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Drug–drug interaction between diclofenac, cetirizine and ranitidine

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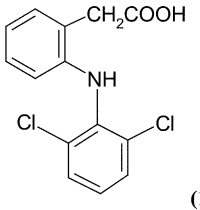
Abstract

The interactions between diclofenac (**1**), cetirizine (**2**) and ranitidine (**3**) were investigated by thermal analyses and UV, IR and ^{1}H NMR spectroscopic studies. In aqueous solution interaction occurred only between **1** and **2**, yielding a high molecular weight (1:1), water insoluble ionic salt. Weak charge transfer (CT) interaction exists between the doubly charged piperazine moiety in **2**, acting as an electron acceptor and (**1**). This CT interaction originates from the aromatic groups in **1**. The CT band observed at ~315 nm exhibits very low absorbance as a result of the partial neutralization of the two positive charges present in the ionic salt. The IR bands of the mixture have wave numbers at ν 3323.1, 1695.3, and δ 1321.1–1210 cm^{-1} indicating the presence of the NH group and the neutralized carbonyl group of **1**, as well as the carboxylic group of **2**. The 1,2,3-substitutions in the benzene ring of **1** in the mixture appear at 1161.1 cm^{-1}. The ^{1}H NMR of the mixed drugs shows singlet, triplet and multiplet proton signals due to the same effect.

Keywords: Drug–drug interaction; Diclofenac sodium; Cetrizine dihydrochloride; Ranitidine hydrochloride; Thermal studies; Charge transfer

1. Introduction

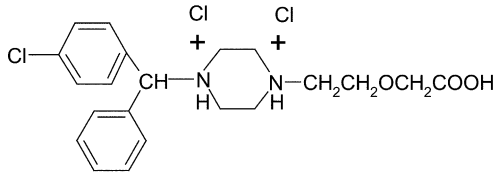
Diclofenac sodium, monosodium {2-[(2,6-dichloroanilino)phenyl acetate, is a potent analgesic, non-steroidal anti-inflammatory drug [NSAID]. It is used in inflammatory and painful diseases of rheumatic and non-rheumatic origin [1]. Its pharmacological effects are thought to be related to the inhibition of the conversion of arachidonic acid to prostalglandins, which are the mediators of the inflammatory



(1)

processes.

Cetirizine dihydrochloride {2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl] ethoxy} acetic acid is a second-generation histamine H_1 antagonist possessing an effective treatment for a wide range of allergic diseases [2]



(2)

Ranitidine hydrochloride is *N*-{2-[[[5-[(dimethylamino) methyl]-2-furanyl]methyl]thio]ethyl}-*N*′-methyl-2-nitro-1, 1-ethene diamine. It is a histamine H_2-receptor antagonist with a furan ring structure that increases its potency to inhibit gastric acid secretion induced by various stimuli, while lacking the anti-androgenic and hepatic microsomal enzyme inhibiting effects [3]. IR analysis confirmed **3** to being a tautomer, with the enol form dominating [4]; as follows:

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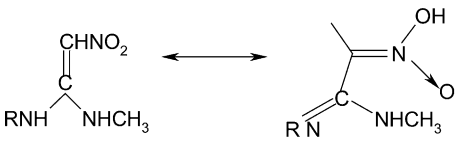
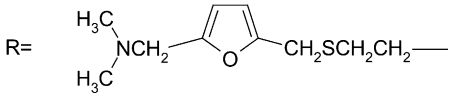


Keto-form Enol-form



The question of whether or not these three drugs may interact was the basis of this study. Kamath et al. [5] stated that paracetamol interfered with the determination of diclofenac sodium studied by flow-injection analysis. Anti-inflammatory drugs are mostly characterized by low aqueous solubility at lower pH values. The solubility increases rapidly with pH's higher than the pK_a. Herzfeldt et al. [6] established the pK_a values of these drugs to range between, 3.5 and 6.3, with a mean directed towards the 4.6 value. The sodium salt shows higher dissolution rates than the acid in the pH range (∼6–7.4). Zecchi et al. [7] showed these rates to be dependent on the solubility of both the dissociated and non-dissociated forms. Low pH (∼2) favours dissociation, while the differences disappear at higher values where the dissolution form dominates. O'Connor et al. [8] showed that the inclusion of a soluble ionizable excipient at high loadings enhanced the dissolution rate of some diclofenac salts. The approximate pK_a values of diclofenac, cetrizine and ranitidine are 4, 1.5 and 2.2, respectively. Thus, by mixing the drugs diclofenac will always be enhanced to dissociate at an earlier stage than either cetirizine or ranitidine. In vitro testing was carried out on the interaction of these drugs utilizing thermal analysis and UV, IR and ^{1}H NMR spectroscopy.

