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Research Article

FTIR AND RAMAN SPECTROSCOPIC INVESTIGATIONS OF A CONTROLLED RELEASE CIPROFLOXACIN / CARBOPOL940 MUCOADHESIVE SUSPENSION

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ABSTRACT

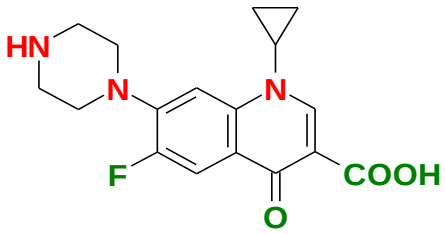
Very few formulations are available, at present, from which the drug is absorbed uniformly, so that safe and effective blood level of Ciprofloxacin could be maintained for a prolonged period. Considering this limitation, a controlled release mucoadhesive suspension of Ciprofloxacin with Carbopol polymer (Carbopol940) has been prepared following a novel method of ultrasonication. The chemical interaction between Ciprofloxacin and polymer in formulation has been studied by FTIR and Raman Spectroscopy. From the spectral interpretation, it has been found that in formulation, the carboxylic groups of Ciprofloxacin and hydroxyl groups of Carbopol940 undergo chemical interaction, leading to esterification and hydrogen bonding. The formation of micellies due to esterification and hydrogen bonding causes more drug entrapment and a stable formulation. Due to that the formulation of Ciprofloxacin gives better controlled release and mucoadhesive action in the gastrointestinal tract. Hence, Carbopol940 could be considered as an effective carrier for Ciprofloxacin.

Keywords: Ciprofloxacin, C940, FTIR, Raman Spectroscopy, Mucoadhesive formulation

INTRODUCTION

There is a demand for a dosage form that will provide a controlled release action of the drug in solution, particularly in the basic pH conditions of the intestinal lumen over the full dosage period. By achieving constant blood level, drug benefit is maximized while its potential toxicity is minimized[1]. There are several means of achieving controlled release action; one of them is by utilizing interaction between the drug and a polymer[2].

As frequent dosing is required to maintain the therapeutic plasma concentration, Ciprofloxacin (Cipro) was chosen as a model drug for the controlled release study. Ciprofloxacin, 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid is a fluoroquinolone antibacterial agent[3] (Fig. 1).



Ciprofloxacin

Fig 1: Structure of Ciprofloxacin

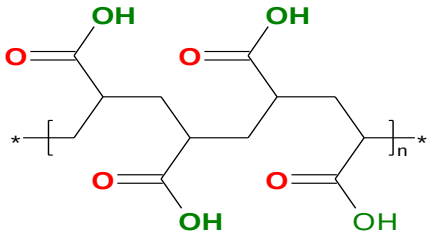


Fig 2: Structure of Carbopol Polymer (Polyacrylic acid)

Carbopol polymers form hydrogel that change their swelling behaviour upon exposure to an external stimulus such as change in pH[4,5], temperature[6], light, or electric field, and are known as "environmentally responsive polymers" or "smart gels"[7,8]. They have recently attracted considerable interest in the field of drug delivery as a means of providing an on-off release by shrinking and swelling in response to the change in pH[9-12]. In stomach, Carbopol polymer forms hydrogen bond with the drug and also with the polysaccharides or proteins of mucosa, which is probably the major mechanism for bioadhesion. In addition, under alkaline condition of the intestine, Carbopol gels are very highly swollen[13]. Carbopol polymer in mucoadhesive formulation may provide a gastric retention system by swelling in the GIT and inducing a pseudofed state, thereby reducing peristaltic contraction. This phenomenon is dependent on viscosity - the higher the viscosity, the lower the contraction[14]. In the present study design, Carbopol940 (C940) is used as a polymer, which consists of chains of polyacrylic acid[15] (Fig. 2). This hydrophilic polymer may form a complex with the low solubility drug like Ciprofloxacin. Because it is known that the solubility is the crucial factor for drug effectiveness, independence of the route of administration[16].

While the functional groups of the molecules can be determined by Fourier Transform Infrared (FTIR) Spectroscopic Analysis, the backbone structures and symmetric bonds of molecules can be checked by Raman spectroscopy. Although it is known that Raman and FTIR are complementary vibrational spectroscopic techniques, there are band intensity differences between the two techniques. Therefore, to obtain more information in detail about chemical interaction between Ciprofloxacin and C940, both FTIR and Raman analyses were carried out[17, 18].

