

# *In vitro* and *In vivo* Interaction of Ketorolac Tromethamine and Cefixime Trihydrate

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(Received: February 7, 2023; Accepted: June 12, 2023; Published (web): July 7, 2023)

**ABSTRACT:** Drug-drug interaction, a major impediment towards safe and effective pharmacotherapy, often leads to adverse outcome or therapeutic failure if not properly identified. The present study employed a number of *in vitro* and *in vivo* methods to conduct a thorough investigation of the interaction potential between ketorolac tromethamine (nonsteroidal anti-inflammatory drug) and cefixime trihydrate (beta-lactam antibiotic). UV-Visible spectrophotometry, FTIR and DSC were carried out to analyze the interaction of ketorolac and cefixime *in vitro*. UV-visible spectrophotometric study at different pH showed hyperchromic shift and blue shift (hypsochromic shift) in the mixture of the studied drugs compared to ketorolac alone. In contrast, only hyperchromic shift was found in the mixture when compared to cefixime alone. In DSC study, the melting endotherm of ketorolac tromethamine shifted from 169.62°C to 149.99°C in the 1:1 mixture. Again, the FTIR spectrum showed that in 1:1 mixture, the lactam (C=O) band of cefixime trihydrate shifted from 1771.68 cm<sup>-1</sup> to 1718.63 cm<sup>-1</sup>, the amide carbonyl band (-CONH) moved from 1669.45 cm<sup>-1</sup> to 1616.4 cm<sup>-1</sup> and the -OH band moved from 3296.46 cm<sup>-1</sup> to 3397.72 cm<sup>-1</sup> which might be indicative of interaction between these two drugs. The *in vivo* study in rat model was designed to determine whether cefixime has any significant impact on the analgesic activity of ketorolac. *In vitro* antimicrobial effect was also performed to evaluate the effect of ketorolac on cefixime. The findings from these study suggested that neither ketorolac nor cefixime imparted any deleterious impact on the biological property of each other which might indicate that co-administration of ketorolac and cefixime are therapeutically effective and safe.

**Key words:** Ketorolac tromethamine, cefixime trihydrate, drug-drug interaction.

## INTRODUCTION

With the emergence of resistance and the complexity of disease patterns, multidrug treatment approach has gained much interest as it offers potentiation of therapeutic activity, improvement in symptomatic and pharmacokinetic profile, slow development of resistance and improved patient compliance. The dark side of this multidrug approach is the emergence of undesirable drug interactions.<sup>1</sup>

Drug-drug interaction (DDI) refers to a clinically meaningful alteration of one drug as a result of the co-administration of another drug. Drugs may interact with each other often by two or more mechanisms acting in concert which may lead to a spectrum of harmful consequences involving loss of therapeutic efficacy or unexpeted increase in pharmacological activity of a drug. This may cause deterioration of patient's clinical status resulting in additional treatment and prolonged hospital stay.<sup>2</sup> A literature survey in medline and embase database from 1990 to 2006 showed that DDIs were held

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Dhaka Univ. J. Pharm. Sci. 22(2): 137-146, 2023 (December)  
DOI: <https://doi.org/10.3329/dujps.v22i2.67405>

responsible for 0.054% of the emergency department visit and 0.12% of the rehospitalizations.<sup>3</sup>

Choice of a non-interacting alternative can be a useful move to avert these undesirable consequences. If no alternative is available, it is possible to administer the interacting drugs together by taking appropriate cautionary measure.<sup>4</sup> Other approaches include- adjustment of dosages of interacting drugs, changes in the molecular pattern, blockade of the reactive sites of the molecule etc.<sup>5</sup> The study of drug-drug interactions is an important field of research particularly in drug design and drug development which can provide a comprehensive understanding of any possible interaction between the drugs under study and the ways of overcoming such interactions.

This study was conducted with a broad spectrum third generation cephalosporin, cefixime trihydrate, and a nonsteroidal anti-inflammatory agent, ketorolac tromethamin. Cefixime trihydrate exerts its bactericidal action by disrupting the synthesis of peptidoglycan layer of bacterial cell wall and has now become standard therapy for treating respiratory and urinary tract infections. Its usage can be extended to cover gonorrhea, biliary infections and soft tissue infections.<sup>6</sup> These infectious diseases are associated with symptoms of pain and inflammation which can be alleviated by the co-administration of ketorolac tromethamine as it offers relief from pain and inflammation by blocking prostaglandin synthesis. Ketorolac is a promising alternative to opioid and to other nonsteroidal analgesics in relieving moderate to severe post-surgical pain.<sup>7</sup>