2. Experimental

All chemicals used were analytical grade and water was twice distilled. Thermogravimetric and differential analyses were run on Shimadzu TGA-50H and Shimadzu DTA-50H, respectively. IR spectra were recorded on a Pye-Unicam SP3-300 (500–4000 cm^{-1}) spectrometer. A Perkin-Elmer lamb 20 UV–vis spectrometer was used for UV-spectral studies. ^{1}H NMR spectra were obtained in $(CD_3)_2SO$ by a Varian EM-390 spectrometer (90 MHz) with TMS as internal reference.

2.1. Drug–drug interaction

UV studies were performed on 6.3×10^{-5} M diclofenac, 4.33×10^{-5} M cetrizine and 5.7×10^{-5} M ranitidine in ethanol. The solid drugs were investigated by thermal analysis, IR and ^{1}H NMR studies. To investigate the interaction between these drugs, equal volumes of 0.01 M aqueous solutions of **1**, **2** and **3** were mixed with each other (1:1, w/w). No reaction occurred between **1** and **3**; or **2** and **3**. A white precipitate was instantaneously formed on mixing **1** and **2**. This was washed, filtered and dried under vacuum, then investigated by thermal analysis, IR and ^{1}H NMR studies.

3. Results and discussion

3.1. Thermal analysis

The solid precipitate of the mixed drugs was investigated by thermal analysis, and the results compared with those of the pure drugs. The TGA curves, Fig. 1, traced the loss steps of 1 into four distinct changes between 25 and 675 °C. Enthalpy variation occurs after ∼225 °C, as Bucci et al. reported [9]. This was confirmed by DTA, Fig. 2, thus agreeing with the cited literature [1]. On the other hand, **2** starts with a very mild loss in weight (7.1%) at 152–225 °C due to the evolution of HCl. This is immediately followed by two more loss steps, all being confirmed by DTA. The IR spectrum of ranitidine, showed it to exist in the predominant tautomeric enol form. Consequently, the TGA curve displayed a minor loss (0.717%) due to the change from enol to keto form; a fact that is confirmed by the presence of C=O in its IR spectrum and a slight endothermic peak in its DTA. It manifests two more loss steps, and its DTA confirmed the above results.

The TGA curve of the mixed drugs manifests four loss steps. The first step starts from ambient temperature up to 140.42 °C, accompanied by a loss of 8.015% by weight. It is observed that this step is different in **1** where it ends at ∼110 °C, with a loss of 20.30%. The second drop of the

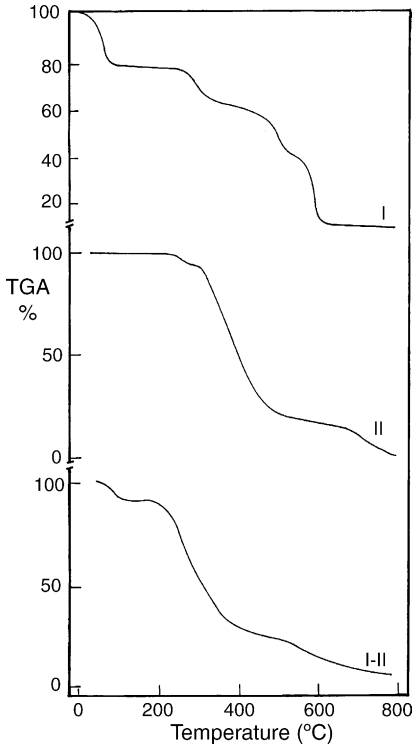


Fig. 1. TGA curves of I, II and (I–II).