MATERIALS AND METHODS

Materials

The following materials were used: Ciprofloxacin was obtained from Dr. Reddy's Lab, Hyderabad, India, as a gift sample. C940, Pluronic F 68 and Soya lecithin were purchased from Himedia Laboratories Pvt. Ltd., India. Glycerol, Methyl praraben sodium, Propyl paraben sodium, Sorbitol solution I.P. and Sucrose were supplied by Cosmo Chem. Laboratory, Pune, India. Ultra pure water was obtained from a Millipore Milli-Q UV water filtration system.

METHODS

Preparation of Formulation

Praparation of Bulk A

In a beaker, 6 ml water was heated up to 80° C. Sucrose (10 gm) was added under continuous stirring. The temperature was monitored in such a way so that it should not fall below 70° C, till the sucrose was completely dissolved. The prepared syrup was cooled properly at room temperature and kept overnight. Syrup was filtered using 120 mesh nylon cloth.

Praparation of Bulk B

Five millilitre of Ultra pure water was taken in a beaker to which 1.8 ml of sorbitol solution and 0.2 ml glycerin were added. The mixture was stirred properly. To this solution, pluronic F 68 (5%), soya lecithin (1%) and C940 (5%) in w/w of drug were added with continuous stirring.

Preparation of Mucoadhesive Suspension and Ultrasonication

Five millilitre of water was taken in another beaker to which 1.25 gm of Cipro was added. To the drug suspension, the bulk B and bulk A were added with continuous stirring. Methyl paraben sodium (0.015%w/v) and Propyl paraben sodium (0.08%w/v) were added as preservatives. The volume was made up to 25 ml by Ultra pure water. The pH was adjusted to 5.5. Homogenization was carried out for at least 20 min by ULTRASONIC HOMOZENIZER LABSONIC^{R} M (SARTORIUS), having operating frequency 30 KHZ and line voltage 230 V/50 HZ, using the probe made up of Titanium of diameter 7 mm and length 80 mm. The setting knob "cycle" was adjusted to 0.8, indicating sound was emitted for 0.8 s and paused for 0.2 s. In this manner, we could expose our sample with 100% amplitude, while reducing the heating effect to 80%. This LABSONIC^{R}M generates longitudinal mechanical vibrations with a frequency of 30,000 oscillations / s (30 KHZ). The probes bolted to the sound transducer were made of high-strength Titanium alloys, built as λ /2 oscillators. It amplified the vertical oscillation, and transferred the ultrasonic energy via its front surface with extremely high power density into the sample that was to be subjected to ultrasonic waves. In our study, stress applied was sound wave and in addition, mild rise in temperature of the sample occurred during ultrasonication which helped in the homogenization of the suspension. The sample was then divided into two parts –one part was for FTIR analysis and the other part was used for Raman spectroscopy.

Fourier Transform Infrared Spectroscopic Analysis

After ultrasonication, the polymeric suspension was sprayed on to an aluminum slip with the aid of an atomizer. The fine droplets were dried overnight at room temperature and the solid samples were then collected and powdered. This powder sample was used for FTIR analysis. The Fourier transform infrared analysis was conducted to verify the possibility of interaction of chemical bonds between drug and polymer. FTIR analysis was performed by FTIR Spectrophotometer interfaced with infrared (IR) microscope operated in reflectance mode. The microscope was equipped with a video camera, a liquid Nitrogen-cooled Mercury Cadmium Telluride (MCT) detector and a computer controlled translation stage, programmable in the x and y directions. Solid powder samples were oven dried at around 30°C, finely crushed, mixed with potassium bromide (1:100 ratio by weight) and pressed at 15000 psig (using a Carver Laboratory Press, Model C, Fred S. carver Inc., WIS 53051) to form disc. The detector was purged carefully using clean dry nitrogen gas to increase the signal level and reduce moisture. The spectra were collected in the 400 cm^{-1} to 4000 cm^{-1} region with 8 cm^{-1} resolution, 60 scans and beam spot size of 10 µm-100 µm[19-21]. The FTIR imaging in the present investigation was carried out using a Perkin Elmer Spectrum RX.