Cefixime and ketorolac are often co-prescribed in the hospital settings and in a variety of clinical conditions. So, a potential for drug interaction and complex formation between these two drugs may occur which may lead to a change in the pharmacokinetic and pharmacodynamic properties of the individual drugs. Consequently, this may affect the bio-availabilities and therapeutic outcomes of these agents. The prime objective of this study was to utilize a variety of *in vitro* and *in vivo* screening procedures to investigate whether there was any potential interaction between Ketorolac

tromethamine and cefixime trihydrate which might considerably hamper the biological properties of the drugs under study and thus hinder the therapeutic outcome in a devastating manner.

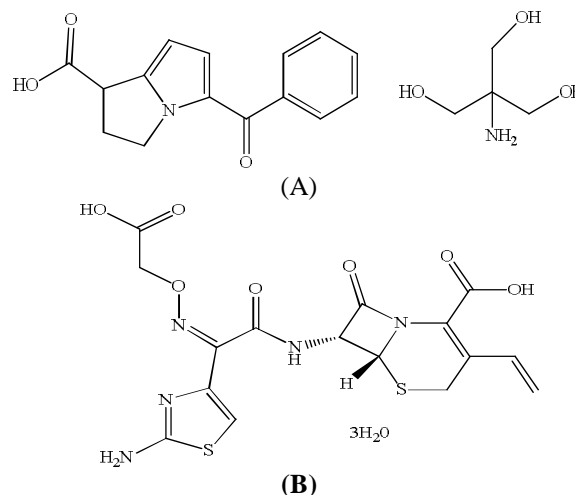


Figure 1, Chemical structure of Ketorolac tromethamine (A) and Cefixime trihydrate (B).

## MATERIALS AND METHODS

Ketorolac tromethamine and cefixime trihydrate were collected from Beximco Pharmaceuticals Ltd. and ACI Pharmaceuticals Ltd., Bangladesh as kind gifts. Di-sodium hydrogen phosphate and sodium dihydrogen phosphate were purchased from Sigma-Aldrich, Germany and Scharlab S.L., Spain, respectively. Analytical grade of methanol and ethanol were purchased from authentic source of Merck, Germany. All other reagents used were of analytical grade and were purchased from authentic source of local suppliers.

### *In vitro* interaction of cefixime trihydrate and ketorolac tromethamine by UV-Vis spectroscopy

**Preparation of buffer solution.** Buffer solutions having pH of 3.4, 7.4 and 8.4 were prepared following methods described earlier.<sup>8</sup>

**Preparation of ketorolac tromethamine (2 x 10<sup>-5</sup> M ) solution.** 100 ml of 0.001 M solution of ketorolac was prepared as a stock solution by taking 0.0376 g of Ketorolac (Mol. Wt. 376.409 g/mol) in a 100 ml volumetric flask and by dissolving in ethanol. The volume was adjusted up to the mark by an

appropriate buffer. The solution is then diluted to 25-fold using the same solvent.

**Preparation of cefixime trihydrate ( $2 \times 10^{-5}$  M) solution.** 100 ml of 0.001M solution of Cefixime was prepared as a stock solution by taking 0.0507 g of cefixime (Mol. Wt. 507.50 g/mol) in a 100 ml volumetric flask and by dissolving in ethanol. The volume was adjusted up to the mark by a buffer of appropriate pH. The solution is then diluted to 25-fold using the same solvent. Then the ketorolac tromethamine ( $2 \times 10^{-5}$  M) solution, cefixime trihydrate  $2 \times 10^{-5}$  M solution and the mixture prepared from them at a ratio of 1:1 and 1:20 were evaluated by UV-visible spectrophotometer (UV-1800, Shimadzu, Japan) at a wavelength range from 200 to 400 nm.

**In vitro interaction of cefixime trihydrate and ketorolac tromethamine by DSC.** 50mg/ml solution of ketorolac tromethamine and 50mg/ml solution of cefixime trihydrate were prepared in two separate beakers using ethanol as solvent. Then the solutions were mixed at ratio of 1:1 and 1:20 and subjected to evaporate the solvent for drying. 2 to 5 mg of each dried sample were taken into an aluminium pan and sealed properly. Then the aluminum pan was placed inside the differential scanning calorimeter (DSC 60 WS, Shimadzu, Japan) and the thermogram was taken. The temperature range for DSC runs for the mixture and the individual drugs were  $30^{\circ}\text{C}$  to  $250^{\circ}\text{C}$ . During the experiment the flow rate of nitrogen gas was 50ml/min and the temperature was raised by  $10^{\circ}\text{C}/\text{min}$ .

