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Research Article

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In vitro interaction study of cefixime with diclofenac sodium, flurbiprofen, mefenamic acid and tiaprofenic acid

Tariq Ali* and Omair Anwar Mohiuddin

Dow College of Pharmacy, Dow University of Health Sciences, Karachi, Pakistan

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ABSTRACT

Cefixime is a third generation broad spectrum cephalosporin used against many strains of bacteria. It is widely used in oral formulations as suspension and tablets. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for oral use in many clinical conditions along with cefixime. The aim of the current study was to determine the effect of interaction between cefixime and NSAIDs on their availability in simulated intestinal environment. First the availability studies of standard cefixime and NSAIDs were performed by in vitro dissolution test, in buffer pH 7.4 at 37^{O}C. Later cefixime along with each NSAID was individually subjected to dissolution test in buffer pH 7.4 and availability of each drug was determined using UV-Visible spectrophotometer. The results obtained from the two sets of experiment were compared to determine the change in drug availabilities after interaction and analyzed statistically by t test. The results indicate highly statistically significant interaction between cefixime and diclofenac sodium, where the availability of cefixime was significantly increased and that of diclofenac sodium was significantly decreased. Cefixime was found to greatly decrease the availability of mefenamic acid in the dissolution medium, where as the availability of tiaprofenic acid was increased. No significant interaction could be identified between cefixime and flurbiprofen. Analysis of the overall results clearly indicates that there is a potential for interaction between cefixime and NSAIDs.

Key words: Cefixime, NSAIDs, Diclofenac Sodium, Mefenamic Acid, Flurbiprofen, Tiaprofenic Acid.

INTRODUCTION

Cefixime is an oral third generation cephalosporin synthesized chemically [1]. The Empirical formula of cefixime trihydrate is $C_{16}H_{15}N_5O_7S_2.3H_2O$ and the molecular weight is 507.49 [2]. It is chemically (6*R*, 7R)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid,7-(*Z*)-[*o*-(carboxy methyl)-oxime] trihydrate [3]. Cefixime is freely soluble in methyl alcohol [4, 5], whereas it is not highly soluble in water and has been reported as BCS class II drug, with an oral bioavailability of 40-50% [6]. Cefixime is available only in oral form as suspension and tablets. These preparations are stable at room temperatures for up to two years. Cefixime suspension retains its potency for 14 days after reconstitution [7]. It is used for the treatment of lower respiratory tract infection, urinary tract infection and infections such as pharyngitis, gonorrhea and otitis media [8].

Non Steroidal Anti inflammatory Drugs (NSAIDs) are widely used for the management of pain, fever and inflammation, particularly arthritis [9]. In the current study, four NSAIDs were selected for the interaction study with Cefixime. The NSAIDs include diclofenac sodium, mefenamic acid, flurbiprofen and tiaprofenic acid.

Diclofenac sodium ($C_{14}H_{10}C_{l2}NNaO_2$) has a molecular weight of 318.1 [10]. Diclofenac sodium is completely absorbed after oral administration [11]. It is highly bound to plasma proteins in the blood, mainly albumin (>99.5 %) [12]. It is commonly used for the treatment of osteoarthritis [13, 14] and also used for the treatment for orthopaedic ailments [15].

Flurbiprofen ($C_{15}H_{13}FO_2$) has a molecular weight of 244.3 [16]. It is poorly soluble in water but dissolves in aqueous solution of alkali hydroxide and carbonates [17]. It is used extensively for the treatment of rheumatoid arthritis, morning stiffness [18], osteoarthritis, and ankylosing spondylitis [19].

Mefenamic acid ($C_{15}H_{15}NO_2$) has a molecular weight of 241.9 [20]. It is has very low solubility in water but soluble in alcohol and dilute solutions of alkali hydroxide [21]. This NSAID possesses anti-inflammatory and antipyretic properties [22] and induces analgesia centrally and peripherally [23].

Tiaprofenic acid ($C_{14}H_{12}O_3S$) has a molecular weight of 260.3 [24]. It is poorly soluble in water. [25]. It is rapidly absorbed from gastrointestinal tract and peak plasma levels are observed within 90 minutes of oral dose [26]. Tiaprofenic acid is used as an anti-inflammatory drug in osteoarthritis [27].

