Assessment of Drug-Drug Interactions between Ketorolac Tromethamine and Rabeprazole Sodium: An *in vitro* Approach

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ABSTRACT: Ketorolac tromethamine and rabeprazole sodium are drugs that are used frequently and certain clinical conditions warrant their concomitant use. Ketorolac has been known to engage in physical interactions with several drugs that share certain structural features with rabeprazole and therefore their degree of chemical association was assayed. 0.05 mM solutions of the two drugs were prepared with buffer solutions of pH 1.4, 2.4 and 7.4. Conductometric titrations were conducted for each. The two drugs were observed to form chemical associations with each other on a nearly 1:1 basis in each buffer solution. Sharp breaks in all cases were recorded. Ketorolac has previously been reported to form intermolecular interactions with drug moieties containing amine groups with non-engaging lone-pair electrons, and this was postulated to be the mechanism of action for the interaction. As certain clinical conditions can warrant the concomitant use of these two drugs, additional care must be taken in such cases to avoid unfavorable clinical complications.

Key words: Ketorolac tromethamine, rabeprazole sodium, drug-drug interaction, conductometric method.

INTRODUCTION

The concomitant use of therapeutically interconnected and non-interconnected drugs is a frequent and efficacious clinical practice; especially in cases of severe ailments or multiple prevalent conditions where simultaneous attention to multitudinous symptoms is required. This brings the challenge of drug-drug interactions (DDI), an adverse clinical event in which one or more drug molecules adversely interact with co-administered drug species, affecting the pharmacokinetic and/or pharmaco-kinetic properties of either or both. DDIs can be broadly classified into three categories: Pharmacodynamic DDIs, Pharmacokinetic DDIs and Physicochemical DDIs.[1,2] A major mode of action for both these types DDIs is physical interactions between concomitant drug moieties. For example, drugs such as acetylsalicylic acid, warfarin, sulfonamides, furosemide and phenytoin can be bound through physical interactions with colestipol and cholestyramine, affecting their absorption and causing consequent DDI.[3] Complex formation can be another mechanism through which absorption-related DDI is observed. Metal ion-containing drugs form complexes with tetracyclines, penicillamines and fluoroquinolones which consequently reduce their absorption.[4-6]

A thorough understanding of drug interactions can facilitate early recognition and prevention of adverse consequences. The most comprehensive approach to clinically significant drug interactions involves combining knowledge of their mechanisms with an awareness of high-risk patients and the identification of drugs with a narrow therapeutic index. Issues arising from drug interactions can often be addressed by modifying molecular patterns, blocking reactive sites, adjusting dosage regimens or

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avoiding the concurrent use of interacting drugs. However, before taking any steps to manage potential interaction problems, it is essential to understand the nature of the interaction. For newly introduced drugs, understanding potential interactions before clinical use is crucial. Similarly interaction studies for conventionally used drugs are important to identify any previously undetected issues.[7]

Ketorolac is a potent non-steroidal analgesic that has moderate anti-inflammatory activity. It is administered via the oral, intramuscular, intravenous and topical route.[8] In fact, the drug was the first approved NSAID for the IV route.[9] Clinical studies of the drug have indicated that, for management of moderate to severe postoperative pain, it demonstrates a single-dose efficacy greater than that of morphine, pethidine and pentazocine.[8] However, long-term exposure to the drug has been found to correlate to an enhanced risk of renal insufficiency in chronic kidney diseases and gastrointestinal bleeding.[10] In addition, the drug has been reported to partake in diverse chemical interactions with several other drug moieties.[11-13]

Rabeprazole sodium is an organic sodium salt containing rabeprazole which acts as a proton pump inhibitor, providing anti-ulcer activity. It inhibits gastric acid secretion by selective and irreversible binding with the H^+-K^+ ATPase (hydrogen-potassium adenosine triphosphatase) enzyme system located on the parietal cell secretory surface.[14] Rabeprazole is used widely for gastroesophageal reflux disease (GERD), especially in the management of atypical GERD conditions such as GERD-associated asthma and chest-pain, GERD-induced dysphagia and for the treatment of Barrett's esophagus.[15] Clinical conditions as such these may warrant the concomitant use of this drug with ketorolac, a drug known for forming molecular interactions with certain drug moieties. However, interactions between these drugs (if any) have not been explored to a sufficient degree. This study aims to address this gap in knowledge and access whether ketorolac tromethamine and rabeprazole sodium interact with each other in appropriate buffer systems that mimic different physiological conditions.