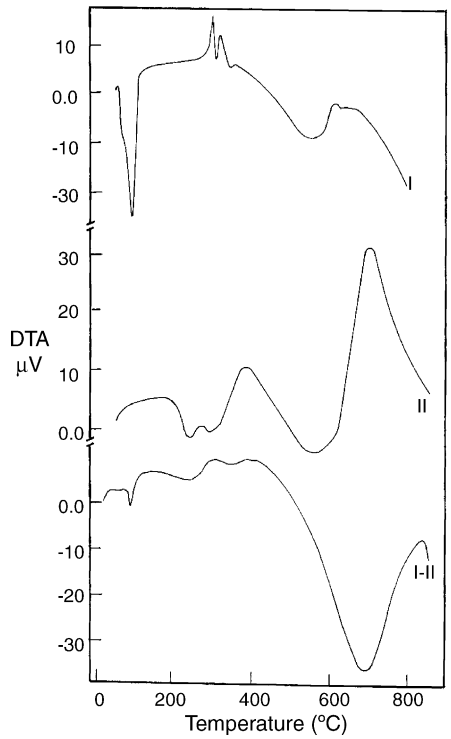


Fig. 2. DTA curves of I, II and (I–II).

mass between the temperature range 144–325 °C (with a loss of 42.927%) may be considered as combination of the second and third steps in **1** (the latter being completely flattened), and the first and the second steps in **2**, where the loss % was much greater. The third loss (19.288%) happens between 325 and 450 °C. The fourth and final loss, starting from ∼450 to ∼780 °C, indicates mostly, the vaporization of the remaining moiety (18.212%). This appears to start at a higher temperature than the third step in **2** (420–600 °C; loss 17.17%). The fourth step in **1** (570–675 °C) appears to have disappeared completely from the curve of the mixture. The DTA shows similar results. Thus, a different compound exists which has similar groups as those present in the parent drugs diclofenac and cetirizine.

Table 1
UV spectra and molar absorptivities of 1, 2, 3 and the mixture

Drug	Maximum wavelength (nm)		Molar absorptivities, ϵ ($\times 10^5$ M)	
Diclofenac	282.6	283[a]	0.086	0.082[a]
Cetirizine	205	205[a]	0.4379	0.437[a]
	229	230[a]	0.3278	0.327[a]
	315		0.2309	
Ranitidine	230.4	228[a]	0.130	0.132[a]
	325	313[a]	0.1789	0.180[a]
Mixed drugs	230.4			
	270			
	340			

[a] Cited in literature [4,10,11].

3.2. Ultraviolet spectra

The UV spectra of 6.3×10^{-5} M (**1**), 4.33×10^{-5} M (**2**) and 5.7×10^{-5} M (**3**) in ethanol (Table 1) showed characteristic bands and molar absorptivities, which were in agreement with previous studies [4,10,11]. A very slight, negligible, hypsochromic shift occurred on buffering **1** with acid or alkali. The very broad band (half-band width 38 nm), appearing in the diclofenac spectrum at 282.6 nm, can be assigned to intra-molecular charge transfer through the whole molecule originating from the carboxylate group. In the case of cetrizine, the bands at ∼315, 229 and 205 nm, are assigned to intra-molecular charge transfer from the negatively charged carboxylate entity to the doubly positively charged piperazine ring. The second and third bands are assigned to π–π^* transitions within the two phenyl rings. Ranitidine has two broad bands with absorbance maxima at about 325 and 230.4 nm. The first band is characteristic of the nitro group olefin conjugation [4]. The second band is assigned to the π–π^* transition within the furan ring.

The UV spectrum of the mixture, Fig. 3, includes bands with absorbance maxima at ∼340, 270 and 230.4 nm. It is to be noted that the band at 340 nm is very broad and of very weak intensity. This can be assigned to inter-molecular charge transfer from **1** to **2** through the transfer of electrons from the phenyl groups in **1** to the piperazine ring in **2** having two positive charges on it. These charges appear to be somewhat

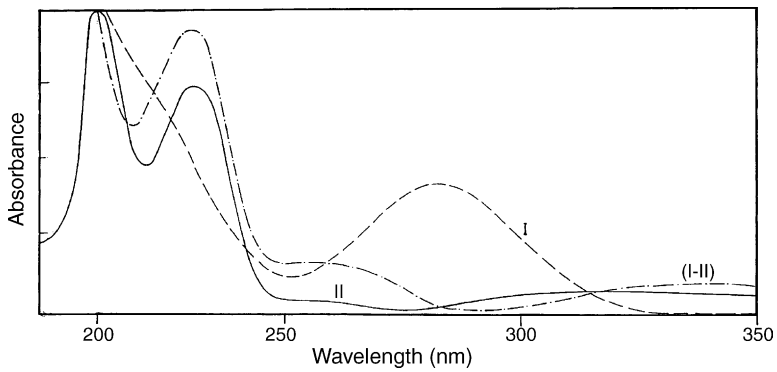


Fig. 3. Ultraviolet spectra of I, II and (I–II).