Previous studies have reported a few interactions between cephalosporins and NSAIDs. According to one study the plasma concentration and antibacterial activity of cefixime is significantly affected by co-administration with paracetamol [28].

During the treatment of different infections with cefixime, NSAIDs are often prescribed to relieve pain and fever associated with the infection. The aim of the current study was to analyze if the dissolution profile of cefixime is affected when the drug is co-administered with NSAIDs and the change in availabilities of NSAIDs due to simultaneous administration of cefixime. The results attained from the study would be useful in determining if the amount of cefixime available for absorption into systemic circulation is affected by the presence of NSAIDs.

EXPERIMENTAL SECTION

Cefixime and NSAIDs

Cefixime trihydrate was acquired from Barret Hodgson Pakistan Limited, Diclofenac sodium and flurbiprofen from Abbot Laboratories, mefenamic acid from Parke-Davis and tiaprofenic acid from Aventis Pakistan.

Buffer pH 7.4

In order to simulate the intestinal environment, phosphate buffer pH 7.4 was prepared. For the preparation of the buffer 0.6gms of Potassium dihydrogen orthophosphate, 6.4gms of disodium hydrogen orthophosphate and 5.8gms of sodium chloride were dissolved in sufficient de-ionized water to produce 1000 ml of buffer pH 7.4.

Dissolution test apparatus

The dissolution test apparatus was manufactured according to BP 2009 standards as apparatus 1. The top of the basked assembly was modified and replaced by a conical head in order to eliminate air entrapment during dissolution. The dissolution vessel had an internal diameter of 100 mm and a capacity of 1 litre for the dissolution medium. The unwanted vibrations in the dissolution test assembly were reduced by modifying the variable speed motor as mentioned by Sultana et al., 2008 [29]. The rotation speed of the basket was kept at 100 $\pm$ 0.5 rpm throughout the study and the temperature was maintained at 37 $\pm$ 1^0C.

In-vitro availability study of cefixime in buffer pH 7.4

The in-vitro availability of cefixime reference standard was studied in buffer pH 7.4 on BP dissolution apparatus 1. 0.1 gm of cefixime was introduced in 1 litre dissolution medium (Buffer pH 7.4) previously maintained at 37^oC. Aliquots of 5 ml were withdrawn intermittently at 15 minutes time interval for 180 minutes. The aliquots were then diluted and assayed for drug concentration.

In-vitro availability study of NSAIDs in buffer pH 7.4

In-vitro availability of each of the NSAIDs was determined in the same manner as adopted for cefixime. Diclofenac sodium 0.05 gm, flurbiprofen 0.05 gm, mefenamic acid 0.2 gm and tiaprofenic acid 0.2 gm were individually added

in buffer pH 7.4 in separate BP dissolution apparatus. Samples were withdrawn intermittently after every 15 minutes time interval for 180 minutes, which were then diluted and assayed.

Cefixime NSAIDs Interaction study

In-vitro interaction of Cefixime with NSAIDS was carried out in buffer pH 7.4 in similar manner as previously mentioned in *in vitro* availability studies at 37^{o}C. Cefixime 0.1 gm was added in buffer pH 7.4 at time 0 in dissolution medium. Diclofenac sodium 0.05 gm, flurbiprofen 0.05 gm, mefenamic acid 0.2 gm and tiaprofenic acid 0.2 gm were added simultaneously with Cefixime in different set of experiments. Aliquots of 5 ml were withdrawn at every 15 minutes time interval for 180 minutes and assayed.

Spectrophotometric analysis of Cefixime NSAIDs interaction

For the determination of *in vitro* availability of Cefixime and NSAIDs, individually and simultaneously, in buffer pH 7.4, UV visible spectrophotometry was utilized. Absorbance of Cefixime (288 nm), diclofenac sodium (276 nm) flurbiprofen (247 nm) mefenamic acid (285 nm) and tiaprofenic acid (315 nm) was determined using 240-Shimadzu double beam spectrophotometer. The percentage of each drug available in the dissolution medium was then calculated based on absorbance of standards and interacting drugs.

Statistical analysis

The data obtained from the dissolution test and spectrophotometric assay was subjected to paired *t* test to observe significance of the impact of interaction between cefixime and NSAIDs on dissolution profile. Graph Pad software (online) was used for statistical analysis.

