed rough particles with fissures and irregular surface (fig. 2H, 2I). In physical mixtures, the particles of LOR and CD were clearly distinguished from each other (fig. 2G, 2J, 2K), this suggests that there is no chemical or physical interaction occurs between them. While in

freeze-dried mixtures, there is more interaction between LOR and CD. The particles are amorphous with a smooth shape and reduced size (fig. 2A, 2D, 2F). This explains the higher solubility of the freeze-dried mixtures than that of physical mixtures [10]. As shown in fig. 2C and 2E, the particles of HPCD complex were more amorphous than β CD complex particles confirming the above results that HPCD forms more soluble complex than β CD. The effect of LOR to CD ratio on solubility was not clearly observed in the SEM micrographs.

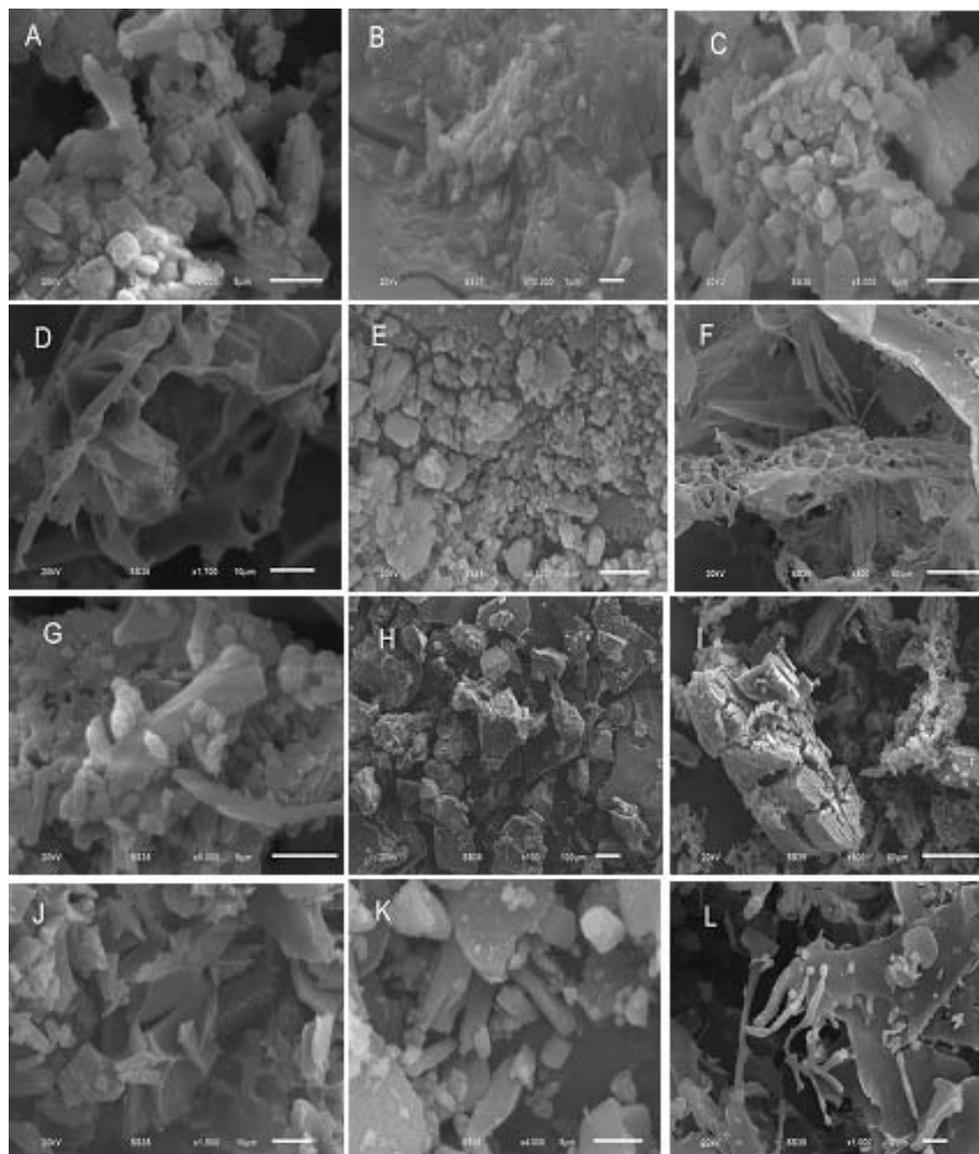


Fig. 2: Showing SEM photomicrographs of (A) fd11b, (B) fd11h, (C) fd12b, (D) fd12h, (E) fd32b, (F) fd32h, (G) pm11b, (H) pm11h, (I) pm12b, (J) pm12h, (K) pm32b, (L) pm32h