neutralized, as shown by the weakness of the band intensity. The weak shoulder at ∼260 nm and the band at 229 nm, appearing in the cetrizine spectrum, were quite intensified. The broad band at 282 nm, appearing in **1**, obviously disappeared. Thus, it would seem that a new entity exists which would appear to possess most of the molecules of both drugs joined partly through charge transfer of electrons from **1** to **2**.

3.3. Infrared spectra

The absorbance bands from the IR spectra (Fig. 4) of the pure drugs and the mixture precipitate are listed in Table 2. The diclofenac spectrum showed the NH stretching band at 3276.8 cm^{-1} and the NH···O band of the intra-molecular hydrogen bonding [1] at 3421.5 cm^{-1} resulting from the hygroscopic form of the sodium salt [12]. The aromatic ring stretch is shown in several split bands from 1604.7 to 1388.7 cm^{-1} assigned to the substituted phenyl groups. The 1454.2 and 869.8–621 cm^{-1} bands indicate a dihalogenated substituted benzene ring, as well as the presence of three adjacent hydrogen atoms. Bands at 771.5–748.3 cm^{-1}, assigned to the presence of three adjacent hydrogen atoms in the ring, are mostly weak, yet relatively stable in position. The 1604.7 cm^{-1} band is assigned to an *ortho*-disubstitution. The 1,2-substitution in the second ring is shown at 1234.4–1201.6 cm^{-1} and at 682.8–416.6 cm^{-1} frequencies. The carbonyl group [13] appears between 1800 and 1950 cm^{-1} as a weak absorbance; and again as the neutralized entity of the carboxylic acid in the ranges 1610–1554.5 and 1409.9–1292.2 cm^{-1}.

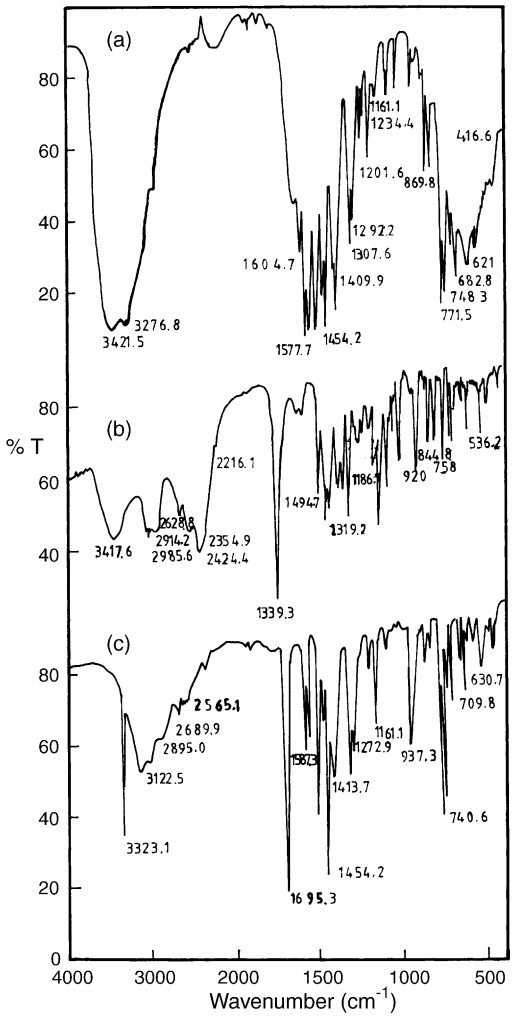


Fig. 4. Infrared spectrum of (a) diclofenac; (b) cetrizine; (c) diclofenac–cetrizine mixture.

