DETECTION OF LEVOCETIRIZINE INTERACTIONS WITH NSAIDS BY SPECTROPHOTOMETRIC TECHNIQUE

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خلاصہ

Levocetirizine ،antihistamine cetirizine کا ایک levorotatory enantiomer ،hydrochloride کے طور پر دستیاب ہے اور وقفے وقفے سے یا مسلسل الرجک ناک کی سوزش اور گھاس بخار کے انتظام میں مفید ہے۔ Levocetirizine سمیت مختلف دوائیں آپس میں تعامل کر سکتی ہے جو منشیات کے تعامل کے نتیجے میں شدید منفی اثرات کا سبب NSAIDs بن سکتی ہے۔ یووی سپیکٹروسکوپی ایک درست اور قابل اطلاق طریقہ ہے جس میں انشانکن وکر کے مطالعہ کے لیے کم وقت لگتا ہے، دوائیوں کی مقدار کا تعین کیا جاتا ہے اور یہ بھی کہ اکیلے یا کسی اور دوا کی موجودگی میں منشیات کی دستیابی کا اندازہ لگایا جاتا ہے۔ موجودہ مطالعہ میں، لیووسیٹیریزائن، ڈیکلوفیناک سوڈیم، فلوربیپروفین، میفینامک ایسڈ اور میلوکسیکم (حوالہ جات کے معیارات) کو کیلیبریشن کریو اسٹڈیز، لونقانٹیفیکیشن اور آخر میں لیووسیٹیریزائن کے منشیات کے تعامل کے بعد فی صد دستیابی کے لیے ڈیکلوفیناک سوڈیم، فلوربیپروفین، میفینامک ایسڈ، میلوکسیکم اور پی ایچ 4 پر جمع کیے گئے تھے۔ 7.4 اور 9 جس کے نتیجے میں ادویات کی دستیابی میں اضافہ، کمی یا حتیٰ کہ نقصان بھی ہو سکتا ہے۔ پر بڑھ گئی۔ 7.4 pH کی دستیابی میں 0.0% تک کمی کی لیکن levocetirizine اور 9 پر pH 4 سوڈیم نے Diclofenac اور 7.4 pH کی کمی کی لیکن pH4 سوڈیم کی فی صد دستیابی میں 4.9% diclofenac نے levocetirizineدوسری طرف، pH4 تعاملات اور Flurbiprofen9 میں 170% اور 206.57 % کا اضافہ ہوا۔ مختلف بفروں میں لیووسیٹریزائن کے ساتھ میں نمایاں اضافہ ہوا۔ تین بفروں میں فلوربیپروفین کی pHمیں لیووسیٹائیزائن کی دستیابی میں نمایاں اضافہ ہوا لیکن تمام دستیابی میں کمی۔ میفینامک ایسڈ کی وجہ سے پی ایچ 7.4 میں کمی واقع ہوئی لیکن پی ایچ 9 میں اضافہ ہوا۔ تاہم، دونوں پی ایچ کی دستیابی بہت levocetirizine کی موجودگی میں meloxicamمیں میفینامک ایسڈ کی دستیابی میں کمی واقع ہوئی۔ اگرچہ pH 4 زیادہ متاثر نہیں ہوتی لیکن میلوکسیکم کی اور 7.4 میں نمایاں کمی واقع ہوئی تھی۔ اس کے علاوہ، ان تعاملات کے نتیجے میں ہونے والے منفی اثرات کو یقینی بنانے اور ان سے بچنے کے لیے ویوو اسٹڈیز کا انعقاد کیا جانا چاہیے۔ احتیاط کے مشترکہ استعمال سے گریز کیا جانا چاہیے اور ان دوائیوں levocetirizine کے ساتھ NDSAIDsبرتی جانی چاہیے اور کے درمیان وقت کی مدت کو ایڈجسٹ کیا جانا چاہیے۔