**In vitro interaction of cefixime trihydrate and ketorolac tromethamine by FTIR.** The samples prepared as in DSC evaluation were also used for FT-IR evaluation by KBr disc method both for pure drug and their mixtures. Each sample (50 mg) was gently triturated with 1 g of KBr powder followed by formation of disc by pressing powders at pressure of 80 KN using a pressure gauge. The disc was placed in the sample holder of fourier transform infrared spectrophotometer (FTIR 8400, Shimadzu, Japan) and scanned from  $4000\text{ cm}^{-1}$  to  $400\text{ cm}^{-1}$ .

#### **In vivo interaction of cefixime trihydrate and ketorolac tromethamine**

**Evaluation of analgesic activity by acetic acid-induced writhing test.** Screening of peripheral analgesic activity was done by utilizing acetic acid induced writhing method.<sup>9</sup> Rats were divided into four groups (five rats in each group). At the beginning, rats of group number 1, 2, 3 and 4 were fed with cefixime trihydrate (25 mg/kg) or ketorolac tromethamine (10 mg/kg) or both. After 30 minutes of administration of test drugs, the rats were subjected to painful stimuli as they were offered intraperitoneal injection of 0.9% acetic acid (10 ml/kg). The counting of number of writhes (muscular contraction ions) was done for across a duration of 20 minutes, initiating just after injecting acetic acid and number of writhing was counted. Writhing movements consisting of abdominal muscle contraction, drawing up of hind limbs toward abdominal walls, stretching of hind limbs, and periodic arching of the body were counted for twenty minutes before calculating percent inhibition of writhes. Percentage of writhes, one of the parameters to exhibit analgesic activity was determined using equation depicted below<sup>10</sup>:

$$\left\{ \frac{\text{Control mean} - \text{Treatment mean}}{\text{Control mean}} \right\} \times 100$$

Where, *Control mean* = The mean number of the writhing of acetic acid control group

*Treatment mean* = The mean number of the writhing of each test group.

#### **In vitro interaction of cefixime trihydrate and ketorolac tromethamine**

**Antimicrobial activity by optical density test.** Evaluation of interaction of antimicrobial activity of cefixime was performed by growing the *E. coli* with the antibiotics in presence or absence of ketorolac and determining the optical density as described before.<sup>11,12</sup> *E. coli* was cultured in liquid broth medium and incubated at  $37^{\circ}\text{C}$  with shaking for 16 hours. 10 mg of the mixed dried sample (prepared for

SEM) was dissolved in 100 ml of sterile nutrient broth medium to make 50 µg/ml of cefixime and 50 µg/ml of ketorolac. In the same way 50 µg/ml of cefixime solution in nutrient broth was prepared. After 16 hours 0.5 ml of the of the broth culture was mixed with sterile 15 ml of nutrient broth medium in presenc of 50 µg/ml of cefixime 50 µg/ml of ketorolac. After proper mixing in sterile environment, all the test tubes were incubated 37°C with shaking for 24 hours. The optical density of the culture medium as determined at 600 nm using UV-VIS spectrophotometer. Each experiment was performed three times.

## RESULTS AND DISCUSSION

**Analysis of interaction between ketorolac tromethamine and cefixime trihydrate by UV-Vis spectrophotometry.** The UV absorbance values of  $2 \times 10^{-5}$  M cefixime and  $2 \times 10^{-5}$  M ketorolac, their 1:1 and 1:20 mixtures were measured within the range of 200–400 nm (Figure-2). Each of the drugs under study showed absorption in definite UV-VIS region. The molecular species of cefixime trihydrate when mixed with ketorolac tromethamine, showed some changes in absorption characteristics of these drug molecules including some shifts in the absorption maxima. These alterations in the spectral pattern may be regarded as an indication of primary interaction between these two drugs.

