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Spectroscopic characterization of *in vitro* interactions of cetirizine and NSAIDS

Hina Shamshad[1*], M Saeed Arayne[1] and Najma Sultana[2]

Abstract

Background: Cetirizine (anti-allergy agent) and non-steroidal anti-inflammatory drugs (NSAIDs; anti-inflammatory agents) are co-administered drugs. Cetirizine, a P-glycopretein substrate may be affected by the use of NSAIDs. In the present work, quantification of cetirizine in the presence of commonly co-administered NSAIDs such as diclofenac sodium, ibuprofen, flurbiprofen, tiaprofenac acid, meloxicam and mefenamic acid were studied using the RP-HPLC technique.

Methods: A high-throughput HPLC method for the analysis of cetirizine was developed, validated in the presence of NSAIDs and was further used to study the interactions of cetirizine in the presence of NSAIDs at four different pH levels. Purospher Star, C18 column (5 μm, 25 cm × 0.46 cm) with a mobile phase of methanol/water (90:10 v/v, pH adjusted to 3.5) at a flow rate of 1.0 mL/min and a wavelength of 240 nm was used.

Results: The synthesis of cetirizine in the presence of NSAIDs was carried out, and complexes were characterized using infrared (IR) and nuclear magnetic resonance (NMR) techniques. The method was found to be applicable in serum and was found useful for therapeutic purposes. The differences in availabilities of cetirizine with NSAIDs at three pH levels clearly indicated the interactions of afore mentioned drugs.

Conclusions: The findings suggested further studies on the co-administration of these two drugs simultaneously in order to know the pharmacokinetic and pharmacodynamic profiles of the drugs. It is highly recommended to have a suitable time lapse between the oral uses of these drugs.

Keywords: Cetirizine; Drug interaction; HPLC method; NSAIDs

Background

Second- and third-generation antihistamines are P-glycoprotein substrates. Drugs that affect the P-glycoprotein may lead to drug-drug interactions (Scott and Kelly 2003; Jarkko et al. 2006; Renwick 1999). Cetirizine being a P-glycoprotein substrate may interact with commonly co-administered drugs such as NSAIDs that may affect the P-glycoprotein expression (Lee et al. 2007), as celecoxib and diclofenac, were found to inhibit the function of P-glycoprotein (Wageh et al. 2004). It has been established that synergistic effect was exhibited by the combined use of cetirizine with nimesulide (Rewari and Gupta 1999). Moreover, cetirizine was found to possess analgesic activity in mice (Priya et al. 2013). Cetirizine and mefenamic acid combination was also developed for the treatment of respiratory disorder (Philip and Philip 2010). Nimesulide and cetirizine combination was also prepared which was found to possess anti-leukotriene, antihistamine, anti-allergy, and anti-inflammatory actions (Singh and Jain 2003). Drug interactions of cetirizine have also been reported in literature (Ihsan et al. 2005; Arayne et al. 2010a; Sultana et al. 2010).

Simultaneous HPLC method for the determination of paracetamol, phenylpropanolamine hydrochloride, and cetirizine was reported; however, the mobile phase consisted methanol and disodium hydrogen phosphate dihydrate buffer which could be corrosive to the column (Suryan et al. 2011). Another simultaneous method of paracetamol, acetyl salicylic acid, mefenamic acid, and cetirizine was achieved using disodium hydrogen phosphate buffer and acetonitrile combination which could once again be corrosive and expensive altogether (Freddy and Dharmendra 2010). Separation method of ibuprofen, phenylephrine HCl, and cetirizine from soft gels was

* Correspondence: chemdoc9@gmail.com
[1]Research Institute of Pharmaceutical Sciences, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Karachi, Karachi 75270, Pakistan
Full list of author information is available at the end of the article

reported using the mobile phase of acetonitrile and hexanosulphonate (Cosmes and Rodriguez 2012). Simultaneous determination of cetirizine and aceclofenac was achieved by using mobile phase of acetonitrile and heptane sulphonic acid (Padmavathi and Niranjan 2011). Nimesulide, cetirizine, and pseudoephedrine hydrochloride separation was done by using acetonitrile/phosphate buffer/triethyl amine as the mobile phase (Jain et al. 2012). Our group also reported methods of simultaneous determination of cetirizine with anti-diabetic drug (Arayne et al. 2010b) and with H_2 receptor antagonists (Sultana et al. 2010).