Abstract

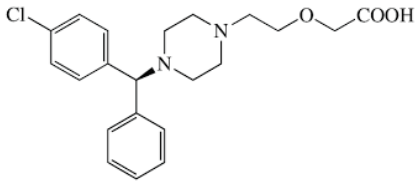
Levocetirizine, a levorotatory enantiomer of anti-histamine cetirizine, available as hydrochloride and useful in the management of intermittent or persistent allergic rhinitis and hay fever. Levocetirizine may interact different drugs including NSAIDswhich may cause severe adverse effects as a result of drug interactions. UV spectroscopy is a precise and applicable method with less time consumption for the calibration curve study, quantification of drugs and also to estimate drug availability alone or in the presence of another drug. In the present study, levocetirizine, diclofenac sodium, flurbiprofen, mefenamic acid and meloxicam (reference standards) were submitted for calibration curve studies, lonequantification and finally percentavailability after drug interaction of levocetirizine with diclofenac sodium, flurbiprofen, mefenamic acid and meloxicam at pH 4, 7.4 and 9 whichmight resulted in increased, decreased or even loss of availability of the drugs. Diclofenac sodium decreased availability of levocetirizine up to 0.0% at pH 4 and 9 but increased at pH 7.4. On the other hand, levocetirizine decreased percent availability of diclofenac sodium by 4.9% pH4 but increased 170% and 206.57 % at pH 7.4 and 9.Flurbiprofen interactions with levocetrizine in different buffers and showed significant rise in availability of levocetirizine in all pH but showed significant decreased availability of flurbiprofin in three buffers. Mefenamic acid caused decreased in pH 7.4 but increased in pH 9. However, availability of mefenamic acid was decreased

in both pH. Although, availability of levocetirizine doesn't seem to be effected a lot in the presence of meloxicam but meloxicam was significantly decreased in pH 4 and 7.4. Further, *in vivo* studies should be conducted to ensure and avoid the adverse effects as result of these interactions. Precaution should be taken and co-administration of levocetirizine with NDSAIDs should be avoided and time duration between these drugs taken should be adjusted.

Keywords: Levocetirizine; NSAIDs; UV spectroscopy; Drug interaction; Co-administration.

Introduction

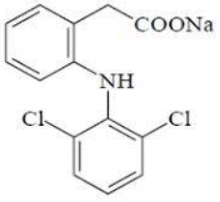
Levocetirizine is an antihistamine is levorotatory enantiomer of anti-histamine cetrizine, available as dihydrochloride and useful in the management of intermittant or persistant allergic rhinitis and hayfever (McCue JD., 1996). Although it is reported that levocetirizine does not produce adverse effects in acute and sub acute administration on cardiac repolirization (Hulhoven *et al.*,2007), memory and attention (Devalia *et al.*,2001) as well as on cognitive and mental performance but skin rashes, fatigue and headache are also rarely reported adverse effects associated with levocetirizine (Gandon *et al.*,2002, Hindmarch *et al.*,2001). Therefore, higher or lower than required quantity of levocetirizine may produce adverse effects and should be monitored (Mehboob *et al.*,2017).



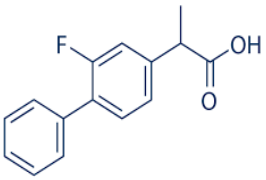
Levocetirizine

Similarly NSAIDs may also cause severe adverse effects and reported to have drug interactions (Moore *et al.*,2015). NSAIDs are heterogenous group of chemical compound which are unrelated and use in acute and chronic inflammation with or without high grade fiver. They consist of approximately 97 diverse which includes aryl acetic aids such as ibuprofen and naproxen, indene derivatives such as indomethacin and sundilac, fenamic acids such as mefenamic acids and diclofenac acids (Leon S., 1994). Different NSAIDs decreased response of different anti-hypertensive drugs such as captopril andhydralazine, increased methotrexate toxicity, decreased diuretic effects of furosemide and decreased renal function of triaterene (Hansten PD, 1992).