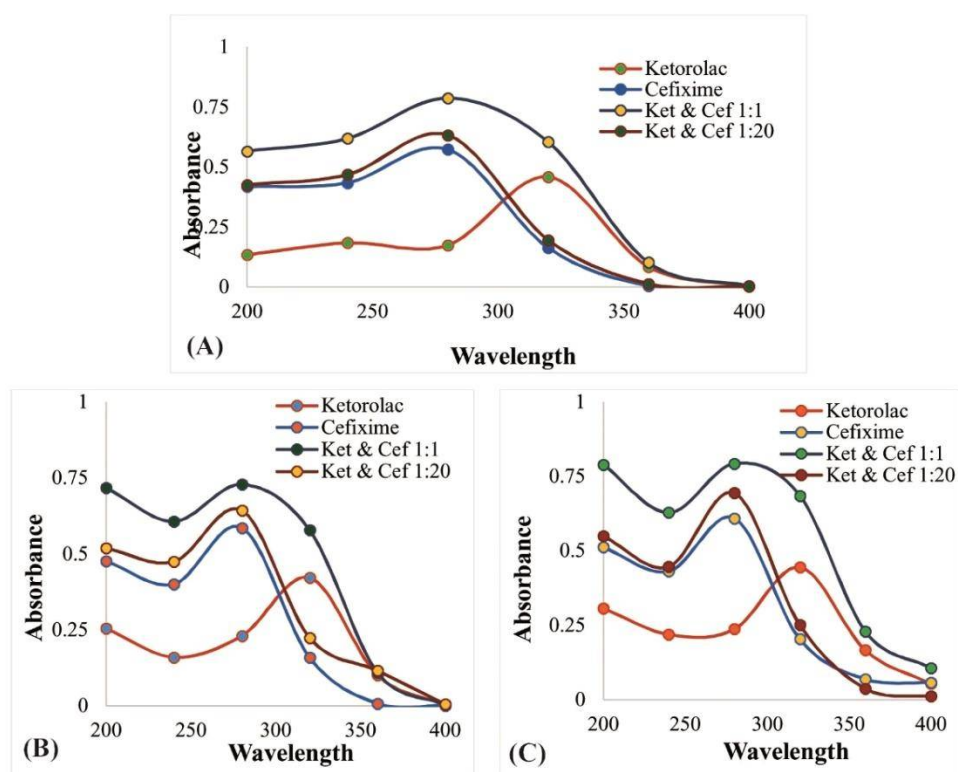


Figure 2. UV spectra of ketorolac, cefixime and mixture of cefixime and ketorolac at pH 3.4 (A), pH 7.4 (B) and at pH 8.4 (C).

The absorbance values of ketorolac at 320 nm was judged against the absorbance values of the mixture of ketorolac and cefixime. The absorbance values of 1:1 mixture of ketorolac and cefixime were

found to be increased by 31.66%, 36.97% and 53.93% in buffers of pH 3.4, pH 7.4 and pH 8.4, respectively. So, in 1:1 mixture a hyperchromic shift was observed. On the other hand, the absorbance

values of 1:20 mixture of ketorolac and cefixime were found to be decreased by 57.42%, 46.92% and 43.59% compared to ketorolac in buffers of pH 3.4, pH 7.4 and pH 8.4 respectively table-1. A blue shift (hypsochromic shift) was also found in both 1:1 and 1:20 mixtures compared to ketorolac alone (Figure 2).

When the absorption spectra of both 1:1 and 1:20 mixture was compared to that of cefixime at its  $\lambda_{\max}$

at 280 nm, a hyperchromic shift was observed (Figure 2). The absorbance values of 1:1 mixture of ketorolac and cefixime were found to be increased by 37.41%, 24.4% and 30.21% in buffers of pH 3.4, pH 7.4 and pH 8.4, respectively. While, in 1:20 mixture, the absorbance values were increased by 24.37%, 9.72% and 13.96% in buffers of pH 3.4, pH 7.4 and pH 8.4, respectively (Table 2).

**Table 1. Percentage of absorbance change in the mixture compared to ketorolac at its  $\lambda_{\max}$ .**

Buffer	Absorbance of ketorolac at 320 nm	Absorbance of mixture (Ket:Cef=1:1) at 320 nm	% Increase of absorbance (1:1)	Absorbance of mixture (Ket:Cef=1:20) at 320 nm	% Increase of absorbance (1:20)
pH 3.4	0.458	0.603	31.66%	0.195	57.42%
pH 7.4	0.422	0.578	36.97%	0.224	46.92%
pH 8.4	0.445	0.685	53.93%	0.251	43.59%

**Table 2. Percentage of absorbance change in the mixture compared to cefixime at its  $\lambda_{\max}$ .**

Buffer	Absorbance of cefixime at 280 nm	Absorbance of mixture (Ket:Cef=1:1) at 280 nm	% Increase of absorbance (1:1)	Absorbance of mixture (Ket:Cef=1:20) at 280 nm	% Increase of absorbance (1:20)
pH 3.4	0.572	0.786	37.41%	0.632	24.37%
pH 7.4	0.586	0.729	24.4%	0.643	9.72%
pH 8.4	0.609	0.793	30.21%	0.694	13.96%