MATERIALS AND METHODS

Preparation of buffer solution. Buffer solutions of pH 1.4, 2.4 and 7.4 were prepared for the conduction of this experiment. For the preparation of the pH 1.4 buffer, 250 ml of 0.2 M H_3PO_4 was mixed thoroughly with an equal volume of 0.1 M KH_2PO_4. The volume of this mixture was adjusted to 1000 ml through the addition of demineralized water, and the pH was adjusted to 1.4 through the addition of 85% phosphoric acid. The pH 2.4 buffer was prepared in a similar fashion, albeit 40 ml of 0.2 M H_3PO_4 and 140 ml of 0.1 M KH_2PO_4 was taken. Volume and pH were adjusted as mentioned previously. The pH 7.4 buffer solution was prepared by mixing 235 ml of 0.01 M K_2HPO_4 to 65 ml of 0.01 M KH_2PO_4, the volume of which was adjusted to 1000 ml with demineralized water.[16,17]

Preparation of stock solution. 2.56 mg of ketorolac tromethamine and 38.24 mg of rabeprazole sodium were individually dissolved in the prepared buffer solutions to prepare 0.1 mM stock solution of ketorolac and rabeprazole sodium, respectively. The volume was adjusted to 100 ml. The ultrasonicator apparatus was utilized at room temperature for 10 min for proper dissolution. The stock solution was 2X diluted by adding the respective buffer solutions to obtain the desired concentrations of 0.05 mm.[18]

Conductometric titrations. Complex formation was assayed through the help of conductometric titrations. For the titrations, 40 ml of the 0.05 mm stock solutions (ketorolac tromethamine and rabeprazole sodium) of various pH values were taken individually in 100 ml beakers. For each case, the opposing stock solutions (rabeprazole sodium for ketorolac tromethamine and vice versa) of the same pH value were taken in the burettes as titrants. Conductance values of the solution in the beaker were recorded in microsiemens (μS) as the titrants were added gradually to the beakers. The beakers were maintained on a magnetic stirrer with constant stirring to ensure homogeneity of the mixtures at all times. The conductance values were plotted against

the ml of titrant added and sharp breaks in the plotted graphs (if any) were recorded.[19-20]

RESULTS AND DISCUSSION

Titration of pH 1.4 solutions. During the titration of the ketorolac tromethamine stock solution using rabeprazole sodium as titrant in pH 1.4 buffer, a sharp break was observed after addition of 45 ml of the titrant. The reverse titration, i.e. employing rabeprazole sodium as analyte and ketorolac tromethamine as titrant, displayed a sharp break after 43 ml of the titrant. In both cases, the analytes and titrants can be said to interact on an almost 1:1 ratio; analyte: titrant = 1:1.125 in case of the first and 1:1.075 in case of the second. Prior to and following the abrupt point of change, the graph followed specific patterns, indicating a set moment of change taking place in the mixture under observation. The data from these titrations have been displayed in figures 1 and 2.

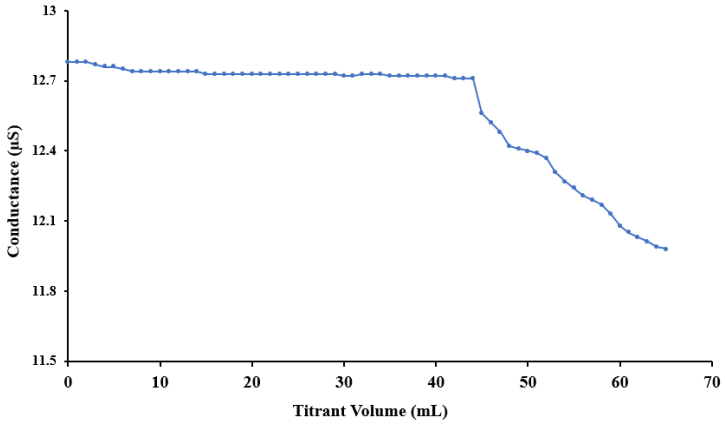

Figure 1. Titration of ketorolac tromethamine using rabeprazole sodium as titrant in pH 1.4 buffer.