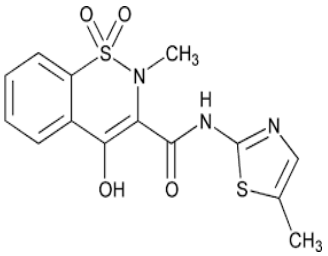
Aspirin, prototype of NSAIDs, interact a number of drugs such as tolbutamide, chlorpropamide, methotrexate, phenytoin, probenecid and valproic acids. Aspirin also reported to enhance intoxication of salicyclates and alcohol (Payan, D. G., and Katzung, B. G, 1995) .Hence, it is very important to monitor the quantity of NSAIDs to avoid harmful effects as a result of drug interaction and to avail benefits of these drugs.



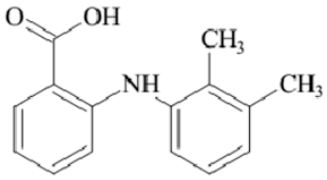
Diclofenac sodium



Flurbiprofen



Meloxicam



Mefenamic acid

UV spectroscopy is a precise and applicable method with less time consumption for the quantification of many marketed drugs such as ciprofloxacin and levofloxacin (Talpur *et al*, 2020). Several UV spectrophotometric methods are also available to estimate levocetirizine availability in products to determine its purity (Van Eeckhaut, A., and Michotte, Y., 2006) to detect drug interactions in-*vitro* studies (Aftab *et al*, 2017).

The object of the present study is to detect interaction between levocetirizine and different NDAIDs (diclofenac sodium, flurbiprofen, mefanamic acids and meloxicam) by UV spectroscopic technique using simultaneous equation. Many patients are observed with co morbidity of inflammation, pain and other clinical symptoms with allergic rhinitis (Mehboob *et al*, 2019, Cingi *et al*, 2017). The current study may be helpful for these patients to avoid any consequence of drug interaction between levocetirizine and mentioned NSAIDs and may appeal health care takers to conduct the same interaction study in-*vivo*.

Materials and Methods

Collection of Reference Standards and Brand Drugs: Levocetirizine, diclofenac sodium, flurbiprofen, mefenamic acid and meloxicam (reference standards) were gifted by different pharmaceutical companies with expiry date not earlier than two years at the time of study but brand drugs were as levocetirizine 5mg, diclofenac sodium 50mg, flurbiprofen 50mg, mefanamic acids 250 mg and meloxicam 7.5 gm purchased from market.

Preparation of Standard Solutions: All reagents used to prepare buffers of pH 1 to 9 were of analytical grade. Primary solution of levocetirizine was prepared by taking 0.04254 gram in one liter flask and dissolved in simulated gastric pH (0.1 N HCl) and volume was made up to produce 1mMole solution. To prepare stock solution of 0.1 mMole, 25 ml of primary solution was diluted in 250ml volumetric flask with the same buffer. Different working solutions of 0.01 to 0.09 mMoles were prepared by dissolving 5, 10, 15, 20, 25, 30, 35, 40 and 45 ml of stock solution in 50 ml volumetric flask into0.1 N HCl solution. Same procedure was adopted to prepare solutions in buffers from pH 1 to 9. Primary, stock and working solutions NSAIDs were also prepared in the same way taking 0.0318 gm of diclofenac sodium, o.0244gm of flurbiprofen, 0.0241gm mefanamic acids and 0.0351gm meloxicam in different bufferes. These solutions were used in calibration curve studies.

Calibration Curve Studies: In order to conduct calibration curve studies, working solution in simulated gastric pH (0.1 N HCl) of levocetirizine of each concentration was scanned in the region of 200 to 700 nm against reagent blank. Maxima was obtained and calibration curve was plotted for levocetirizine This procedure was repeated in the solutions of pH 1 to 9. In the same way, calibration curve studies were carried out for NSAIDs and epsilon were calculated from these observations (Prasad *et al*., 2013).

