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## **SYNTHESIS AND EVALUATION OF SOME AMINO ACID CONJUGATES OF KETOPROFEN**

Ashish Nandakumar Phuge<sup>1\*</sup>

<sup>1</sup>Assistant Professor, Department of Pharmaceutical Chemistry, RJSPMs College of Pharmacy, Pune - 412105.

### **Keywords:**

Ketoprofen, Prodrug,  
Conjugates, Synthesis

### **For Correspondence:**

**Ashish Nandakumar Phuge**

Assistant Professor,  
Department of Pharmaceutical  
Chemistry, RJSPMs College  
of Pharmacy, Pune - 412105.

### **ABSTRACT**

The emphasis of present research work is to improve solubility behavior of NSAIDs by different amino acid conjugation. Present conjugate approach stands for modification to overcome pharmaceutical barriers like solubility behavior. The prodrugs designed by classical approach increase lipophilicity of the drug, which decreases the water solubility thus decreasing the concentration gradient, which controls drug absorption. To overcome the limitations of traditional prodrug approach, water soluble conjugates are designed by adding selected amino acid to the drug moiety that are the substrates for the enzyme located at the intestinal brushborder. Amino acid conjugate of ketoprofen was synthesized by conventional coupling method and it was characterized by Melting Point, TLC, UV, IR, NMR and Mass Spectroscopy. Serine - Ketoprofen conjugate has maximum water solubility. Present research work indicates that conjugates synthesized with amino acid possess more water solubility. From the pH rate profile it was found that all the synthesized compounds, are stable at low pH values (pH 1.2), while undergo hydrolysis as the pH is increased (pH 7.4). This indicates that the synthesized compounds will be hydrolyzed and subsequently absorbed through intestine. In future this approach can be applied to other NSAIDs having free carboxyl functional group as well as in vivo bioavailability study can be undertaken in animals and can be correlated in humans.

## INTRODUCTION

Almost all the currently available agents which are non-selective COX-1 and COX-2 inhibitors, shares the undesirable properties of producing effect to gastric and intestinal mucosa, resulting in erosion, ulcers and gastric bleeding and represent the major adverse reactions to the use of NSAIDs. NSAIDs induce gastric damage by dual insult mechanism, they are acidic in nature damage the GI tract by changing the permeability of cell membrane allowing a back diffusion of hydrogen ions, causing cell damage; on the other hand the nonselective inhibition of prostaglandin biosynthesis in the GIT prevents the prostaglandin from exerting their therapeutic efficacy can be improved or eliminating the undesirable properties while the approach of the drug design. This can be achieved through biological, physical or chemical means.<sup>[1]</sup> The biological approach is to alter the route of administration which may or may not be acceptable to patient. The physical approach is to modify the design of dosage form, such as controlled drug delivery system. The third and best approach is to enhance drug selectivity while minimizing its toxicity is the chemical approach. Prodrug approach is one of the chemical approaches for optimizing the drugs therapeutics.<sup>[1, 2, 3]</sup>

A Prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent compound. Chemical modification of a drug via the attachment of promoiety generates the prodrug. The properties of the prodrug enable it to cross the limiting barrier and it is designed ideally to be cleaved efficiently by enzymatic or non-enzymatic processes. This is followed by rapid elimination of the released promoiety.<sup>[1]</sup>

The term is a chemically modified inert drug precursor, which upon biotransformation prior to eliciting a pharmacological response. This definition includes metabolites if administered drugs that are true active drugs as well as latentiated drugs.<sup>[1]</sup>

Soft drugs are pharmacologically active but undergo controlled and predictable conversion in vivo, generating non-toxic metabolites after having its therapeutic effect. Double-prodrug approach a more advanced prodrug design is applied to overcome the stability problems the seldom occur in the formulations of carriers linked prodrug. This is also termed as prodrug.

The major objectives behind prodrug design are improved formulation, improved chemical stability, improved patient acceptance, improved bioavailability, prolonged action, selectivity and reduced toxicity. Prodrug design, therefore aims to overcome numbers of barriers of the drug usefulness like – Taste and odor, slow dissolution rate, Poor solubility, Irritation/ Pain (Pharmaceutical barrier) and Insufficient oral absorption, Short duration, Presystemic metabolism,

Unfavorable distribution, non specificity (Pharmacokinetic Barriers), Toxicity or side effects (Pharmacodynamic barrier).<sup>[1]</sup>

Prodrug approach is very effective and helpful in decreasing the problem related with solubility, absorption, distribution, site specificity, instability, toxicity, formulation and bioavailability problem. Among various type of prodrugs, ester and amide prodrugs are most common type. In body, these prodrugs break in to parent drug and coupled moiety. Ester prodrugs synthesized by reacting carboxylic acid group and alcohol group while amide prodrugs synthesized by coupling of amine and carboxylic acid.<sup>[4]</sup>

Almost all drugs possess some undesirable physicochemical and biological properties. Their therapeutic efficacy can be improved by minimizing or eliminating the undesirable properties while retaining the desirable ones. This can be achieved through biological, physical or chemical means.<sup>[2, 3]</sup>