Raman Spectroscopic Analysis

The Raman system R-3000 instrument (Raman systems INC.USA), a low resolution portable Raman Spectrometer using a 785 nm solid state diode laser, was adjusted to deliver 250 mw to the sample having spectral resolution 10 cm^{-1} and 12 v dc/5A power supplies and USB connectivity. The solid powder samples i.e., both pure drug and polymers were enclosed in plastic poly bags and tested directly. For our study, the fibre optic sampling probe was directly dipped into the formulation (prepared as per the above-mentioned procedure) to collect the spectra at room temperature. The interference of the outside light was also prohibited to prevent photon shot noise. The spectra were collected over the wave number range from 140 to 2400 cm^{-1}.

RESULTS

The infrared spectra are recorded on Fourier Transform Spectrometer in the mid –infrared region (MIR) within the range (400-4500 cm^{-1})[22]. Due to the complex interaction of atoms within the molecule, IR absorption of the functional groups may vary over a wide range. However, it has been found that many functional groups give characteristic IR absorption at specific narrow frequency range. Multiple functional groups may absorb at one particular frequency range but a functional group often gives rise to several characteristic absorptions. Thus, the spectral interpretations should not be confined to one or two bands only; actually, the whole spectrum should be examined.

While the FTIR bands at 4000-1300 cm^{-1} represented functional group region, the appearance of strong absorption bands in the region of 4000 to 2500 cm^{-1} was due to stretching vibrations between hydrogen and some other atoms with a mass of 19 or less. The O-H and N-H stretching frequencies were in the 3700 to 2500 cm^{-1} region with various intensities. Hydrogen bonding has a significant influence on the peak shape and intensities, generally causing peak broadening and shifts in absorption to lower frequencies. The C-H stretching vibration occurred in the region of 3300 to 2800 cm^{-1} [19, 20].

In FTIR spectra of Cipro, one prominent characteristic peak was found between 3500 and 3450 cm^{-1}, which was assigned to stretching vibration of OH groups and intermolecular hydrogen bonding (Fig. 3). Another band at 3000-2950 cm^{-1} represented alkene and aromatic C-H stretching, mainly $\upsilon_{=C-H}$. The 1950 to 1450 cm^{-1} region exhibited FTIR absorption from a wide variety of double-bonded functional groups. The band at 1750 to 1700 cm^{-1} represented the carbonyl C=O stretching i.e., $\upsilon_{C=O}$. The peak between 1650 and 1600 cm^{-1} was assigned to quinolones. The band from 1450 to 1400 cm^{-1} represented υ_{C-O} and at 1300 to 1250 cm^{-1} suggested bending vibration of O-H group which proved the presence of carboxylic acid. A strong absorption peak between 1050 and 1000cm^{-1} was assigned to C-F group [19,20,23,24] (Table 1a).