In Vitro Availability Studies: Before interaction studies, the assay methods for levocetirizine and NSAIDs were established under four reaction environment. For this purpose, four mediums having pH simulated to internal body environment were selected. These solutions were 0.1N hydrochloric acid which is simulated gastric juice, having pH 1 of empty stomach, second was buffer of pH 4 which is also simulated to gastric juice but have pH of filled stomach, third one was buffer of pH 7.4 which is simulated to blood PH and fourth one was buffer of pH 9 which is simulated to intestinal fluid. The *in vitro* availability of levocetrizine was conducted in B.P dissolution apparatus using 1 liter of four mediums pH1, 4, 7.4 and 9 (one by one) maintained at 37°C (human body temperature) at

controlled speed with ±0.5 rpm [215]. Tablet form of each drug was introduced at the start of the experiment and after each 15 minutes aliquot of 5 ml was withdrawn for 120 minutes. the volume of fluid taken was maintained with the same buffer. The samples were scanned and absorbance was observed at respective lambda maxima (Aryan *et al*., 2014).

Drug Interaction Studies: To determine interaction between levocetirizine and diclofenac sodium, first of tablets of both drugs were introduced at zero minute to the dissolution apparatus having buffer of pH 1. After every 15 minutes, aliquots of 5ml were taken for scanning and the volume was maintained with respective fluid. In the same way, tablet of levocetirizine with flurbiprofen, mefanamic acids and meloxicam were introduced in dissolution apparatus one by one and samples were collected. Availabilities of levocetirizine with interacting drugs were calculated after interaction with the help of simultaneous equation.

Results and Discussion

The calibration curve of levocetirizine in the present study was obtained by plotting the absorbance against concentration at pH1, 4, 7.4 and 9. Beer Lambert's law was obeyed at all concentrations as shown in fig. 1. Maxima for levocetirizine was obtained at 231nm at pH1, 4, 7.4 and 9, flurbiprofen at 247nm, meloxicam at 362nm and mefenamic acid at 285nm at pH 4, 7.4 and 9 but diclofena sodium showed maxima at 271nm at pH 4 and 276nm at pH 7.4 and 9. Table1 to 4 showed absorbance of interacting drugs which were diclofenac sodium, flurbiprofen, mefanamic acids and meloxicam at different concentrations.

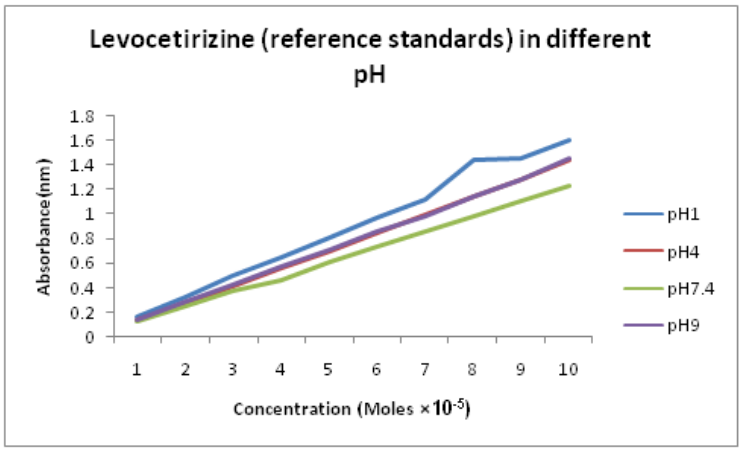


Fig. 1: Levocetrizine absorbance at different pH verses concentration.

Table-1: Absorbance of diclofenac sodium at different pH.

S. No.	concentrations	pH4	pH7.4	pH9
1	0.01	0.8259	0.9017	0.888
2	0.02	0.9232	1.0062	0.9785
3	0.03	1.0183	1.1068	1.0737
4	0.04	1.1162	1.2174	1.1697
5	0.05	1.2072	1.3247	1.18
6	0.06	1.2955	1.432	1.3757
7	0.07	1.3856	1.5369	1.474
8	0.08	1.4775	1.6481	1.5608
9	0.09	1.5725	1.7533	1.673
10	0.1	1.6445	1.8303	1.7594

Table-2: Absorbance of flurbiprofen at different pH.