The IR spectrum of cetirizine shows an OH stretching mode of water at 3417.6 cm^{-1}, together with a broad band assigned to the aromatic CH (3110–3000 cm^{-1}) and aliphatic CH_2 (2985.6–2914.2 cm^{-1}). While the OH dimer of the amino-carboxylic acid appears at 2628.8–2354.9 cm^{-1}, the quaternary nitrogen atom stretch in the neutral hydrochloride amino acid is at ∼3070 cm^{-1} and the hydrochloride absorbs at 2216.1 cm^{-1} with a very weak band. The OH dimer is shown to be a mono-substitution to a $-CH_2CH_2OCH_2-$ by the 758 cm^{-1} out of plane deformation mode. The halogen substitution (1739.7 cm^{-1}) appears as a mono-substitution (1078.1 cm^{-1}) in the *para*-position with a ring stretch between the (1650–1494.7 cm^{-1}) frequency range. The presence of two adjacent benzene rings is shown at 844–808.1 cm^{-1}. While the carboxylic C–O bond frequency is at 1456.2–1319.2 and 1274.9–1242.1 cm^{-1}, the aliphatic chain C–O bond in $-CH_2CH_2OCH_2COOH$ appears at 1186.1 and at 740 cm^{-1}.

By comparing the spectra of the pure drugs with that of the mixed precipitate, the presence of bands characteristic of diclofenac and cetirizine was obvious. A very sharp, well resolved band assigned to the NH stretching mode of **1** appears at 3323.1 cm^{-1}; while a weak band at 3070 cm^{-1} signifies the presence of the amino acid hydrochloride found in **2**. The absorbance of hydrochloride is so weak that it is almost non-apparent, a fact which often happens [13]. The OH dimer of this amino acid appears as a weak signal between 2700 and 2400 cm^{-1}. The aliphatic CH_2 ($CH_2CH_2OCH_2$ COOH) and the aromatic CH clearly absorb at 2850.6 and 2920 cm^{-1}, respectively. A considerably modified band appears at 1695.3 cm^{-1} indicating the neutralization of the carboxylic group into a carbonyl group. The position of the band shows that neutralization occurred through a nitrogen atom [13]. The ring stretch vibrations show *para*-substitution (1654.8–1587.3 cm^{-1}), mono-substitution (1587.3–1508.2 cm^{-1}) and halogenated benzene (1454.2 cm^{-1}); all of which are assignments of the pure drugs. The δ-bending carbonyl mode (1413.7–1272.9 cm^{-1}) is also found in **1** (1409.9–1292.2 cm^{-1}). OH dimer deformation vibration due to carbonyl presence (1321.1–1210 cm^{-1}), appears once more at 937.3 cm^{-1} indicating the single free hydrogen present in cetirizine. The aliphatic chain $(CH_2)_nO(CH_2)_n$ appears at 1180 and 740.6 cm^{-1} as in **2**. The 1,2-phenyl substitutions (1225–1175 cm^{-1}) are shown to be in the *ortho*-position (667.3–443.6 cm^{-1}) with respect to each other, as in **1**. The 1,2,3-phenyl substitutions of the dichloroanilino ring are present at 1161.1 cm^{-1}, and are shown to be dihalogenated by the out of plane stretch between 837 and 603.7 cm^{-1}.

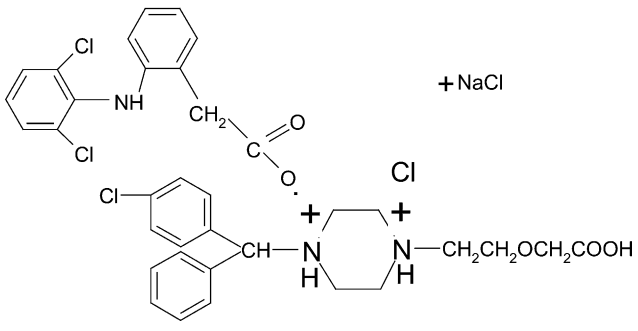
Table 2
Selected IR absorbance bands for diclofenac, cetirizine and the mixture