Both the ketorolac tromethamine and cefixime trihydrate have several sites of hydroxyl, amino and carbonyl groups that might be involved in the formation of intramolecular hydrogen bonds. These intramolecular hydrogen bonds might have been disrupted in solution due to solute-solvent interaction. When these two molecules are mixed in solution, new intermolecular hydrogen bonds might have been formed due to presence of polar functional groups. Association between ketorolac and cefixime might have occurred by electrostatic interaction or by the formation of charge transfer complex (donor-acceptor type). Thus the association between them might have decreased the force constant for the central bonds and caused the intensity to rise leading to the hyperchromic effect.<sup>13</sup> Both of these molecules have a carbonyl group in their structures. The increased association involving non-bonded electrons ( $n \rightarrow \pi^*$  transition) of the carbonyl group might have

increased the energy of excitation. This greater energy might be responsible for the blue shift (hypsochromic shift) in the mixture compared to ketorolac alone.<sup>14</sup> Based on the result, it can be concluded that the 1:1 and 1:20 mixtures of cefixime and ketorolac showed noticeable changes in the absorption intensities than the individual drugs which might be viewed as a pointer for communication among these drugs.

**DSC thermogram interpretation of the studied drugs.** DSC thermogram of ketorolac tromethamine showed a long, sharp, characteristic endothermic peak at 169.62°C ( $\Delta H$  -131.63 J/g) corresponding to the melting point of ketorolac tromethamine. Cefixime is a trihydrate molecule that showed a broad endothermic peak at 149.99°C representing the evaporation of water molecule from the crystal lattice and an exothermic event was observed at 184.32°C which could be related to a

crystalline state transition. DSC curves of the physical mixture have evidenced significant shifts of the endotherm compared to the endotherm of the pure drugs. The melting point peak of ketorolac shifted from 169.62°C to 149.99°C in the 1:1 mixture (Figure-3). These shifts suggested the presence of drug-drug interaction, which was also evidenced by changes in the values of heat of fusion of the drugs. In a 1:1 weight/weight ratio mixture, the  $\Delta H$  values

of the melting peaks must be half of the pure drug.<sup>15</sup> But the  $\Delta H$  value of the melting peak in 1:1 mixture of the studied drugs was -31.26 J/g which was less than one-fourth of the pure ketorolac tromethamine where the  $\Delta H$  value was found to be -131.63 J/g. On the other hand, in 1:20 mixture, the endothermic peak of cefixime trihydrate shifted from 122.28°C and became very broad. No significant shift was observed for the exothermic peak.