It is clearly evident from the above literature that most of the simultaneous methods used acetonitrile as solvent which is quite expensive. In others, buffers were also used which is column corrosive. In order to quantify the drugs and understand the degree of interactions, a fast, least expensive, efficient HPLC method was required, which could be used for therapeutic purposes and could also be employed for routine analysis work.

So, in the present work, cetirizine method was developed and validated in the presence of NSAIDs such as diclofenac sodium, ibuprofen, flurbiprofen, meloxicam, and mefenamic acid using the RP-HPLC method. The method was further used to study the interactions of the cetirizine in the presence of NSAIDs at three pH levels, i.e., 4, 7.4, and 9. Cetirizine complexes were also synthesized with interacting drugs. The synthesized complexes were characterized by their physical parameters as well as by the techniques of infrared (IR) and nuclear magnetic resonance (NMR).

Methods

Materials

Raw materials used were of pharmaceutical purity and formulations as cetirizine (Zyrtec), mefenamic acid (Ponstan), diclofenac sodium (Voren), flurbiprofen (Froben), meloxicam (Melfex), tiaprofenic acid (Surgam), and ibuprofen (Brofen) were purchased from local markets. Analytical grade reagents were used during the whole experimental procedures. Methanol of HPLC grade (TEDIA®, USA) and other reagents included were hydrochloric acid, sodium hydroxide, sodium chloride, potassium dihydrogen orthophosphate, disodium hydrogen orthophosphate, ammonium chloride, 10% NH_3 solution, phosphoric acid 85% (Merck, Darmstadt, Germany) were utilized.

Equipment

Shimadzu HPLC system (Kyoto, Japan) equipped with LC-10 AT VP pump, with a 20-μl loop, Purospher® Star, RP-18 endcapped (5 μm) column and SPD-10 A VP UV-vis detector was utilized. IR studies were carried out using a Shimadzu Model Fourier transform infrared (FTIR) Prestige-21 spectrophotometer. Spectral treatment was performed using Shimadzu IR solution 1.2 software. The ^{1}H-NMR spectra were recorded on a Bruker AMX 500 MHz spectrometer (Madison, WI, USA) using TMS as an internal standard.

Method development

Optimized conditions for separation

The chromatographic analysis was performed at laboratory temperature (25°C) with isocratic elution. The optimized conditions for the separation of the eluents were achieved by using the mobile phase of methanol/water 90:10 monitored by UV detection 240 nm at a flow rate of 1 ml min^{-1} with pH 3.5 adjusted by orthophosphoric acid. The samples from these solutions were injected in to the system six times.

Reference standard solutions

Stock reference standard solutions of all drugs were prepared by dissolving appropriate amounts of each drug in a mobile phase to yield concentrations of 100 μg ml^{-1}. For calibration curve studies, serial dilutions in the concentration range of 50 to 3.12 μg ml^{-1} were injected in triplicate.

Pharmaceutical dosage form samples

Commercially available pharmaceutical formulations of the respective brands were evaluated by groups of 20 tablets for each drug and dissolved in mobile phase according to the labeled claim. The samples from this solution were injected into the system in triplicate.

Standard drug plasma solutions

The supernatant obtained by centrifuging blood samples was deprotonated by acetonitrile, spiked daily with working solutions, and chromatographed.

Method development protocol

Certain parameters such as mobile phase composition and pH, flow rate, diluents of solutions, and wavelength of analytes were altered in order to achieve symmetrical and well-resolved peaks at a reasonable retention time.

Method validation

All validation steps were carried out according to the ICH guidelines such as system suitability, selectivity, specificity, linearity (concentration-detector response relationship), accuracy, precision, and sensitivity, i.e., detection and quantification limit.

System suitability

System suitability was assessed by examining the six replicates of the drugs at a specific concentration for repeatability, peaks symmetry (symmetry factor), theoretical plates, resolution, and capacity factors.

Specificity

The drugs were spiked with pharmaceutical formulations containing different excipients.