X-ray diffraction

The solid-state form, like as crystalline, polymorphs, solvates or amorphous solids of a drug substance, can have a significant impact on drug's solubility, dissolution rate, stability in a pharmaceutical formulation and bioavailability [37, 38]. A crystal has an ordered arrangement of molecules and atoms, maintained in contact through non-covalent interactions while amorphous solids are characterised by a random state.

Although the amorphous solids are often susceptible to changes during storage, the amorphous form of a drug is generally more soluble, due to free energies involved in the dissolution process. This characteristic of solubility is a useful property for low aqueous solubility drugs [39]. Fig. 3 represents the reflectograms of the mixtures. Fig. 3A shows that β CD in crystal form. Fig. 3B shows that HPCD in amorphous form. Fig. 3C shows that LOR in crystal form. In physical and freeze-dried mixtures, it was observed that the peaks size was reduced. This indicated the formation of amorphous solid as in fig. 3D, 3E. Also, it was noticed that HPCD form more amorphous mixtures than that of β CD. It was observed in fig. 3E, 3G and 3I that 1:2 complexes were more amorphous than 1:1 complex

and 3:2 complex as the peaks size were highly reduced indicating high solubility of 1:2 complex and confirming the above results. 3:2 inclusion complexes were obtained when two LOR molecules were included into cavities of two CD molecules while the third one appears in the interstitial region formed by the wider rims of the cavities of two CD molecules. Similar examples were found in the complexes of β CD with 1-propanol and 4-iodophenol [40]. In fig. 3E and 3K, it was observed that freeze-drying method from slightly more amorphous crystals than physical mixing method [26, 33].

Nuclear magnetic resonance spectroscopy

Fig. 4 presented ^1H NMR data of the complexes prepared by the physical mixture and freeze-drying. The results suggested that LOR is externally associated with CD as there is an interaction between H_4 of HPCD (3.31-3.37 ppm) and hydrogen's of the aromatic ring of LOR (7.56-7.72 ppm). These data suggest that at least part of the drug molecule interacts with the CD cavity and is encapsulated [25].

Similar effects have been previously described in the interaction between ABPP and β -CD [41]. The association complexes formed increase the aqueous solubility of LOR