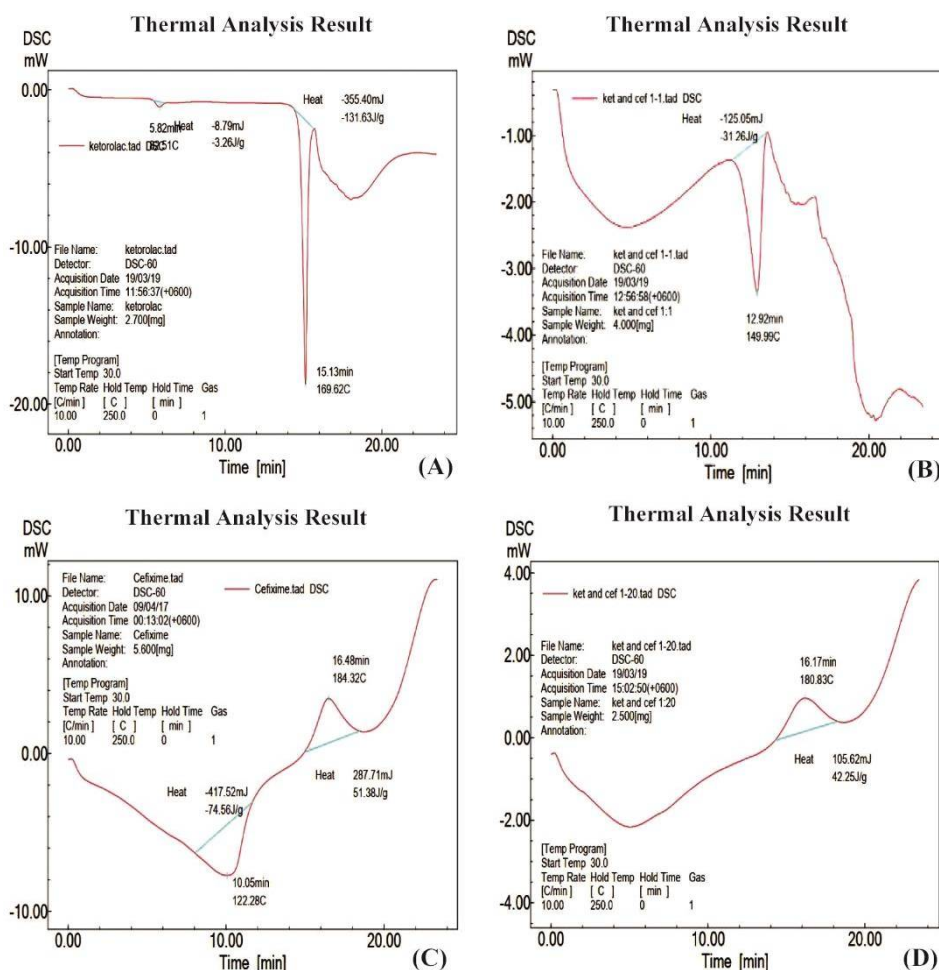


Figure 3. DSC thermogram of ketorolac tromethamine (A), cefixime trihydrate (B), their 1:1 mixture (C) and 1:20 mixture (D).

**FTIR spectroscopic investigation of the studied drugs.** The FTIR imaging of the present work has been undergone to determine the functional groups in the studied drugs (ketorolac and cefixime) and in their 1:1 and 1:20 mixtures (Figure 4). The absorption frequency corresponding to important

functional groups of ketorolac tromethamine and cefixime trihydrate have been shown in table 3. The FTIR spectra of ketorolac-cefixime complexes were judged against those of the pure drugs.

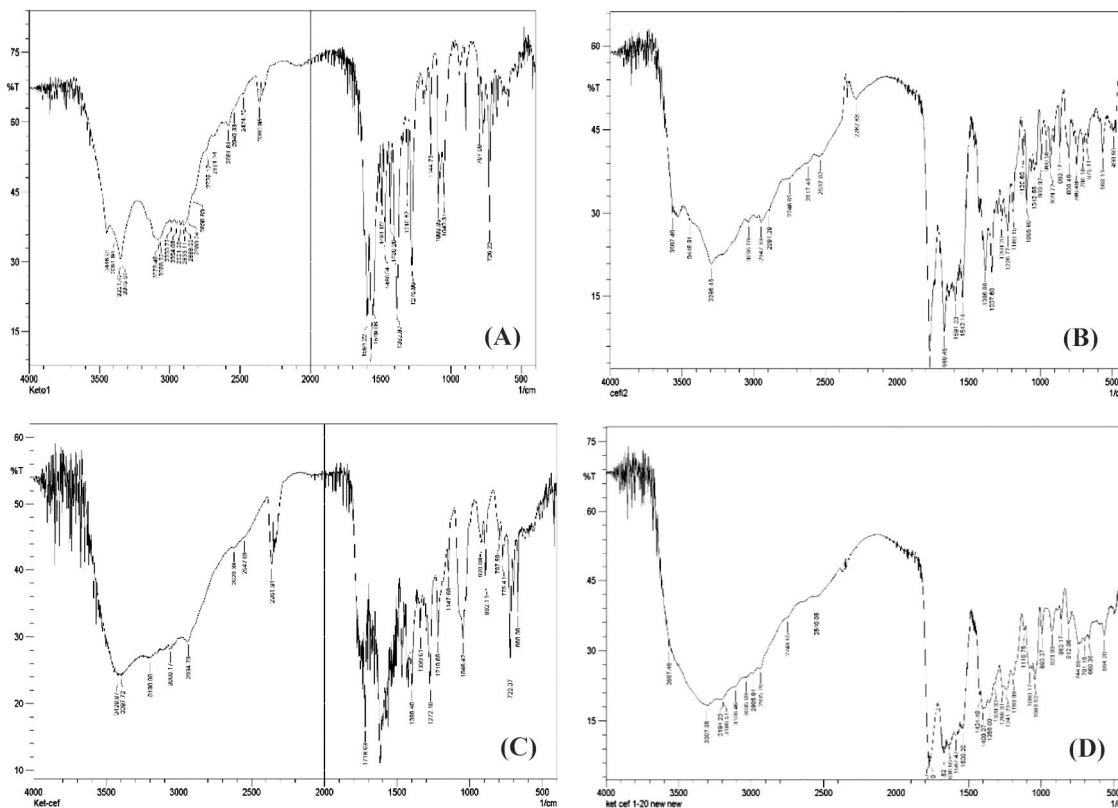


Figure 4. FTIR spectra of ketorolac tromethamine (A), Cefixime trihydrate (B), Their 1:1 mixture (C) and 1:20 mixture (D).