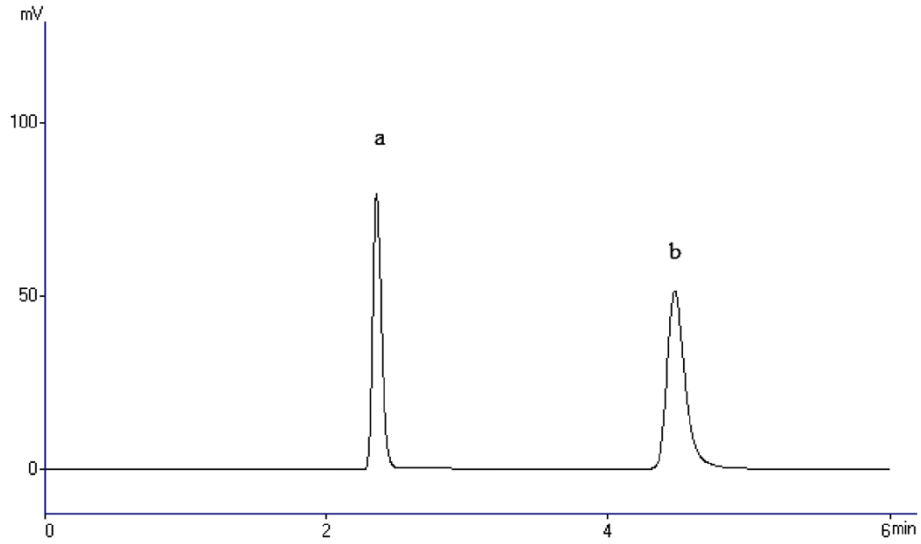


Figure 1 Representative chromatograms of (a) cetirizine and (b) meloxicam.

Linearity

The linearity of the method was evaluated at different concentrations. Linear correlation coefficient, intercept, and slope values were calculated for statistical analysis.

Accuracy

The accuracy of the method was established at three concentration levels (80%, 100%, and 120%) in triplets, and percent recovery (%recovery) was calculated in each case.

Precision

Six replicates of a concentration range were injected to system on two different non-consecutive days and percent relative standard deviation (%RSD) was calculated.

Limit of detection and quantification

The LOD and LOQ of the method were calculated.

Drug-drug interaction studies

The 50-μg ml^{-1} solutions of all the drugs alone and those in combination with cetirizine were made and kept on water bath for 120 min at 37°C. Five milliliters of an aliquot was withdrawn after every 15-min interval, after making dilutions was filtered and injected in to the HPLC system in triplicate. The concentration of each drug was determined and %recovery was calculated.

Synthesis of cetirizine and interacting drugs

Different complexes of cetirizine with NSAIDs (diclofenac sodium, flurbiprofen, ibuprofen, meloxicam, mefenamic acid, tirprofenac acid) were synthesized. Equimolar solution

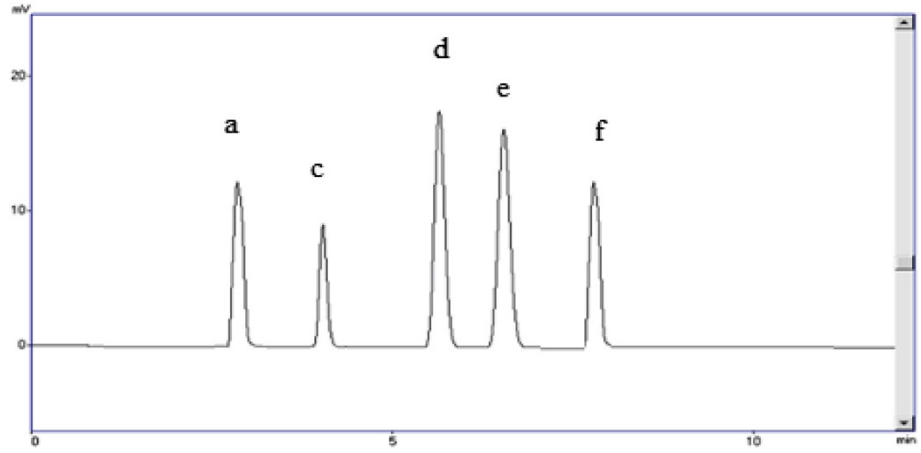


Figure 2 Representative chromatograms showing peaks of (a) cetirizine, (c) tiaprofenac acid, (d) flurbiprofen, (e) ibuprofen, and (f) mefenamic acid.