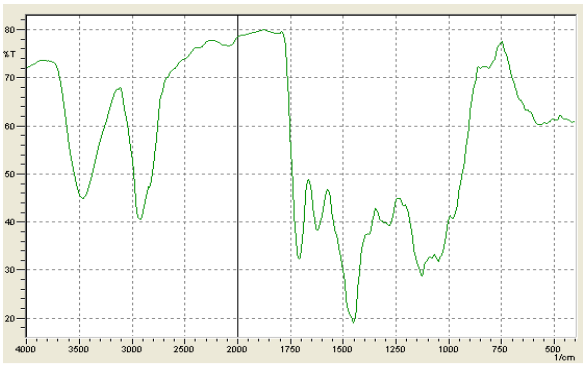


Fig 3: FTIR Spectra of Ciprofloxacin

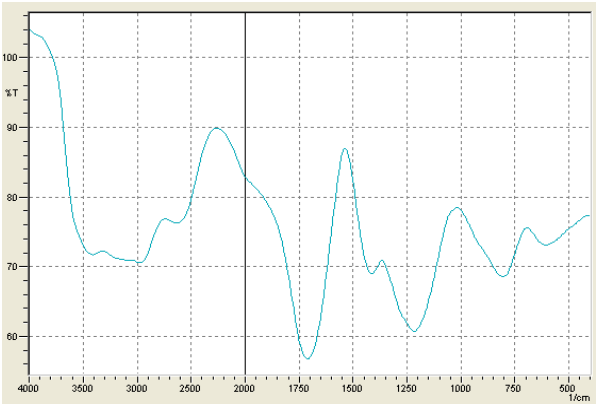


Fig 4; FTIR peaks of C940

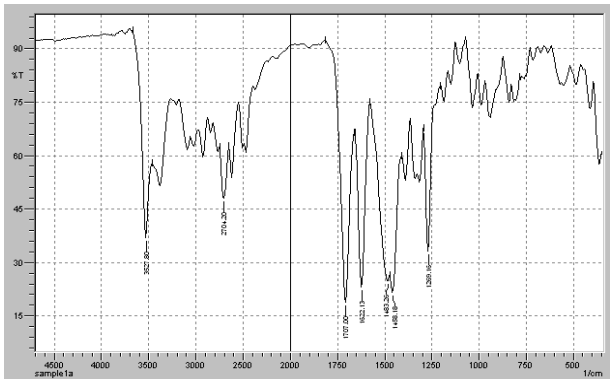


Fig. 5. FTIR Spectra of Ciprofloxacin Mucoadhesive Formulation.

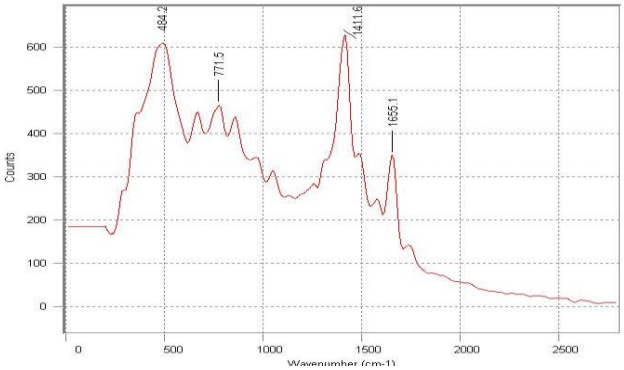


Fig 6: Raman Shifts of Ciprofloxacin

In case of C940, the FTIR spectra having peak between 3000 and 2950 cm^{-1} represented OH stretching vibration, i.e., υO-H and intramolecular hydrogen bonding (Fig. 4). The prominent band between 1750 and 1700 cm^{-1} was assigned to carbonyl C=O stretching vibration i.e., $\upsilon_{C=O}$. While the peak at 1450 to 1400 cm^{-1} was for $\upsilon_{C\text{-}O}$ / $\delta_{O\text{-}H}$, the band at 1250 to 1200 cm^{-1} was due to $\upsilon_{C\text{-}O\text{-}C}$ of acrylates[20,22]. The band between 850 and 800 cm^{-1} was for out of plane bending of =C-H i.e., δ=C-H[19,22] (Table 1b).

In case of FTIR spectra for Cipro with C940, the prominent peak found at 3527.80 cm^{-1} was assigned to polymeric $\upsilon_{O\text{-}H}$ group (Fig. 5). The band between 3040 and 3010 cm^{-1} represented $\upsilon_{=C\text{-}H}$ (m). While the peak at 2704.2 cm^{-1} suggested intermolecular hydrogen bonding, the band at 1707 cm^{-1} was assigned to $\upsilon_{C=O}$. Moreover, the bands at 1622 cm^{-1} and 1463.25 cm^{-1} represented both asymmetric and symmetric stretching vibration of O-C-O group of carboxylic acids, respectively. The peak at 1259.16 cm^{-1} indicated $\upsilon_{C\text{-}O\text{-}C}$ of acrylates and ethers. In addition, the band at 1050 to 1000 cm^{-1} was assigned to $\upsilon_{C\text{-}F}$ and at 800 cm^{-1} was for bending vibration of Ar-H groups[19,20] (Table 1c).