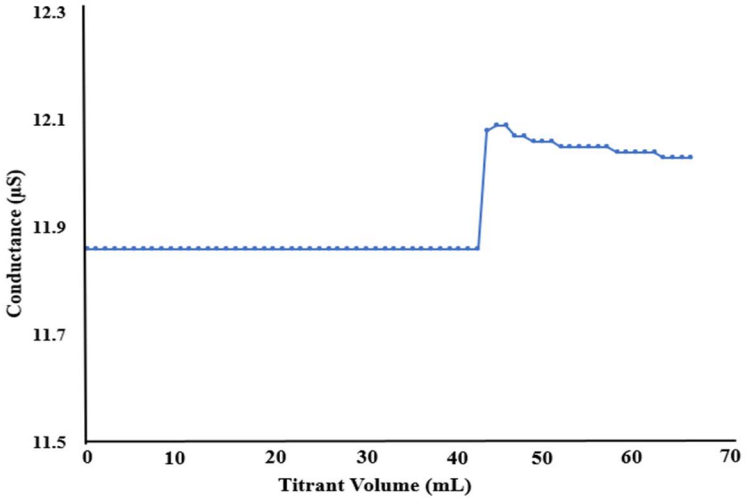

Figure 2. Titration of rabeprazole sodium using ketorolac tromethamine as titrant in pH 1.4 buffer.

Titration of pH 2.4 solutions. The pH 2.4 drug-buffer solution titrations followed a similar pattern to their lower pH counterpart. During the titration of the ketorolac tromethamine stock solution using rabeprazole sodium as titrant, a sharp break was observed after addition of 40 ml of the titrant,

displaying a perfect 1:1 analyte-titrant interaction. In case of the reverse titration, a sharp break was recorded after adding 43 ml of the titrant, surmounting to an analyte-titrant ratio of 1:1.075. As observed previously, the end points of the titrations were marked by singular sharp, abrupt changes and the graphs prior to and following these particular points showed homogeneity in their development. The data from these titrations have been displayed in figures 3 and 4.

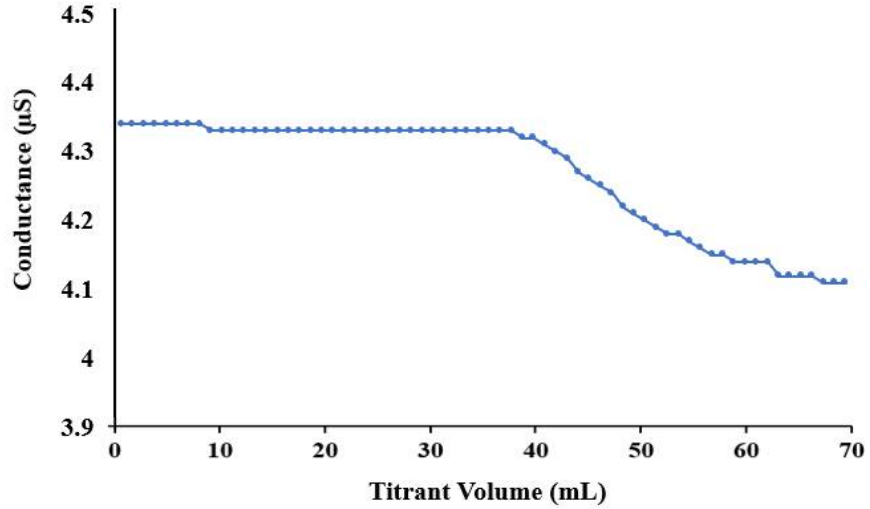

Figure 3. Titration of ketorolac tromethamine using rabeprazole sodium as titrant in pH 2.4 buffer.