Table 1 Regression statistics and sensitivity of the proposed method

Drugs	r^2	LOQ (μg ml^{-1})	LOD (μg ml^{-1})
Tiaprofenac acid	0.998	0.47	0.14
Diclofenac sodium	0.999	0.56	0.24
Flurbiprofen	0.999	0.7	0.76
Ibuprofen	0.998	1.78	0.53
Mefenamic acid	0.997	0.81	0.24
Meloxicam	0.997	0.16	0.05

of each NSAIDs solutions were mixed with cetirizine solution and were refluxed for 3 h. They were then filtered and left for drying at room temperature. Melting point and physical characteristics of these complexes were observed.

Spectroscopic studies of complexes

Infrared studies

Cetirizine and its complexes were characterized by FTIR spectrophotometry using the potassium bromide disc method in the region of 400 to 4,000 cm^{-1}. The infrared spectra were recorded as attenuated total reflection (ATR) or smart performer accessory was used for the sample (minimum amount).

^{1}H NMR studies

Proton NMR studies were carried out on a Bruker instrument in deuterated water, methanol, and chloroform using TMS as an internal standard.

Table 2 Accuracy and precision of method

Drugs	Conc. (μg ml^{-1})	%RSD	%recovery
Cetirizine	80	0.02	101.72
	100	0.52	100.64
	120	0.87	99.62
Tiaprofenac acid	80	0.99	100.44
	100	0.67	101.11
	120	0.47	100.84
Diclofenac sodium	80	0.14	99.83
	100	0.34	102.36
	120	0.56	99.98
Flurbiprofen	80	0.6	97.42
	100	0.87	96.35
	120	0.45	98.11
Ibuprofen	80	0.36	103.55
	100	0.74	104.87
	120	0.88	104.12
Mefenamic acid	80	0.12	102.66
	100	0.14	100.22
	120	0.72	103.99
Meloxicam	80	0.41	100.21
	100	0.21	98.77
	120	0.87	98.14

Results and discussion

Method development and validation

User friendly method in active, pharmaceutical preparations and in serum by UV detection (240 nm) was developed for cetirizine and tiaprofenac acid, flurbiprofen, ibuprofen and mefenamic acid eluting out simultaneously at 2.5, 3.8, 4.8, 5.30, and 7.1 min, respectively (Figures 1 and 2). Meloxicam and diclofenac sodium eluting out at 4.4 and 5.30 min were determined separately in the presence of cetirizine. The mobile phase consisted of methanol water at a ratio of 90:10 (pH 3.5) and a flow rate of 1 ml min^{-1}. NSAIDs and cetirizine separated efficiently with well-resolved and symmetrical peaks of all the drugs. Linearity was demonstrated by running pharmaceutical standards at seven concentrations over the range of 50 to 3.12 μg ml^{-1} for two consecutive days. The correlation coefficient in each case was monitored and shown in Table 1.

The mean linear regression equations of tiaprofenac acid, diclofenac sodium, flurbiprofen, ibuprofen, mefenamic acid, and meloxicam were found to be $y = 28{,}166x + 54{,}952$, $y = 19{,}567x + 8{,}726.8$, $y = 12{,}759x + 10{,}846$, $y = 6{,}296.4x - 6{,}507.9$, $y = 11{,}989x + 59{,}294$, and $y = 19{,}498x - 8{,}130$,

Table 3 Intermediate precision of the method

Conc. (μg ml^{-1})	Cetirizine %RSD		Tiaprofenac acid %RSD		Diclofenac sodium %RSD		Flurbiprofen %RSD		Ibuprofen %RSD		Mefenamic acid %RSD		Meloxicam %RSD	
	Intra	Inter	Intra	Inter	Intra	Inter	Intra	Inter	Intra	Inter	Intra	Inter	Intra	Inter
3.12	0.03	2.25	0.53	1.18	0.8	0.97	0.73	1.72	0.16	1.1	0.45	1.12	0.68	1.1
6.25	0.65	0.24	0.85	0.16	0.78	0.36	0.8	1.55	0.31	1.6	0.87	1.2	0.99	1.12
12.5	0.07	0.82	0.33	0.64	0.62	0.47	0.71	0.34	0.56	0.49	0.12	0.99	0.47	1.14
20	0.21	0.335	0.99	1.12	0.47	0.88	0.38	0.66	0.93	1.87	0.06	0.87	0.64	1.21
25	0.599	0.87	0.74	0.85	0.23	0.29	0.36	0.22	0.12	0.55	0.77	0.64	0.74	1.34
30	0.366	0.85	0.79	0.82	0.69	0.72	0.031	0.85	0.4	0.87	0.87	0.97	0.54	1.65