S. No.	pH4	pH7.4	pH9
1	0.3904	0.3367	0.4448
2	0.4911	0.4424	0.5349
3	0.5967	0.536	0.642
4	0.6942	0.639	0.767
5	0.7911	0.7484	0.8567
6	0.986	0.8472	0.9679
7	0.9915	0.9655	1.0823
8	1.0795	1.0758	1.2194
9	1.1704	1.165	1.2715
10	1.292	1.2617	1.4047

Table-3: absorbance of mefenamic acid at different pH

S. No.	pH7.4	pH9
1	0.084	0.0798
2	0.1434	0.1532
3	0.2195	0.2279
4	0.2904	0.2968
5	0.3612	0.3718
6	0.431	0.4453
7	0.507	0.5223
8	0.577	0.5912
9	0.65	0.6681
10	0.7294	0.7324

Table-4: Absorbance of meloxicam at different pH.

S. No.	pH4	pH7.4	pH9
1	0.1506	0.1329	0.1265
2	0.2922	0.2585	0.2573
3	0.4224	0.3832	0.3945
4	0.5656	0.5031	0.5171
5	0.7081	0.6219	0.6389
6	0.8215	0.7426	0.7908
7	0.9482	0.842	0.95
8	1.0844	0.9482	1.0623
9	1.1926	1.0795	1.223
10	1.295	1.2266	1.35

Availability of levocetirizine (lone) in pH 1, 4, 7.4 and 9 was 106.25%, 108.36%, 128.14% and 115.46%, respectively. Percent availabilities (lone) of interacting drugs (NSAIDs) were also determined which was 100%±20 in different pH. These variations in availabilities may be due to the effects of pH on drug molecules because rest of the conditions were remained the same. Moreover, availability of NDSAIDs was very low in pH 1 due to which availability and interaction studies o levocetirizine with NSAIDs was not performed at this pH. Table 5 showed interacting studies that diclofenac sodium decreased availability of levocetirizine up to 0.0% at two pH which were 4 and 9 but increased more than 1000% at pH 7.4. On the other hand, levocetirizine decreased percent availability of diclofenac sodium by 4.9% t pH 4 but increased 170% and 206.57 % at pH 7.4 and 9.

Table-5: Percent availability (%) of levocetirizine and interacting NSAIDs at different pH after interaction.

S. No.	Drugs	pH 4	pH 7.4	pH 9
1	Levocetirizine with diclofenac sodium	0.00	1118.73	0.00
2	Levocetirizine with flurbiprofen	343.84	716.65	6462.97
3	Levocetirizine with Mefenamic acid	_____	47.55	2917.09
4	Levocetirizine with Meloxicam	116.83	111.89	139.32
5	Diclofenac sodium	4.9	170	206.57
6	Flurbiprofen	7.87	41.81	46.5
7	Mefenamic acid	_____	44.53	3.65
8	Meloxicam	10.62	28.50	91.77