RESULTS AND DISCUSSION

The first set of experiments was performed to determine the availability of standard cefixime and NSAIDs in the dissolution medium by *in vitro* dissolution test and the results obtained are tabulated in Table 1. *In vitro* dissolution study of cefixime indicated that 24.74% drug was dissolved in the first 5 minutes and maximum drug dissolved in 45 minutes, where the percentage of drug available was found to be 99.02%. Diclofenac sodium was available 39.41% in the dissolution medium after 5 minutes and maximum amount of drug was available after 45 minutes (98.69%). Flurbiprofen was found to be 40.86% available in dissolution medium after 5 minutes and attained maximum availability after 30 minutes (95.42%). Mefenamic acid was found to be 21.66% available after 5 minutes and attained maximum availability after 45 minutes (84.97%). Tiaprofenic acid was found to be available 21.94% after 5 minutes and maximum availability of the drug was achieved after 45 minutes (99.58%).

The second set of experiments was aimed to determine the impact of interaction between cefixime and NSAIDs on the availability of these drugs in the dissolution medium. For this purpose cefixime was subjected to dissolution test along with each NSAID in different set of experiments. The results obtained from the interaction study are tabulated in Table 2 and 3.

The interaction study between cefixime and diclofenac sodium shows that maximum drug percentage attained in the dissolution medium by cefixime and diclofenac sodium were 115.68% and 65.63% respectively (Table 2). In the interaction study between cefixime and flurbiprofen, maximum availability of cefixime was 97.29% and that of flurbiprofen was 99.37% (Table 2). In the interaction study between cefixime and mefenamic acid, maximum availability of cefixime and mefenamic acid was 99.70% and 39.03% respectively (Table 3). In the interaction study between cefixime and tiaprofenic acid, maximum drug availability of cefixime and tiaprofenic acid was 96.76% and 118.73% respectively (Table 3).

Figure 1 shows comparison of the percentage of standard cefixime and percentage of cefixime available after interaction with NSAIDs. From the figure it is clearly evident that there is a marked difference in the availability of cefixime when interacted with diclofenac sodium. Lesser variation is observed in the amount of available cefixime when subjected to dissolution test with other NSAIDs. Figures 2-5 show the effect on the amount of NSAIDs available in the dissolution medium after interaction with cefixime. There is a clear decrease in the availability of diclofenac sodium (Figure 2) and mefenamic acid (Figure 4) after interaction with cefixime, where as the availability of tiaprofenic acid is increased due to cefixime interaction (Figure 5).

Statistical analysis was performed to determine the significance of the effect of interaction between cefixime and NSAIDs on drug availability. *t* test was performed for this purpose and the results obtained are available in Table 4. The most statistically significant effect ($P < 0.01$) of drug interaction was found in the interaction study of cefixime with diclofenac sodium, where there is a significant change in the availability of both drugs after interaction. The effect of cefixime interaction with flurbiprofen on the availability of both drugs was found to be significant ($P< 0.05$). Mefenamic acid was not found to affect the availability of cefixime significantly, but the effect of cefixime on the availability of mefenamic acid was found to be highly significant. The effect of cefixime on the availability of tiaprofenic acid was also found to be extremely significant.

The overall results obtained from the study clearly indicate a potential for interaction between cefixime and NSAIDs. The most notable effect is observed when cefixime and diclofenac sodium were co-subjected to dissolution test, this resulted in an increased availability of cefixime and decreased availability of diclofenac sodium. The greatest effect of interaction with cefixime was observed on mefenamic acid, where the availability of mefenamic acid was decreased by more than half as compared to the availability of standard mefenamic acid.

Cefixime and NSAIDs are commonly prescribed together during the treatment of certain infections. There is clear evidence to indicate that the availability of these drugs for absorption into systemic circulation is affected when administered together. Further studies would be useful to confirm that similar interaction occurs *in vivo* as well.