Table 4 %recoveries of proposed method

Conc. (μg ml^{-1})	Cetirizine		Tiaprofenac acid		Diclofenac sodium		Flurbiprofen		Ibuprofen		Mefenamic acid		Meloxicam	
	Rec	Fou	Rec	Fou	Rec	Fou	Rec	Fou	Rec	Fou	Rec	Fou	Rec	Fou
3.12	102.3	3.19	100.7	3.14	99.82	3.11	101.8	3.18	105.3	3.28	102	3.19	107.9	3.37
6.25	100.6	6.28	102.3	6.4	98.22	6.14	98.25	6.14	98.32	6.15	108	6.72	102.4	6.4
12.5	100.8	12.61	103.5	12.93	99.63	12.45	96.36	12.05	96.14	12.02	105	13.15	101.5	12.68
20	99.88	19.98	101.6	20.33	102	20.4	98.48	19.7	101.4	20.27	103	20.69	100.3	20.06
25	97.54	24.39	102.7	25.67	103.8	25.95	97.57	24.39	102.7	25.67	103	25.67	99.78	24.95
30	96.21	28.86	99.55	29.87	95.66	28.7	103.7	31.1	103	30.9	101	30.37	97.65	29.3

Rec, %recovery; Fou, found (μg ml^{-1}).

respectively. The coefficients of variation (C.V.%) was less than 3%, and sensitivity of the method was also evaluated. Precision and repeatability of the method was determined covering the entire linearity range on two different days as shown in Table 2. Precision of the method was expressed in %RSD and accuracy of the method as shown in Table 3 was achieved at three concentration ranges.

Robustness was observed by varying the wavelength in the range of 230 to 240 nm; peak areas and retention time changes were also observed. Results clearly indicated that peak areas were influenced less, up to 2% for all the drugs assayed (Table 4). Moreover, the excellent chromatograms with good peak symmetry, unchanged retention times of the drugs in different pH solutions also proved the robustness of the method.

To evaluate the selectivity of developed method for the analysis of formulated products, cetirizine, tiaprofenac acid, flurbiprofen, ibuprofen, mefenamic acid, and meloxicam tablets were analyzed, and chromatograms were compared with the standard solution of these drugs where no interference of excipients was observed.

The method was found to be applicable for therapeutic purposes as the calculated %recovery (Table 5), for all the drugs were found to be in the range of 92.45% to 107.45% by spiking serum samples at five different concentrations.

In vitro interaction studies

The application of the method involved the determination of cetirizine in the presence of NSAIDs at different pH levels. The results showed the increase and decrease in peak area values of NSAIDs when compared with those of alone standards at the same pH levels. The results clearly indicated the changes in availability values of cetirizine and NSAIDs in the presence of each other. From these, it could be stated that %availabilities of NSAIDs were affected in presence cetirizine and vice versa. For further verification of the results, complexes of cetirizine were synthesized with NSAIDs and characterized (Table 6).

Characterization of complexes

Infrared studies The assignments of IR bands were made by comparing the spectra of the pure drugs and interacting species with the complexes. The major absorption bands for the infrared frequencies and the corresponding assignments are discussed.