In present work, calibration curve studies, *in vitro* availability of levocetirizine as well as of interacting drugs were done along with interacting studies in pH 1, 4, 7.4 and 9. For this purpose, UV spectroscopic method was used because it is a sensitive and reliable quantitative method for the detection of a chemical or drug alone or in the presence of other chemical using calibration curve study (Prasad *et al*., 2013, Shihab, I. A., and Al-Sabha, N. T. 2020)) and *in vitro* availability of a single or more than one drug can be determined by UV spectroscopic method (Talpur *et al*, 2020). Co-administration of two drugs may lead to the drug interaction resulting increased, decreased or even loss of therapeutic dose. Levocetirizine can also be prescribed and taken simultaneously with other drugs and reported to interact with other drug (Arayne et al., 2010). Levocetirizine was reported to interact with atenolol, losatan potassium and cimetidine (Mehboob *et al*.,2017, (Aftab *et al*, 2017, Mehboob *et al*, 2019).Besides levocetirizine, NSAIDS can also interact with calcium channel blockers (Prasad *et al*., 2013, Aryan *et al*., 2014) and many other drugs (Shihab, I. A., and Al-Sabha, N. T. , 2020, Aryan *et al*., 2010, Sultana *et al*., 2013, Somia *et al*., 2012, Siddiqui *et al*., 2011, Fowler P. D. 1979) such as carbamazepine, losartan and ciprofloxacin was reported (Sultana *et al*., 2013) NSAIDs was also reported to interact with sparfloxacin (Somia *et al*., 2012) and tizanide (Siddiqui *et al*., 2011). In present study, commonly used NSAIDS were used to determine possible interaction with an ant-allergic levocetirizine to avoid resulted adverse effects due to this interaction. Simultaneous equation was used to calculate availability of a levocetirizine and interacting drug present in the same solution without separating them because both drug interfered at each other wavelength which gave the concentration of two drugs simultaneously when measured at their absorption maxima (Aryan *et al*., 2014). Levocetirizine and diclofenac sodium absorb maximum at 231nm and 271nm, respectively. Therefore, if Ca is the concentration of levocetirizine and Cb is the contration of diclofenac sodium then simultaneous equation can be written as following;

$$Ca = \frac{A_{231}.b_2 - A_{271}.b1 \ldots\ldots\ldots (1)}{a_1b_2 - a_2b_1} \quad \text{and}$$

$$Cb = \frac{A_{231}.b_2 - A_{271}.b1 \ldots\ldots\ldots (2)}{a_2b_1 - a_1b_2}$$

Similarly, availabilities of all drugs were calculated. Flurbiprofen interactions with levocetrizine in different buffers and showed significant rise in availability of levocetirizine in all pH but showed significant decreased availability of flurbiprofin in three buffers. Mefenamic acid caused decreased in pH 7.4 but increased in pH 9. However, availability of mefenamic acid was decreased in both pH. Availabilty of levcetirizine in the presence of meloxicam was calculated without simultaneous equation because both of the drugs do not interact at each other

wave length. Although, availability of levocetirizine doesn't seem to be effected a lot in the presence of meloxicam but meloxicam was significantly decreased in pH 4 and 7.4.

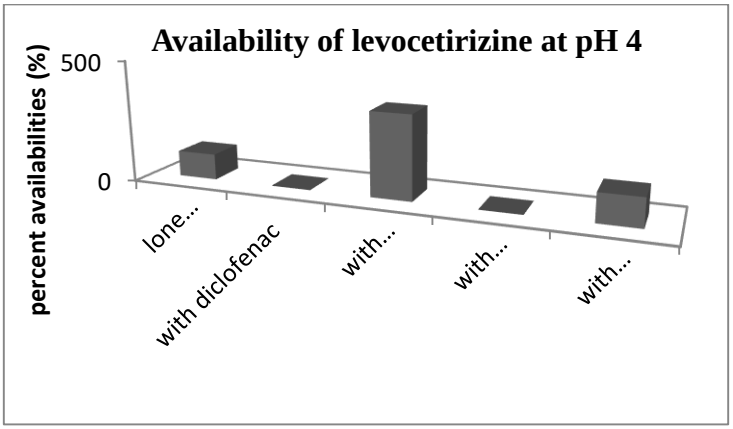


Fig. 2: Availability of levocetrizine in the presence of diclofenac sodium, flurbiprofen, mefenamic acid and meloxicam at pH 4.