Table 1: *In vitro* availability of cefixime and NSAID reference standards in buffer pH 7.4 at 37°C

Time (mins)	Percentage of drug available (%)				
	Cefixime	Diclofenac sodium	Flurbiprofen	Mefenamic acid	Tiaprofenic acid
5	24.74	39.41	40.86	21.66	21.94
15	96.20	97.43	91.65	76.72	96.96
30	98.61	96.49	95.42	81.56	98.77
45	99.02	98.69	94.92	84.97	99.58
60	96.15	98.38	94.42	82.63	98.47
75	98.87	96.17	93.29	83.16	95.33
90	98.28	96.49	93.03	83.28	97.46
105	93.58	98.38	93.41	82.31	98.66
120	98.63	98.38	89.01	83.28	95.33
135	96.38	96.17	92.53	82.69	96.95
150	97.99	93.33	93.03	84.16	94.01
165	95.98	96.49	92.03	82.22	94.42
180	93.95	96.80	91.80	84.28	92.90

Table 2: *In vitro* availability after cefixime interaction with diclofenac sodium and flurbiprofen in buffer pH 7.4 at 37°C

Time (min)	Cefixime/diclofenac interaction		Cefixime/flurbiprofen interaction	
	Cefixime availability (%)	Diclofenac availability (%)	Cefixime availability (%)	Flurbiprofen availability (%)
5	24.50	37.14	23.84	35.97
15	89.60	60.07	89.98	98.33
30	110.45	55.93	96.49	98.42
45	115.28	55.21	96.38	99.27
60	115.68	60.70	97.08	99.32
75	115.38	64.50	97.18	99.18
90	111.93	57.33	96.87	99.37
105	112.14	60.66	97.29	96.38
120	113.06	65.32	94.58	97.75
135	112.35	66.01	94.93	96.56
150	112.69	66.04	94.67	97.28
165	111.94	65.63	95.38	95.44
180	111.73	65.55	93.99	95.13

Table 3: *In vitro* availability after cefixime interaction with mefenamic acid and tiaprofenic acid in buffer pH 7.4 at 37ºC

Time (min)	Cefixime/Mefenamic acid interaction		Cefixime/Tiaprofenic acid interaction	
	Cefixime availability (%)	Mefenamic acid availability (%)	Cefixime availability (%)	Tiaprofenic acid availability (%)
5	19.32	22.52	33.46	21.26
15	85.45	33.92	96.76	111.72
30	96.75	34.12	94.05	115.37
45	97.17	34.93	91.34	118.73
60	98.87	39.03	91.19	114.79
75	94.81	34.98	92.72	118.22
90	98.99	35.15	91.93	113.35
105	99.31	35.32	89.00	116.84
120	99.70	34.65	91.31	111.11
135	98.28	35.12	93.88	111.11
150	99.29	35.18	93.88	111.11
165	99.40	35.18	93.88	111.72
180	99.40	35.21	94.05	111.18

Table 4: Results obtained from *t* test performed on the data in table 1-3

	Cefixime/ Diclofenac sodium	Cefixime/ Flurbiprofen	Cefixime/ Mefenamic acid	Cefixime/ Tiaprofenic acid
Effect on cefixime	HS	S	NS	S
Effect on NSAIDs	HS	S	HS	HS

HS (highly significant) = P < 0.01, S (Significant) = P < 0.05, NS (Not significant) = P > 0.05.