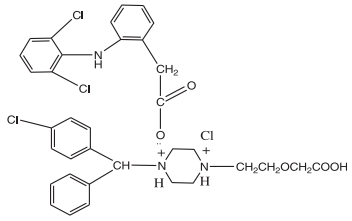
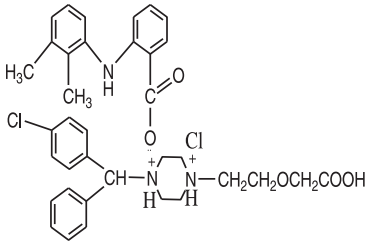
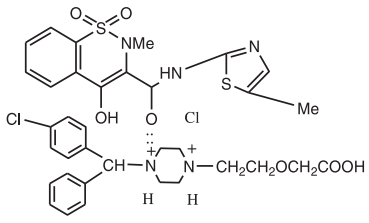
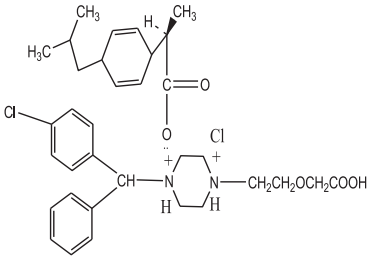
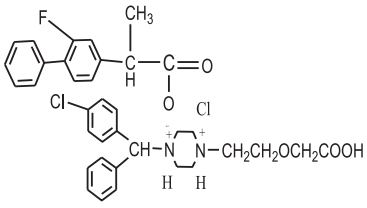
In comparison with the reported spectra of cetirizine and diclofenac sodium (Ihsan et al. 2005; Moffat (2004); Sultana et al. 2011; Fini et al. 2001), the infrared spectrum of the complex showed that NH dimer from 2,700 to 2,400 cm^{-1} disappeared and the quaternary nitrogen atom stretching shifted from 3,070 to 3,040 cm^{-1}. Similarly, the aromatic CH and aliphatic CH_2 absorption band ranges shifted from 3,110 to 3,000 and 2,985.6 to 2,914.2 to 3,165 to 3,024 and 2,925.31 to 2,847.61 cm^{-1}, respectively. A modified band appeared at 1,638.14 cm^{-1} which indicated neutralization of the carboxylic group into a carbonyl group. The δ-bending carbonyl mode shifted from 1,421.57 to 1,200.91 cm^{-1} to 1,409.31 to 1,237.68 cm^{-1}. From the above results, it has been concluded that, weak charge transfer interaction exists between the doubly charged piperazine moiety in cetirizine and diclofenac.

By comparing the cetirizine-flurbiprofen complex from standard (Ihsan et al. 2005; Moffat 2004; Sultana et al. 2011; Paradkar et al. 2003), the quaternary nitrogen atom stretching shifted from 3,070 to 3,043 cm^{-1}. The

Table 5 Analysis of drugs in serum (%recovery)

	Conc. (μg ml^{-1})					
	3.12	6.25	12.5	20	25	30
Cetirizine	100.35	102.66	101.54	96.12	96.12	100.54
Tiaprofenac acid	101.36	100.74	100.77	102.45	92.45	98.72
Diclofenac sodium	100.22	101.99	107.45	102.66	100.29	98.76
Flurbiprofen	103.57	98.65	98.64	103.77	107.45	94.45
Ibuprofen	107.45	97.45	99.12	101.44	101	97.11
Mefenamic acid	105.21	96.21	96.11	108	100.12	99.87
Meloxicam	107.28	100.38	99.21	97.65	96.14	95.46

Table 6 Possible structures and characterizations of complexes

Complex	Chemical structure	Appearance	Solubility	Melting point (°C)
Dic-cet		White crystalline	Soluble in methanol, chloroform, and acetonitrile	108
Mef-cet		Off-white amorphous	Soluble in methanol, chloroform, and acetonitrile	Decompose at 210
Mel-Cet		Off-white amorphous	Soluble in methanol, chloroform, and acetonitrile	230
Ibu-cet		Off-white amorphous	Soluble in methanol, chloroform, and acetonitrile	225
Flu-cet		White amorphous	Soluble in methanol, chloroform, and acetonitrile	110

Dic-cet, diclofenac and cetirizine complex; Mef-cet, mefenamic acid and cetirizine complex; Mel-Cet, meloxicam and cetirizine complex; Ibu-cet, ibuprofen and cetirizine complex; Flu-cet, flurbiprofen and cetirizine complex.

NH dimer of amino acid from 2,700 to 2,400 cm^{-1} appeared as a weak signal with respect to cetirizine. Characteristic broad peaks in the range of 2,500 to 3,500 and 2,920 cm^{-1} due to hydrogen bonding and hydroxyl stretching disappeared whereas carbonyl peak shifted from 1,698 to 1,654 cm^{-1} with diminished intensity.