The  $\beta$ -lactam band observed at  $1771.68\text{ cm}^{-1}$  in pure cefixime trihydrate got shifted to  $1718.63\text{ cm}^{-1}$  in the 1:1 mixture of ketorolac and cefixime whereas the peak at  $1669.45\text{ cm}^{-1}$  due to carbamate C=O stretching in pure drug moved to  $1616.4\text{ cm}^{-1}$  in the 1:1 mixture indicating interaction. Again, the  $\text{-NH}_2$  stretching absorption peak of cefixime trihydrate found at  $3296.46\text{ cm}^{-1}$  shifted to  $3397.72\text{ cm}^{-1}$  in the 1:1 mixture of ketorolac and cefixime. In contrast, in the 1:20 mixture of ketorolac and cefixime, there was

no significant change in the position of  $\beta$ -lactam band, carbamate C=O stretching, and  $\text{-NH}_2$  stretching absorption frequency. But the peaks are somewhat broader than cefixime trihydrate alone.

From the observation, it was revealed that, the absorption frequency corresponding to several functional groups of pure cefixime trihydrate shifted towards lower wave number in the 1:1 mixture of this two molecules (ketorolac and cefixime) which might

Table 3. Absorption frequency ( $\text{cm}^{-1}$ ) of different functional groups of ketorolac tromethamine and cefixime trihydrate in FTIR spectra.

Ketorolac tromethamine		Cefixime trihydrate	
Functional group	Frequency ( $\text{cm}^{-1}$ )	Functional group	Frequency ( $\text{cm}^{-1}$ )
Amine (N-H) stretching	3446.31	Primary amine ( $\text{-NH}_2$ ) stretching	3296.46
-OH stretching	3346.61	$\beta$ -lactam (C=O stretching)	1771.68
Carboxylic acid (C=O stretching)	1594.22	The carbamate C=O stretching	1669.45
Diaryl ketone (C=O stretching)	1566.25	C=N stretching	1591.33

indicate alteration of the force constant or the bond strength resulting from the interaction between ketorolac and cefixime. However, 1:20 mixture didn't show any noticeable shift in the position of the spectrum. The shift in peak position might be due to changes in the hybridization state or electronic distribution of the molecular bonds. It also might result from a change in vibrational frequency which could come about either because of change in force constant or change in bond strength which further evidenced the presence of interactive systems.<sup>16</sup> When two molecules interact with each other, the frequency of only those vibrational mode changes which participate in the interaction.<sup>17</sup> The shifting of frequency towards lower wavenumber was observed for the lactam band, amide carbonyl band and the exchangeable protons (-NH<sub>2</sub>) of cefixime molecule. These groups might be involved in intermolecular hydrogen bonding with the functional groups present in the ketorolac molecule. Association between ketorolac and cefixime might have occurred due to charge transfer from a donor to an acceptor present within these molecules leading to a decrease in the force constant or bond strength causing the frequency to be shifted towards lower wavenumber.

**Analgesic activity screening by acetic acid induced writhing method.** Acetic acid induced writhing method is a model which is extensively used for the evaluation of analgesic drugs.<sup>18</sup> Acetic acid induces the writhing reflexes through the stimulation of chemo sensitive nociceptors.<sup>19</sup> Administration of 0.6% glacial acetic acid through intraperitoneal injection has been reported to enhance the biosynthesis of prostaglandin E<sub>2</sub> that brings about abdominal writhing in animals.<sup>20</sup>

For the evaluation of analgesic activity, the effect of cefixime, ketorolac and their mixture on acetic acid induced rats were presented in table-4. It was evident that treatment with only cefixime trihydrate couldn't decrease abdominal writhing count in rats whereas, ketorolac tromethamine at a dose of 10 mg/kg demonstrated significant inhibition of writhing responses. Again, the mixture of cefixime and ketorolac at the same dose displayed almost same extent of inhibition as the ketorolac alone. This was indicative of the fact that cefixime was unable to interfere with the pharmacological action of ketorolac.