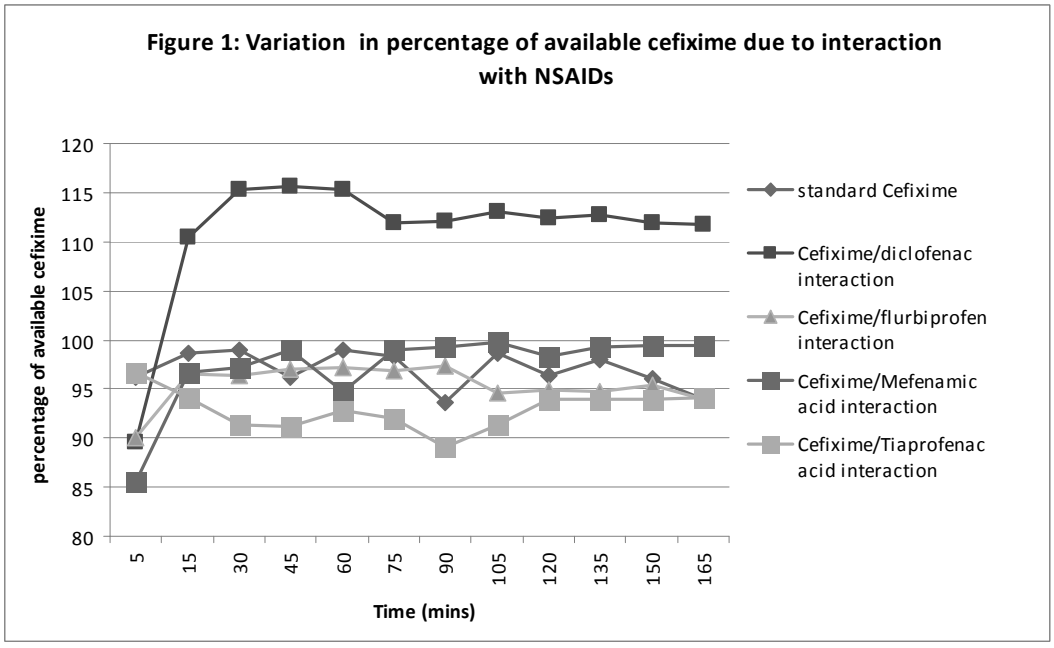


Figure 2: Variation in percentage of available diclofenac sodium due to interaction with ceifixme