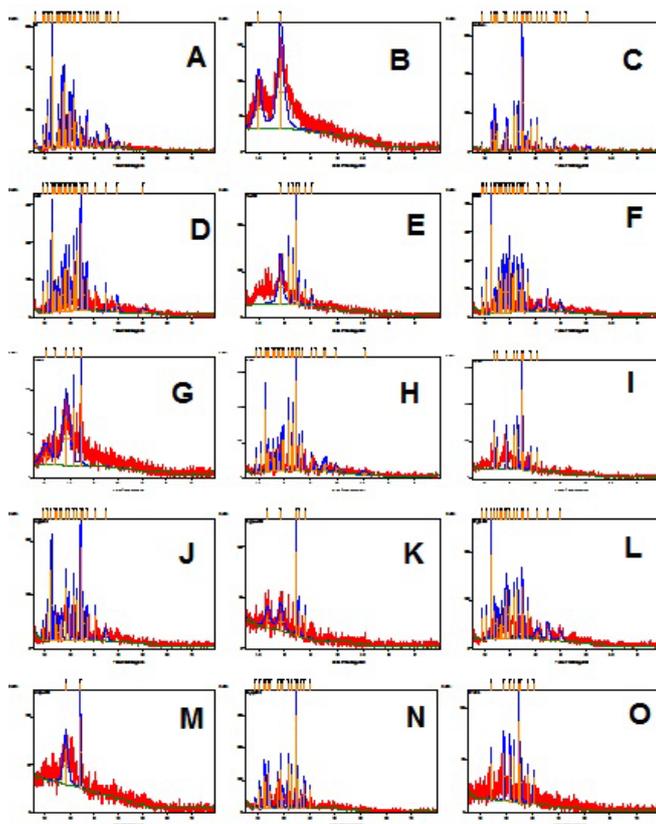


Fig. 3: Showing the representative X-ray diffraction patterns for of (A) β CD, (B) HPCD, (C) LOR, (D) pm11b, (E) pm11h, (F) pm12b, (G) pm12h, (H) pm32b, (I) pm32h, (J) fd11b, (K) fd11h, (L) fd12b, (M) fd12h, (N) fd32b, (O) fd32h

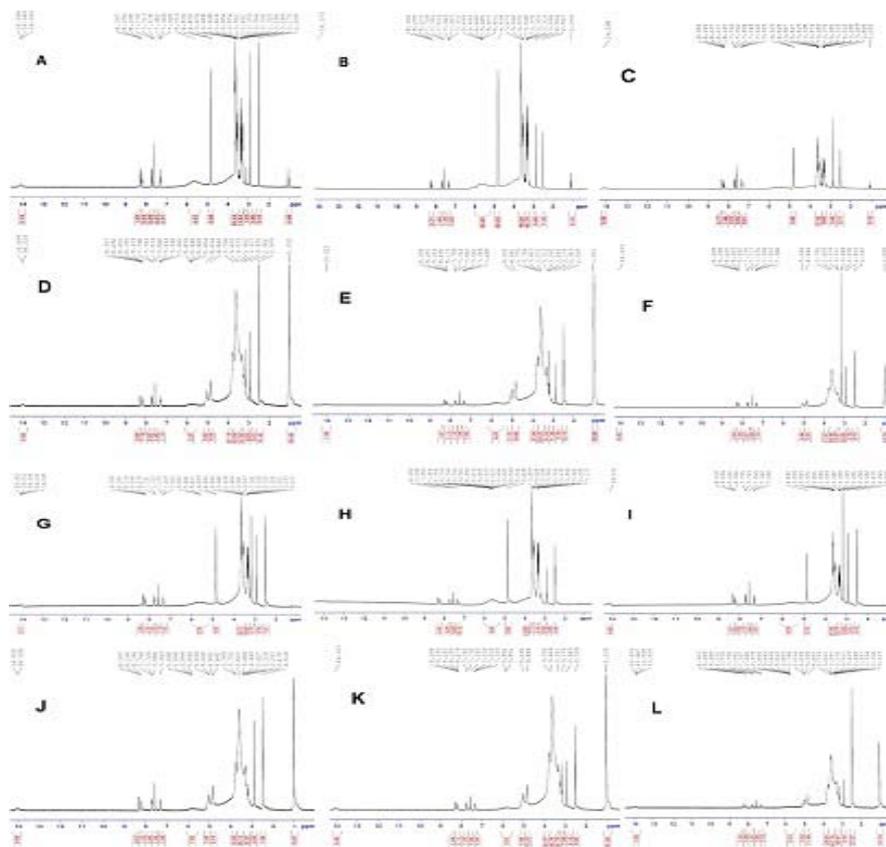


Fig. 4: (A) pm11b, (B) pm12b, (C) pm32b, (D) pm11h, (E) pm12h, (F) pm32h, (G) fd11b, (H) fd12b, (I) fd32b, (J) fd11h, (K) fd12h, (L) fd32h

Fourier transform infrared (FT-IR)

FT-IR spectra are presented in fig. 5. LOR spectra showed the band at 3412 cm^{-1} . The FT-IR spectrum of β CD presents a large band and a peak in the region of $3500\text{--}3000\text{ cm}^{-1}$ that belongs to stretching vibrations of primary OH [31]. Absorption bands of stretching vibrations of C–O, C–C, and deformation vibrations of O–H bonds from

primary and secondary alcohols of β CD occur in the range $1600\text{--}1000\text{ cm}^{-1}$ [42]. The FT-IR spectrum of HPCD presented a profile without distinctly high peaks. The physical mixture FT-IR spectrum showed approximately the superposition of the drug and HPCD, while the inclusion complex showed spectra with broader and shifted bands, suggesting the formation of hydrogen bonds between the carbonyl group of LOR and the hydroxyl group of the host cavity [33].