**Table 4. Evaluation of the analgesic activity of cefixime and ketorolac by acetic acid writhing test.**

Group	Group specification	Number of writhing	% Inhibition
1	Control (Saline)	86	N/A
2	Acetic acid + Cefixime trihydrate	85.20	0.93%
3	Acetic acid + Ketorolac tromethamine	46.20*	46.27%
4	Acetic acid + Cefixime trihydrate+ Ketorolac tromethamine	47.60*	44.65%

\* Indicates (p<0.05) statistical significance when compared to control.

**Assessment of antimicrobial activity by optical density method.** In the antimicrobial study by optical density method, the control exhibited sufficient growth of *E. coli* and *S. aureus* as indicated by the optical density value,  $2.18 \pm 0.05$  and  $2.31 \pm 0.08$ , respectively. The optical density value was significantly diminished by cefixime in the presence or absence of ketorolac (Table 5) while ketorolac demonstrated no antibacterial effect. The result

suggested that interaction between cefixime and ketorolac was unable to interfere with the antibacterial effect of cefixime.

In our *in vitro* study, ketorolac and cefixime displayed potential interaction while the *in vitro* antimicrobial effect of cefixime was not interfered by ketorolac. The possible reason might be the breakdown of the complex while penetrating the outer membrane of the bacteria leaving free cefixime



**Table 5. Optical density of the drugs alone and in mixture.**

Group	Optical density	
	<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>
Media without bacteria	0	0
Media with bacteria (Control)	2.18 ± 0.05	2.31 ± 0.08
Cefixime (50 µg/ml)	0.27 ± 0.07*	0.28 ± 0.05*
Ketorolac (50 µg/ml)	2.23 ± 0.08	2.43 ± 0.09
Cefixime(50 µg/ml) + Ketorolac (50µg/ml)	0.31 ± 0.04*	0.31 ± 0.03*
Amoxicilline (30 µg/ml)	0.15 ± 0.04*	0.17 ± 0.02*

\* Indicates (p<0.05) statistical significance when compared to control.

to permeate through the outer membrane and bind with PBP receptors there by showcasing its pharmacological action without any interference posed by ketorolac.<sup>21</sup> On the other hand, *in vivo* analgesic study revealed that analgesic effect of ketorolac in rat model was uninterrupted in complex form with the cefixime. The interacting complex of ketorolac and cefixime might have dissociated due to the variations of physiological factors inside gastrointestinal tract. The complex formed between ketorolac and cefixime might not be strong enough to cross the physiological barriers and might have broken down before reaching systemic circulation and the site of action. As a consequence, the pharmacological activities of either drugs were uninterrupted. Again the potent functional groups of each drug that are crucial for receptor binding and pharmacological activities might not have participated in the complex formation between two drugs. As a consequence, even though the complex has been formed, the functional groups from both drugs remained free to interact with the respective receptors and to display pharmacological activities. As neither ketorolac nor cefixime showed any significant deleterious effect on the biological activity of each other, we may conclude that concurrent administration of ketorolac and cefixime may be safe and effective.

## CONCLUSION

Drug-drug interaction is a very common phenomena now a days that may potentially hamper the therapeutic outcomes of the interacting drugs.

Therefore, understanding drug-drug interaction is extremely important to offer appropriate multidrug therapies. The aspire of the present study was to investigate the *in vitro* interaction between two commonly prescribed medications- ketorolac tromethamine and cefixime trihydrate by using reliable UV-Vis spectroscopy, DSC and FTIR methods and to employ *in vivo* methods to determine whether the interaction is clinically meaningful, thus to infer about the combination therapy. Though the obtained results from *in vitro* study revealed a clear indication of the interaction between ketorolac tromethamine and cefixime trihydrate, findings from *in vivo* analysis told a different tale demonstrating no significant alteration of the pharmacological profile of the studied drugs when they are given simultaneously. Therefore, it may be concluded that concurrent administration of these two drugs may not bring about unintended effects. However, this was a preliminary study performed to analyze the physical and chemical interactions between ketorolac and cefixime and to investigate whether these drugs hamper each other biological activity in a significant manner. Further investigation is required to measure the strength of the interacting complex and to have insight on the mechanisms that are responsible for breakdown of the complex. To gain more idea about the interaction profile between the studied drugs, it is also necessary to determine whether ketorolac or cefixime cause any significant alteration of the pharmacokinetic parameters (i.e. protein binding, metabolism) of each other.

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