The complex formed between cetirizine and meloxicam showed quaternary nitrogen atom stretching at 3,070 cm^{-1} and NH dimer of amino acid in the region of 2,700 to 2,400 cm^{-1} completely disappeared with respect to cetirizine. Characteristic peaks of meloxicam at 1,620 and 3,292 cm^{-1} for C=O and secondary –NH or –OH stretching disappeared (Sharma et. al. 2005) while other sets of signals were the same.

In the complex of mefenamic acid, NH dimer of amino acid and the quaternary nitrogen atom stretching from 2,700 to 2,400 cm^{-1} and 3,070 to 3,040 cm^{-1} disappeared. Shifting of some measured peaks was observed with respect to mefenamic acid (Derle et al. 2008); peaks of neutralized entity of the carboxylic acid shifted from 1,610 to 1,554.5 and 1,409.9 to 1,292.2 to 1,654 to 1,587 and 1,442 to 1,270 cm^{-1}.

In comparison with IR spectrum of cetirizine (Moffat 2004; Sultana et al. 2011), ibuprofen (Gavrilin and Pogrebnyak 2001) proved that the quaternary nitrogen atom stretching and NH dimer of amino acid from 2,700 to 2,400 and 3,070 to 3,040 cm^{-1} completely disappeared. Strong absorption bands due to the carboxyl group shifted from 1,708 to 1,768.90 cm^{-1}.

^{1}H NMR studies The ^{1}H NMR spectra of cetirizine confirmed the above results. The de-shielding effect was evident in complexes on the aromatic NH proton as the resonance downfield shifted to δ 7.6 ppm. Thus, this proton appeared in the broad multiplet between δ 6.27 and 7.56 ppm showing 16 aromatic CH protons and the 2 NH^+ protons. A singlet was observed at δ 3.3 ppm for methyl diphenyl CH proton. Triplet at δ 3.71 ppm was obvious due to four protons on the acyclic CH_2 groups adjacent to NH^+ in the piperazine ring and at δ 3.36 ppm was observed for the groups adjacent to the nitrogen hydrochloride entity. Another singlet at δ 3.61 ppm with two protons was shown for the CH_2 in CH_2CH_2O entity. The CH_2 in the CH_2COOH group appeared as a singlet δ 3.71 ppm. A very weak singlet was present at δ 10.8 ppm for the one proton of the carboxylic acid group. In spectra of the mefenamic acid complex, downfield shift was observed for aromatic protons. Triplets at δ 3.16 and 3.51 ppm observed for protons on the acyclic CH_2 groups adjacent to NH^+ in the piperazine ring. Singlet at δ 10.8 ppm was present for one proton of the carboxylic acid group. Similar result was observed for cetirizine-flurbiprofen complex, i.e., singlet of carboxylic group proton remained at δ 10.8 ppm and downfield shift observed for aromatic protons. The protons of piperazine were observed at δ 3.31 to 3.50 ppm. The other properties are shown in Table 6.

Conclusion

The present work described the applicability of simultaneous and validated method for the determination and *in vitro* interactions of cetirizine in the presence of NSAIDs as diclofenac sodium, flurbiprofen, ibuprofen, meloxicam, mefenamic acid, and tirprofenac acid. Furthermore, the method was also found to be applicable in serum and was found useful for therapeutic purposes. The differences in availabilities of cetirizine with NSAIDs at three pH levels clearly indicated the interactions of aforementioned drugs. It was further supported by synthesis of complexes and their characterization. The findings suggested further studies on the co-administration of these two drugs simultaneously in order to know the pharmacokinetic and pharmacodynamic profiles of the drugs whether they create synergistic or negative interactions. Till further research is pursued in this direction, it is highly recommended to have a suitable time lapse between the oral uses of these drugs.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HS designed, coordinated, and carried out experiments in the study. HS and NS drafted the manuscript. MSA supervised the project. All authors read and approved the final manuscript.

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Author details

[1]Research Institute of Pharmaceutical Sciences, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Karachi, Karachi 75270, Pakistan. [2]Department of Chemistry, University of Karachi, Karachi 75270, Pakistan.

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