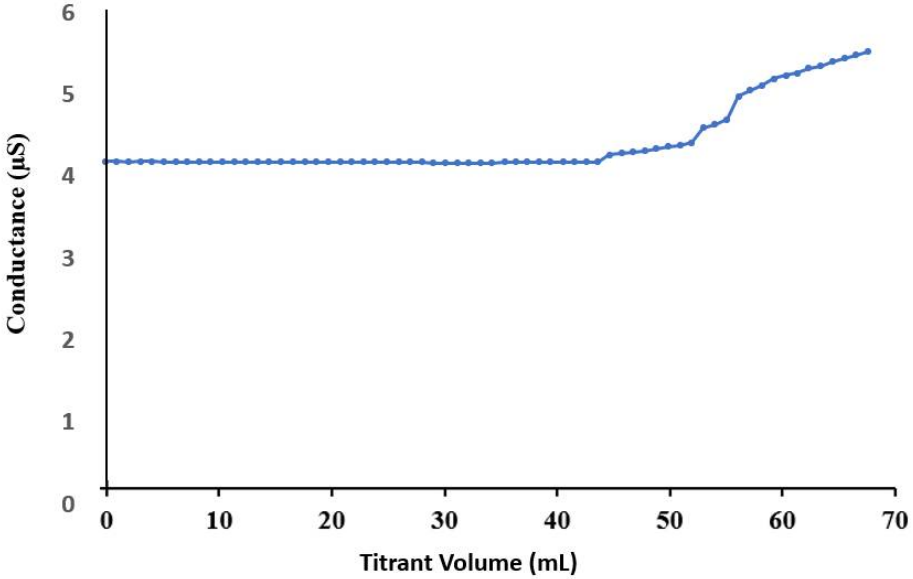

Figure 4. Titration of rabeprazole sodium using ketorolac tromethamine as titrant in pH 2.4 buffer.

Titration of the pH 7.4 Solutions. The raised pH of the pH 7.4 drug-buffer solutions did not affect the end result of the titrations and similarities with the lower-pH correlatives were recorded in the experiments. Parallel to our previous observations, the titration of the ketorolac tromethamine stock solution using rabeprazole sodium as titrant yielded a sharp break which was observed after adding 38 ml of the titrant, indicating a 1:0.95 analyte-titrant interaction. For the reverse titration, a sharp break was recorded after 37 ml of the titrant was added, effecting an analyte-titrant ratio of 1:0.925. Similar to

the lower-pH iterations, singular sharp, abrupt changes marked titration end-points and homogeneity in graph-development was recorded prior to and following the break points. The data from these titrations have been displayed in figures 5 and 6.

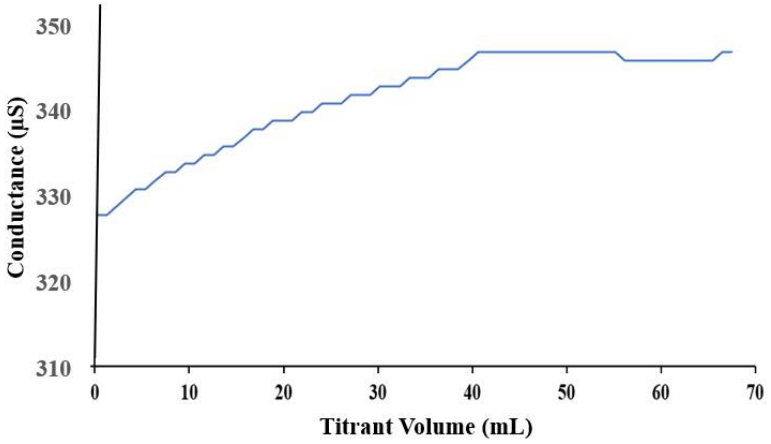

Figure 5. Titration of ketorolac tromethamine using rabeprazole sodium as titrant in pH 7.4 buffer.