In case of Ciprofloxacin, the prominent Raman shifts were observed at 484.22, 771.47, 1411.63 and 1655.11 cm^{-1} (Fig. 6). The Raman shifts at 484.22 cm^{-1} indicated strong bending vibration of C-C of the aliphatic chain of cyclopropyl group and C-N stretching vibration of piperazinyl group[25-27]. The band at 771.47 cm^{-1} represented the symmetric stretching vibration of C-F group[28]. The peak at 1411.63 cm^{-1} was due to symmetric stretching vibration of O-C-O group of carboxylic acid and methylene deformation mode of the piperazinyl group[29]. A band at 1655.11 cm^{-1} was for symmetric stretching of the carbonyl group $\upsilon_{C=O}$ of the pyridone moiety[23]. In addition, it (peak at 1655.11 cm^{-1}) also indicates the $N^{+}H_2$ scissoring of piperzinyl group[23, 25, 29-32] (Table 2a).

The characteristic prominent Raman bands of C940 were observed at 523.9, 876.8 and 1366.5 cm^{-1} (Fig. 7). The bending vibration of C-C-O group was indicated by the Raman shift at 523.9 cm^{-1}. The band at 876.8 cm^{-1} was due to stretching vibration of C-O-C for acrylates and carboxylic acid. The Raman band at 1366.5 cm^{-1} was assigned to symmetric vibration of O-C-O of acids[27] (Table 2b).

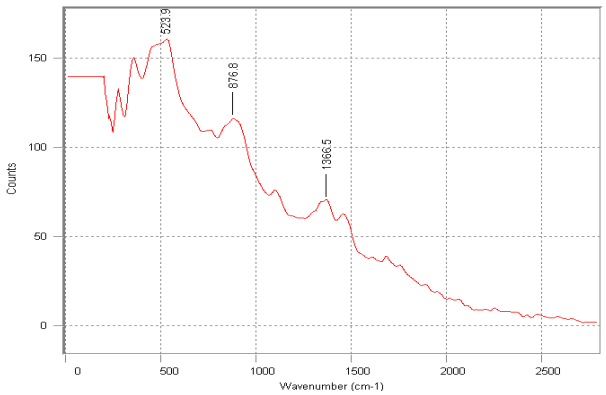


Fig 7: Raman Shifts of C940.

Fig 8: Raman Shifts of Ciprofloxacin Mucoadhesive Formulation.

In the formulation containing both Cipro and C940, the Raman band at 179.2 cm^{-1} was assigned to lattice vibration in Cipro crystal structure. The peak at 352.9 cm^{-1} represented bending vibration of δCC of aliphatic chain (Fig. 8). The band at 862.5 cm^{-1} was assigned to symmetric stretching vibration of both C-F group and C-O-C group for acrylates and esters. The band at 1402.4 cm^{-1} suggested symmetric stretching vibration of O-C-O group. The band at 1680 cm^{-1} was the characteristic of stretching vibration of carbonyl group of esters[25,28,31] (Table 2c).

DISCUSSION

When Infrared (IR) radiation falls on a molecule, it may be absorbed, reflected or transmitted. Absorption leads to the FTIR spectrum, while reflection leads to scattering which is utilized in Raman Spectroscopy[19]. In addition, IR absorption of the functional groups may vary over a wide range. However, it has been found that many functional groups give characteristics IR absorption at specific narrow frequency range[19-21].

In case of FTIR spectra of Cipro, prominent peaks for $\upsilon_{C\text{-}O}$ / $\delta_{O\text{-}H}$ and $\upsilon_{C=O}$ indicated the presence of –CO-, -CHO and -COOH groups (Fig. 3). The involvement of above groups may be confirmed by fermi resonance bands for –CHO; $\upsilon_{C\text{-}O\text{-}C}$ bands for esters; and absence of these two for ketones. This suggests the existence of –COOH group in Cipro (Table 1a).

In case of FTIR spectra of Carbopol940, there were prominent peaks for intramolecular hydrogen bonding, υ_{OH} stretching vibration, carbonylic C=O and C-O stretching vibration, and stretching vibration for the C-O-C, which confirmed the presence of acrylates (Fig. 4). The peak for out of plane bending vibration of =C-H was found between 850 and 800 cm^{-1} (Table 1b).