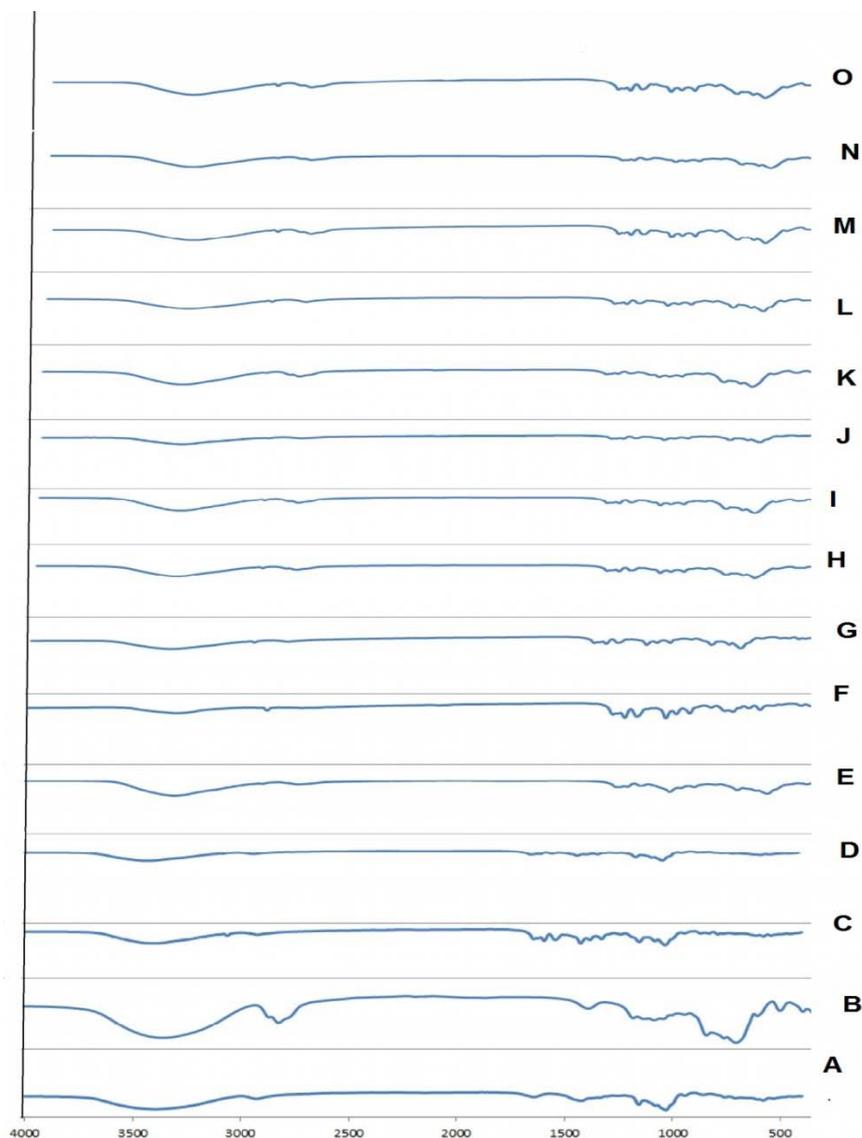


Fig. 5: FT-IR spectra of (A) β CD, (B) HPCD, (C) LOR, (D) pm11b, (E) pm12b, (F) pm32b, (G) pm11h, (H) pm12h, (I) pm32h, (J) fd11b, (K) fd12b, (L) fd32b, (M) fd11h, (N) fd12h, (O) fd32h

CONCLUSION

In this work, LOR solubility was enhanced through its complexation with β CD and HPCD by the physical mixture and freeze-drying techniques. The complexes obtained by freeze-drying presented higher solubility compared to those containing the simple physical mixture. It was noticed that the complexes were transformed to amorphous forms. Finally, HPCD and freeze-drying technique have higher but not significantly different solubilizing effect than β CD and physical mixture technique respectively. It may be statistically different on a large scale. The formation of such complexes could be regarded as a promising strategy for improving the bioavailability of LOR.

CONFLICTS OF INTERESTS

The author has no declaration of interest.

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