Assignment (cm^{-1})	Diclofenac (**1**) (cm^{-1})	Cetirizine (**2**) (cm^{-1})	Mixture (**1**–**2**) (cm^{-1})
ν(OH)	3421.5	3417.6	
ν(NH)	3276.8		3323.1
$\nu(NH^+Cl^-)$		3070	3070
$\nu(CH_{ar})$	2968.2	3110–3000	2920
$\nu(CH_2)$		2985.6–2914.2	2850.6
$\nu(OH)_{dimmer}$		2628.8–2354.9	2700–2400
$\nu(NH^+)_{cyclic}$		2216.1	Very weak
$\nu(COO^-M^{n+})$	1800–1950		
ν(COOH)		1739.7	
$\nu(COO^-)$	1604.7–1554.5		1695.3
ν(mono-subst. ϕ)		1585, 1494.7	1587.3, 1508.2
ν(para-subst. ϕ)		1650–1585	1654.8–1587.3
δ(disubst. Cl-ϕ)	1454.2		1454.2
$\delta(COO^-)$	1409.9–1292.2		1413.7–1272.9
δ(OH)		1319.2–1242.1	1321.1–1210
$\delta(CH_2CH_2OCH_2)$		1186.1	1180
δ(1,2-subst. ϕ)	1234.4–1201.6		1225–1175
δ(1,2,3-subst. ϕ)	1161.1		1161.1
γ(OH)+ free H		920	937.3
(disubst. Cl-ϕ)	869.8–621		837–630.7
(2 adj. ϕ)		844–808.1	837
(3 adj. H atoms)	771.5–748.3		765.7–740.6
(CH mono-subst.)		758	760
$\gamma(CH_2)_n$—O—(CH_2)		740	740.6
γ(1,2-subst.)	682.8–416.6		667.3–443.6

3.4. Drug mixture structure

The pK_b of the NH in diclofenac is 10, thus it is a weak base that would not lose its H easily. On the other hand its pK_a (4) is less acidic than that of cetirizine (1.5); therefore it would be ionized at an earlier stage. The above data leads to the conclusion that besides the presence of some charge transfer (UV spectra), there exists a high molecular weight ionic salt that is water insoluble and precipitates immediately after formation. The interaction occurs between the negative carboxylate ion of the sodium salt of **1** and one of the positively charged quaternary amines in the piperazine ring of **2**, yielding NaCl as a by-product. Since hydrochloride is present in the IR spectrum, most likely the interaction took place only at one NH^+ site giving a 1:1 (w/w) product. The *para*-substituted Cl in one of the phenyl rings will pull the electrons towards it and the adjacent nitrogen would be more electropositive; thus attracting the negative carbonyl moiety to it. The tentative structure would be as follows:

(1-2)



3.5. Nuclear magnetic resonance spectra

The ^{1}H NMR spectra of **1**, **2** and the mixture (**1**–**2**), Fig. 5, confirmed the above results. The spectrum of **1** showed a singlet at δ 3.41 ppm for the two protons of the CH_2COO group, a multiplet at δ 6.23–7.47 ppm for seven aromatic protons of the benzene rings; and finally another broad singlet at δ 10.50 ppm for the aromatic NH proton between the C–N–H attachments. The broadness is attributed to the proton–proton coupling due to hydrogen on the carbon atom adjacent to nitrogen [14].

The spectrum of two manifests bands severely broadened as a result of the proton–proton coupling. The broad NH^+ absorption has humps representing the splitting up of the signals of nitrogen nucleus caused by the protons of the adjacent carbon atoms [14]. The nitrogen in the piperazine is at δ 3.23–3.47 ppm. At δ 2.8 ppm a singlet appears designating two protons for the CH_2 attached to N in the NCH_2CH_2O. A triplet occurs at δ 3.65–3.86 ppm for two protons in the CH_2 near the O in CH_2CH_2O and a singlet at δ 4.09 ppm with two protons identifies the CH_2 adjacent to the carboxylic acid group. The proton of the CH in the methyldiphenyl group is shown by a broad singlet at δ 4.6 ppm. The multiplet at δ 7.1–7.6 ppm is due to nine protons of the aromatic rings; and at δ 10.8 ppm a weak broad singlet is shown for one proton of the carboxylic acid group.

In the spectrum of the drug mixture (**1**–**2**) it is apparent that a deshielding effect is exerted on the aromatic NH proton via inter-molecular charge transfer causing the resonance to be downfield shifted to δ 7.6 ppm, a fact previously detected