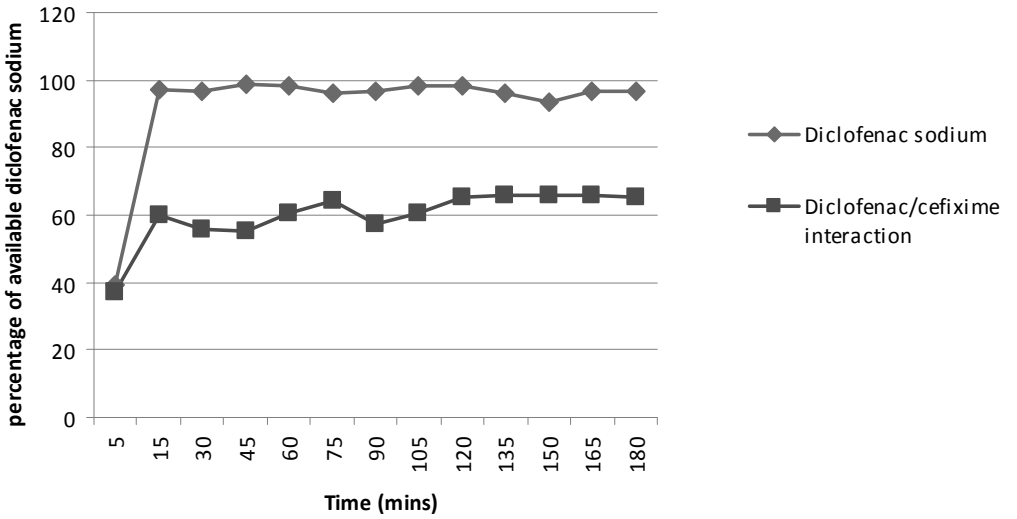
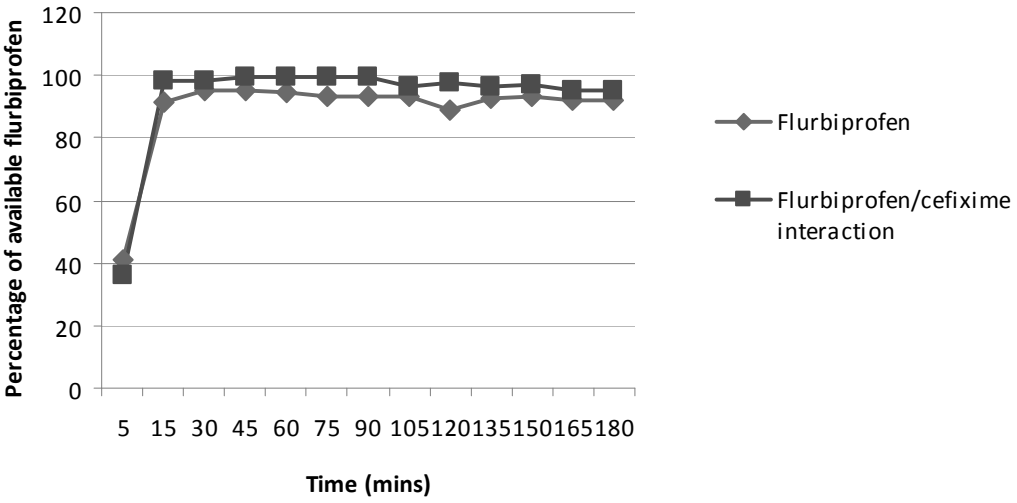
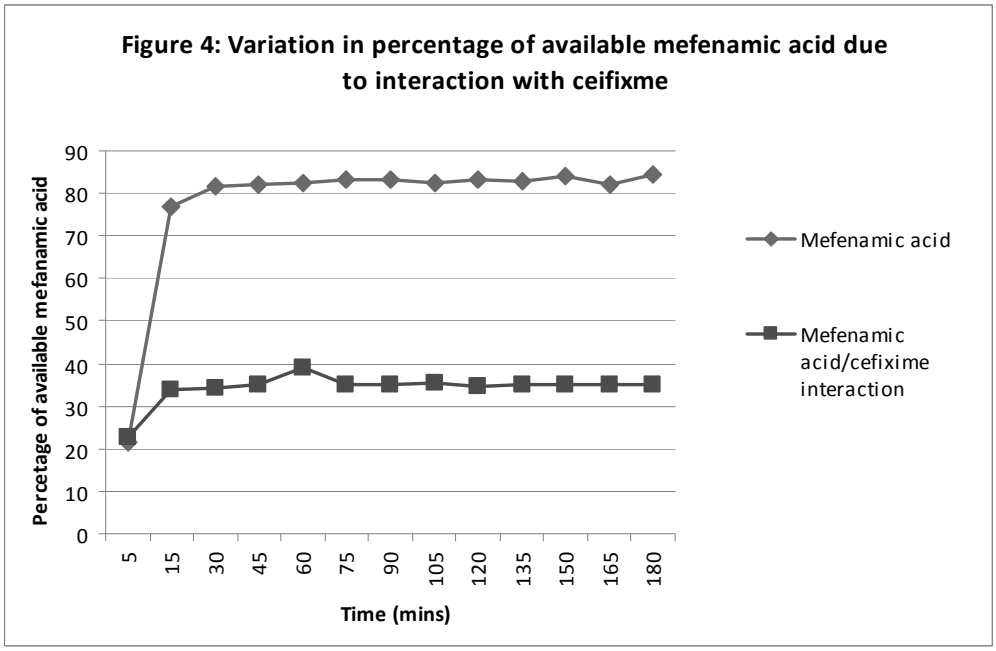
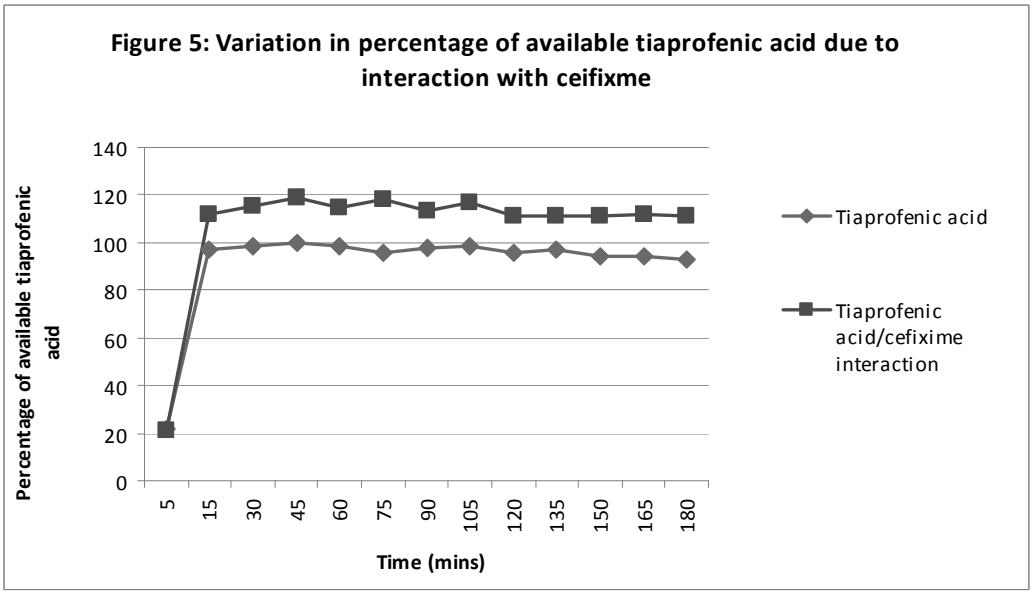


Figure 3: Variation in percentage of available flurbiprofen due to interaction with ceifixme







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