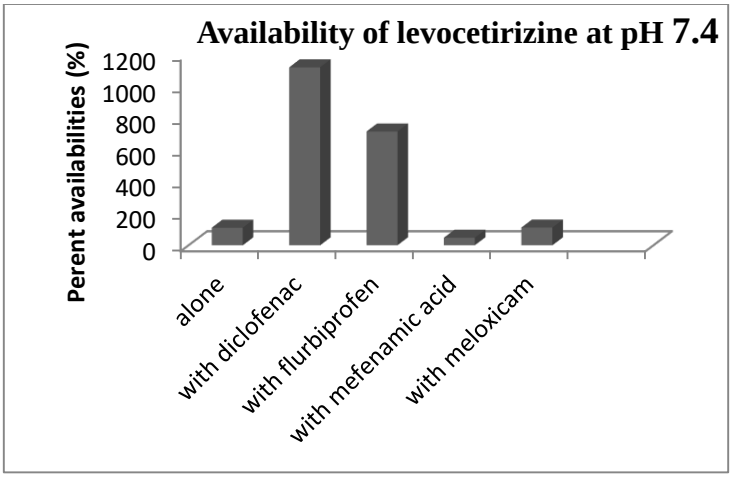


Fig. 3: Availability of levocetrizine in the presence of diclofenac sodium, flurbiprofen, mefenamic acid and meloxicam at pH 7.4

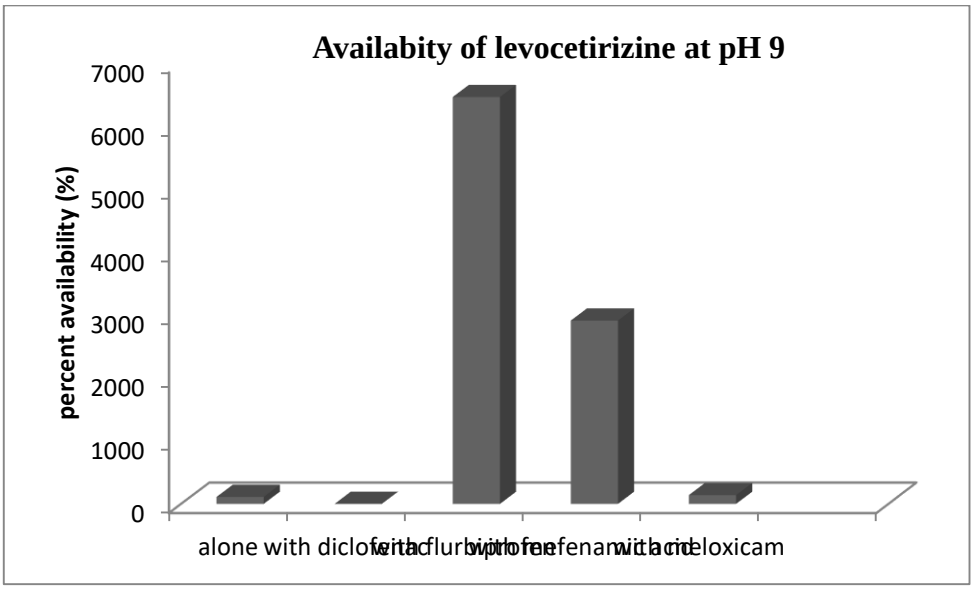


Fig. 4: Availability of levocetrizine in the presence of diclofenac sodium, flurbiprofen, mefenamic acid and meloxicam at pH 9.

Figure 2 to 4 showed availability of levocetirizine before and after interactions with NSAIDs. These results showed significant difference in comparative availability of levocetirizine alone and with NSAIDs in most of the cases. These results focus on the possibility of charge formation, ionization or complex formation between levocetirizine and different NSAIDswhich cause alteration of absorbance within given range of UV spectrum and calculated as significant change in availability of levocetirizine or NSAIDs even up to zero to 1000 times. Therefore, precaution should be taken while prescribing levocetirizine with NSAIDs.

Conclusion

In vitro drug interaction of levocetirizine with diclofenac sodium, flurbiprofen, mefenamic acid and meloxicam at pH 4, 7.4 and 9 resulted in increased, decreased or even loss of availability of the drug. Further, *in vivo* studies should be conducted to ensure and avoid the adverse effects as result of this drug interaction. Precaution should be taken and co-administration of levocetirizine with NDSAIDs should be avoided and time duration between these drugs should be adjusted.

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