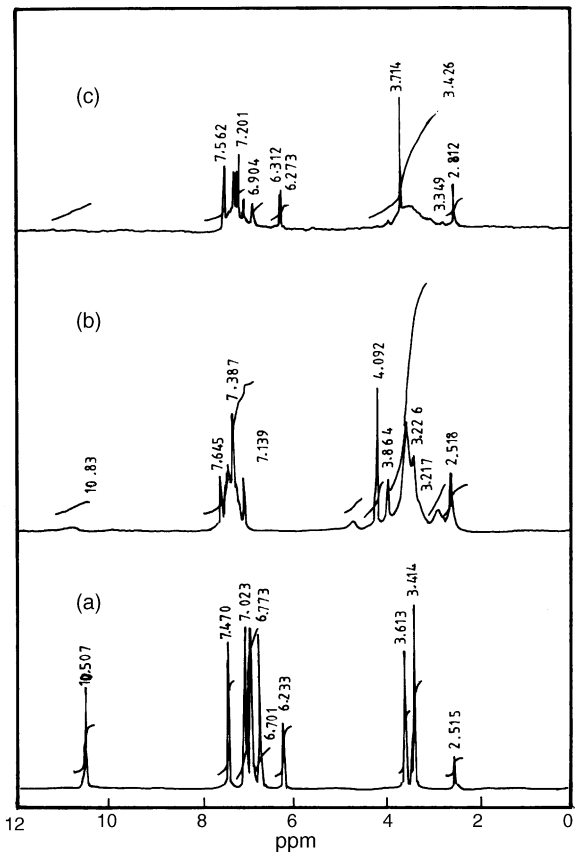


Fig. 5. ^{1}H NMR spectrum of: (a) diclofenac; (b) cetrizine; (c) diclofenac–cetrizine mixture.

in the UV spectra. Thus, this proton appears in the broad multiplet between δ 6.27 and 7.56 ppm showing sixteen aromatic CH protons and the two NH^+ protons, covering a total of 19 protons. A singlet at δ 3.3 ppm marks the methyl diphenyl CH proton. Two triplets at δ 3.71 and 3.36 ppm appear due to four protons on the acyclic CH_2 groups adjacent to NH^+ in the piperazine ring; the first manifests those present near the negatively charged carbonyl group and the second signal is that of the groups adjacent to the nitrogen hydrochloride entity. The acyclic aliphatic CH_2 in $NH^+CH_2CH_2O$ was shifted down-field from δ 2.8 to 3.4 ppm as its proton was in the plane of the carbonyl group. Another singlet at δ 3.61 ppm with two protons is shown for the CH_2 in CH_2CH_2O entity. The CH_2 in the CH_2COOH group appears as a singlet δ 3.71 ppm. A very weak singlet is present at δ 10.8 ppm for the one proton of the carboxylic acid group.

The above results confirm the UV and IR spectra, also confirming the proposed structure. A calculation of the TGA loss percentages would further confirm the structure.

3.6. TGA loss percent calculations

On calculating the loss percents resulting from the TGA of the mixture, according to the above-assumed structure, the experimental and calculated data were compatible. The first loss step from ambient temperature up to 140 °C (−8.015%) was due to loss of ∼4 molecules of crystallization water. This agrees with Fini et al. [12] who stated that sodium salts of diclofenac form hydrates when crystallized from water containing four crystallization water molecules. The second loss step (−45.93%) matches the calculated value (48.32%) for the loss of the dichloro-diphenyl moiety. The third step (−19.288%) is very close to the calculated loss of the chloro-diphenylmethane (18.57%). The fourth loss (−18.212%) is the fusion of the remaining part containing the piperazine ring (19.28%). These facts confirm the structure of the mixture (**1**–**2**) elucidated above.

4. Conclusion

An insoluble salt-like compound of higher molecular weight results from aqueous interaction of diclofenac and cetirizine, yielding NaCl. No reaction was observed on mixing either of these two with ranitidine. Studies carried out on the pure and mixed drugs included thermal analysis, UV, IR and ^{1}H NMR spectroscopy. Finally, the loss percentages were calculated according to the suggested mixture structure to confirm the above studies. The resulting new compound was a 1:1 (w/w) specie that was connected partly through charge transfer from the phenyl rings of **1** to the positive quaternary amine in **2**; and mainly through electrostatic attraction between the negative charge on the ionized sodium salt of **1** and the positively charged NH^+ of **2**. In addition, the Na^+ ion combined with Cl^- from the HCl group in the amine yielding NaCl. The carboxylic acid of the amino acid hydrochloride was unchanged. The interaction site in **2** was at the NH^+ adjacent to the two phenyl rings due to the electron attracting chlorine atom in one of them. This caused the neighboring nitrogen to be more electropositive thus attracting the incoming negatively charged carbonyl ion of **1**.

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