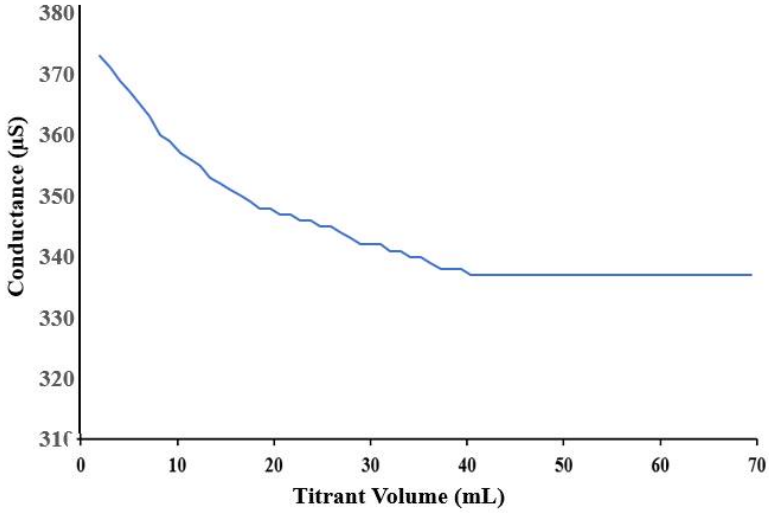

Figure 6. Titration of rabeprazole sodium using ketorolac tromethamine as titrant in pH 7.4 buffer.

Several other studies have reported ketorolac tromethamine to partake in diverse chemical interactions with several other drug moieties. Knapp *et.al.*[11] communicated that ketorolac tromethamine formed visually observable, hazy conjugates in the presence of promethazine hydrochloride, nalbuphine hydrochloride, hydroxyzine hydrochloride and edisylate salt of prochlorperazine in sterile water. The formation of these conjugates suggests potential intermolecular interactions between ketorolac tromethamine and drug moieties containing free lone-pair electron-holding amine groups. Interestingly, the same study found no observable interactions between ketorolac tromethamine and diazepam in the same media.[11] This suggests that the nitrogen lone pair in diazepam might be delocalized due to resonance, thereby reducing its propensity to participate in intermolecular interactions with ketorolac

tromethamine. Further supporting this observation, Hahm *et al.*[19] reported the incompatibility of ketorolac tromethamine with nalbuphine hydrochloride in isotonic saline solutions of physiological pH. Additionally, another study demonstrated that ketorolac tromethamine is incompatible with morphine hydrochloride in the same medium, further highlighting its selective interaction with specific drug molecules.[20,21]

The drugs studied in this work are shown in figure 7. Based on the reports and our own findings, we have postulated a possible mechanism of action for the interactions between these two drug entities. This possible mechanism of action has been illustrated in figure 8.