While comparing the FTIR spectra among the pure Cipro and C940, and the formulation containing both Cipro and C940, it is clear that the band position of C=O group has been affected by esterification and conjugation involving C=O group. The FTIR peaks assigned to $\upsilon_{C\text{-}O}$ and $\upsilon_{C\text{-}O\text{-}C}$ represented acrylates and esters, which confirmed the

esterification between polymeric OH group and –COOH group of Cipro. The stretching vibration of C-F group remained nearly unaltered in the formulation. Another probability of interaction is hydrogen bonding i.e., intermolecular hydrogen bonding due to prominent FTIR peaks at 3527.80 cm^{-1} and 2704.20 cm^{-1} represented polymeric O-H...O-H…O-H and strong carboxylic OH intermolecular hydrogen bonding, respectively. The hydrogen bonded -OH stretching vibration (in the formulation) occurred over a wide range, 3550-2700 cm^{-1}. The FTIR peak at 800 cm^{-1} suggested the probability of out of plane bending of –ene bond and m-substitution of δ_{Ar-H} hydrogen atom[19,20,22] (Table 1c). The C=O group of drug lowers the stretching vibration of C=O frequency in the formulation, indicating deprotonation and probably interaction of the said carboxylic C=O moiety with the polymer. However, a definitive conclusion about the keto group in the bonding to the polymer could be deduced because the corresponding peaks found at 1707 cm^{-1} and 1259.16cm^{-1} was due to probability of formation of β-ketoesters[33]. From the above data, it can be inferred that the carboxylic group of Cipro undergoes the interaction with the polymer. Thus, the nitrogen atoms aren't likely to be involved in binding or the interaction. The nitrogen atom of the quinolone ring, 1-ortho to fluorine, is less electron rich due to electron deficient fluoroquinolone ring. In addition, cyclopropyl and piperazinyl groups of Cipro sterically hinder the involvement of nitrogen atom during the interaction with polymer. The possibility of participation of imino moiety in the piperazinyl group is also less prominent due to intense OH stretching vibration. The bands in the region of 3550-2700 cm^{-1} could be assigned to the asymmetric and symmetric stretching vibrations of the OH groups of the inner and outer sphere of polymer. The shift in the characteristic bands of the FTIR spectra suggests change in their intensity, leading to the appearance of several absorbance bands of the asymmetric and symmetric stretching vibrations and overtone of the deformation vibrations. This indicates the confirmation of the hydrogen bonding[19-21]. In the formulation, the strong characteristic bands at 1622 cm^{-1} and 1463.25 cm^{-1}, which were assigned to $\upsilon_{(O-C-O)}$ asymmetric and symmetric stretching vibrations, respectively, represented the formation of β-ketoesters (as mentioned earlier)[20,34]. The difference Δ [$\upsilon_{(CO2)asym}$-$\upsilon_{(CO2)sym}$] is a useful characteristic for determining the involvement of the carboxylic group of Cipro. The Δ value for the interaction falls in the range of 183 - 250 cm^{-1} indicates the deprotonation of the carboxylic acid group and interaction between drug and polymer[31] (Table 1).

By comparing the Raman spectra of pure drug with the drug incorporated in the Carbopol suspension, the peak at 1418.5 cm^{-1}, assigned to the $\upsilon_{s\ O-C-O}$, is not prominent in the formulation. The symmetric stretching vibration of O-C-O group is found in suspension containing C940. Moreover, the Raman peak for stretching vibration of C=O is prominent in the suspension. From this it is clear that there is esterification reaction between Cipro and Carbopol polymer (Table 2).

The results of both FTIR and Raman spectra indicate that both the spectra show prominent peaks for the stretching vibration of O-C-O and C=O groups, which prove the formation of the esters between the drug and polymer. Moreover, both the intermolecular and polymeric hydrogen bonding are also prominent from the FTIR spectra of the formulation.

CONCLUSION

On the basis of above interpretation, it can be concluded that by preparing mucoadhesive suspension of Ciprofloxacin with Carbopol polymer (C940) following a novel method of ultrasonication, there is a very good interaction between the carboxylic group of drug and hydroxyl group of polymer. This leads to esterification and intermolecular hydrogen bonding, by virtue of which a stable formulation would be produced. Moreover, the drug-polymer complex may aggregate forming a micelle like structure which can absorb and solubilize more drugs to produce a stable formulation. As a result of which Carbopol940 polymer may function as a useful carrier for the Cipro molecule. The main advantage of the present investigation is - higher Cipro drug loading would be possible in dosage forms as compared to conventional formulation strategies.