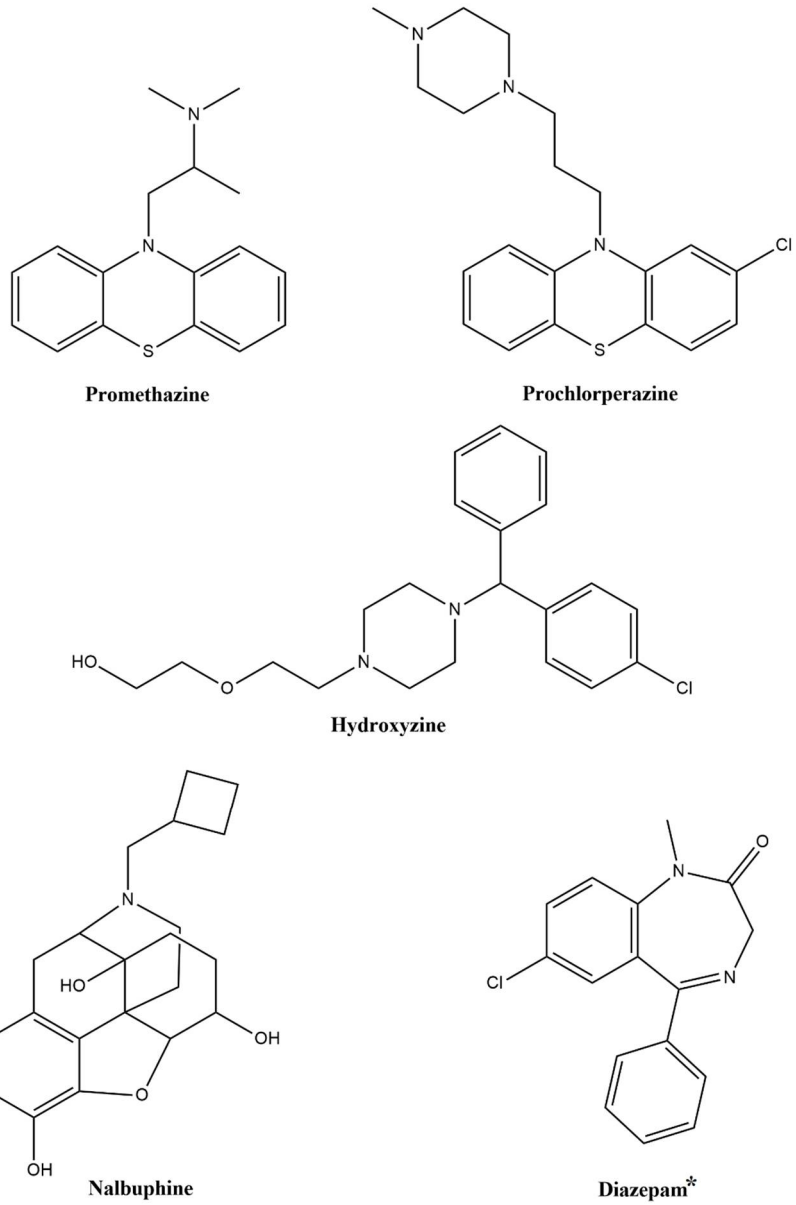

Figure 7. Chemical structures of promethazine, nalbuphine, hydroxyzine, prochlorperazine and diazepam. Knapp *et al.* reported interactions of the first four with ketorolac. However, *-marked diazepam was not reported to engage in such interactions.[11]

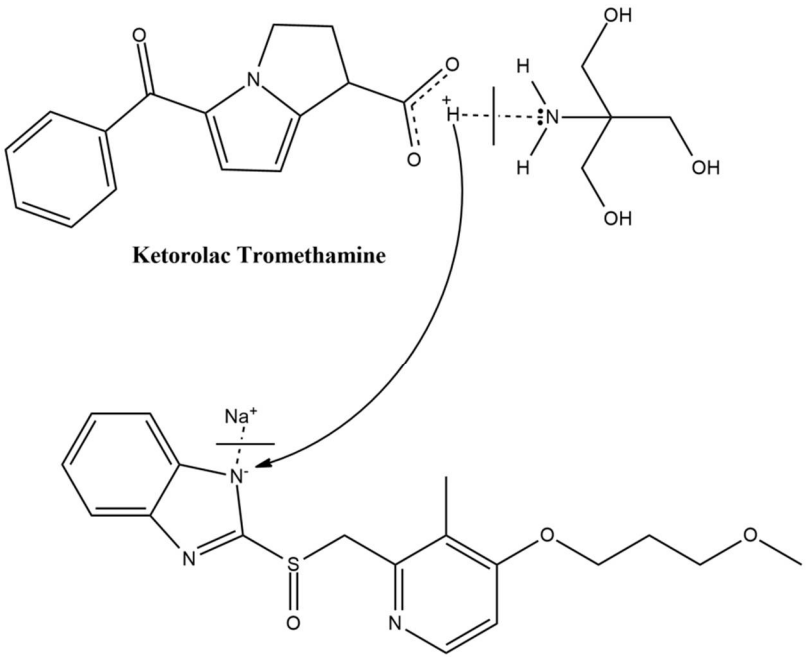

Figure 8. Proposed mechanism of action for the molecular interactions between ketorolac tromethamine and rabeprazole sodium.

CONCLUSION

Drug-drug interactions are of the utmost importance from a clinical perspective, especially in cases where multiple drug therapy is an unavoidable course of action. Understanding drug interactions is crucial for preventing adverse effects. Adverse drug events can result in severe inadequacies in clinical therapy, and can further worsen a patient's condition, and can even result in death. As these two widely-used drugs have been found to engage in molecular interactions, during their concomitant use, caution must be exercised to a great degree to avoid any unfavorable circumstances. Further studies on ketorolac tromethamine including *in silico* and *in vivo* patterns of interactions should be done to assess the possibility of drug-drug molecular interactions.

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