Table 1: FTIR Peaks of Ciprofloxacin, C940 and Ciprofloxacin Mucoadhesive Formulation

a) Prominent FTIR Peaks of Ciprofloxacin

PEAKS(cm-1)	GROUPS	PEAKS ASSIGNMENT
3500-3450	Hydroxyl group	O-H stretching vibration, intermolecular H-bonding
3000-2950	Aromatics,cyclic enes	υ=CH & Ar-H
1750-1700	CO group of acid	C=O stretching vibration
1650-1600	Quinolines	δN-H bending vibration
1450-1400	Carbonyl group	υC-O
1300-1250	Hydroxyl group	δO-H bending vibration
1050-1000	Fluorine group	C-F stretching

b) Prominent FTIR peaks of C940

PEAKS(cm-1)	GROUPS	PEAKS ASSIGNMENT
3000-2950	Hydroxyl group	O-H stretching vibration, intramolecular H-bonding
1750-1700	C=O group of acids	$\upsilon_{C=O}$ stretching vibration
1450-1400	Carbonyl group of acids	υ_{C-O}
1250-1200	Acrylates	C-O-C stretching vibration
850-800	Aromatics & enes	=C-H out of plane bending vibration

c) Prominent FTIR Peaks of Ciprofloxacin Mucoadhesive Formulation

PEAKS(cm-1)	GROUPS	PEAKS ASSIGNMENT
3527.80	Hydroxyl group	Polymeric H- bonding
3040-3010	enes	$\upsilon_{=C-H(m)}$
2704.2	O-H stretching vibration	Strong intermolecular H-bonding
1707	C=O groups	$\upsilon_{C=O}$
1622	O-C-O group of acid	υ_{as} stretching vibration
1463.25	O-C-O group of acid	υ_{s} stretching vibration
1259.16	Acrylates & esters	C-O-C stretching vibration
1050-1000	C-F groups	υ_{C-F}
800	Aromatic & enes	δ_{Ar-H} & $\delta_{=C-H}$

Table 2: Raman Shifts of Ciprofloxacin, C940 and Ciprofloxacin Mucoadhesive Formulation

a) Prominent Raman Shifts of Ciprofloxacin

Raman Shifts(cm^{-1})	Functional Groups / Vibrations
484.22	Strong δ (CC) aliphatic chain and C-N stretching vibration
771.47	Symmetric vibration of C-F bond
1411.63	υ_sO-C-O and methylene deformation of the piperazinyl group
1655.11	υs of C=O group of pyridone moiety and N^+H_2 scissoring of piperzinyl group

b) Prominent Raman Shifts of C940

Raman Shifts(cm^{-1})	Functional Groups / Vibrations
450-300	Strong $\delta_{(CC)}$ aliphatic chain
523.9	C-C-O bending vibration
876.8	$\upsilon_{(C\text{-}O\text{-}C)}$ of acrylates
1366.5	$\delta_{(CH3)}$ medium

c) Prominent Raman Shifts of Ciprofloxacin Mucoadhesive Formulation

Raman Shifts(cm^{-1})	Functional Groups / Vibrations
179.2	Lattice vibration in crystals
359.38	δ(CC) aliphatic chain
862.5	Symmetric stretching vibration of both C-F group C-O-C group for acrylates and esters
1402.4	υ_sO-C-O
1680	υC=O medium

The release of drug from the formulation system may be very slow because the carboxylic group of Cipro interacts with polymeric OH groups. It suggests less active site of the drug is left for the attack by the water molecules for the hydration and solubilization, which may give controlled release action. While the free polymeric carboxylic groups in the formulation may form hydrogen bonding with the polysaccharides and proteins of mucosa in the acidic condition of the stomach, it is highly swollen and stiffened in an alkaline condition of the intestine. Both these properties suggest a very good mucoadhesive property of the formulation in the gastrointestinal mucosa. Considering the above mentioned interpretation, it can be concluded that the mucoadhesive suspension would produce an effective controlled release and mucoadhesive action. The utility of the present work may be improved if their delivery rate, biodegradation and site-specific targeting would be monitored and controlled.

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