## **MATERIALS AND METHODS**

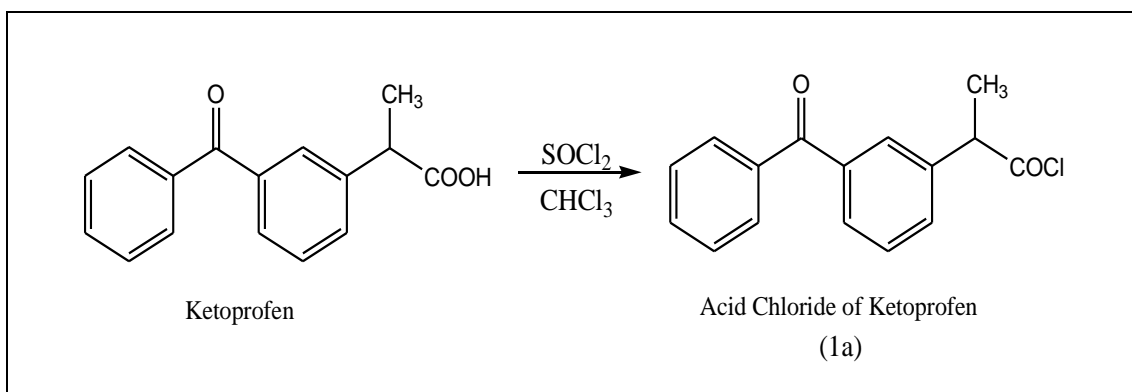
### **General**

All the chemicals and solvents used were purchased from commercial sources and were of high purity. Melting points were taken in open glass capillary using Elico melting point apparatus and are uncorrected. The Purification of synthesized compounds was performed by recrystallization with appropriate solvent system. The purity of the compounds was checked using Thin Layer Chromatography (TLC) technique; spots were developed by exposure to iodine vapors. UV absorbance of the synthesized compound was carried out on UV 2450 (Shimadzu) UV Spectrophotometer in methanol. Infrared spectrums were recorded on Shimadzu FTIR 8400 S Spectrophotometer. Proton resonance magnetic spectra (<sup>1</sup>H NMR) were recorded on Bruker DPX 400 MHz NMR Instrument using solvent CDCl<sub>3</sub> and chemical shifts were expressed in parts per million ( $\delta$  ppm) Mass Spectra was recorded on Agilent Technologies 6540 Shimadzu Instrument. Solubility and Partition Coefficient Study: By using three different systems (Octanol: Water, Octanol: HCl Buffer, Octanol: Phosphate Buffer). Concentration of the drug was determined by measuring the UV absorbance at the  $\lambda_{max}$  of the individual conjugate. Hydrolysis studies of compounds were carried on dissolution Test Apparatus 2- Dissotest Labindia model and estimations were done on UV Spectrophotometer.

### **Chemistry**

STEP 01: Synthesis of Acid Chloride of Ketoprofen<sup>[19, 20]</sup>

IUPAC: 2-(3-benzoylphenyl) propionyl chloride

**Procedure:**

Ketoprofen (0.01 mol; 2.54 gm) was dissolved in minimum amount of chloroform and Thionyl chloride (0.01 mol+ 20%; 0.9 ml) was added slowly to it. The mixture was refluxed for 8 hours at 60-70 °C with continuous stirring. The viscous liquid was vacuum dried to give yellow coloured crude Ketoprofen acid chloride (1a). The compound was recrystallised using ethanol to get pure acid chloride derivative.

**TLC Monitoring of Ketoprofen (KTP) & its Acid Chloride:**

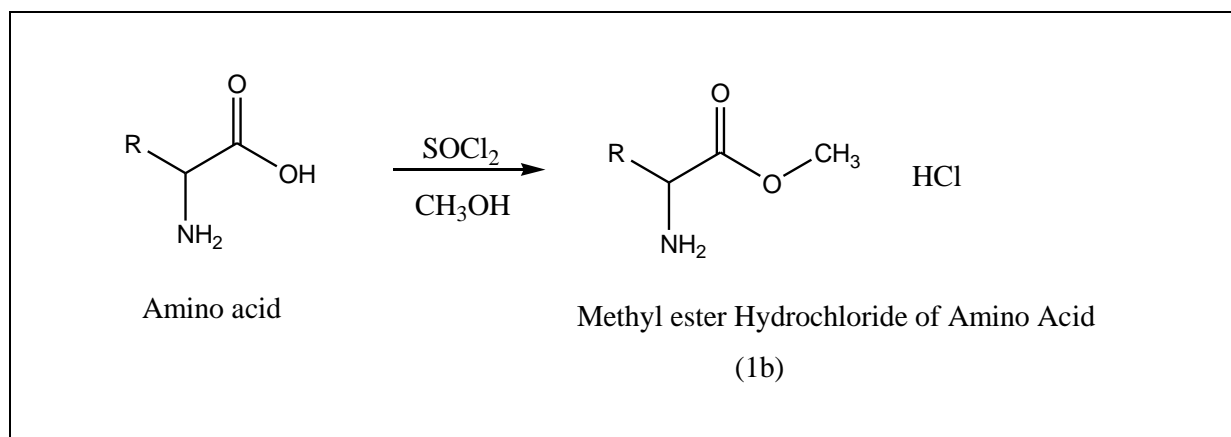
Solubility: Soluble in methanol, chloroform.

Mobile phase used: [Chloroform: Methanol: Acetic acid (8:1:1)]

**Table 1: Physicochemical Data of Synthesized Product in Step 1**

Compound	Mol. Formula	Mol. Weight	M.P. (°C)	Yield (%)	R <sub>f</sub> Value*
Ketoprofen (Pure)	C <sub>16</sub> H <sub>14</sub> O <sub>3</sub>	254.30	92-96	---	0.63
Acid Chloride of Ketoprofen	C <sub>16</sub> H <sub>13</sub> ClO <sub>2</sub>	272.73	174-176	68.20	0.67

STEP 02: Synthesis of Methyl Ester Hydrochlorides of amino acids <sup>[1, 19, 20]</sup>



**Procedure:**

Thionyl chloride (0.05 mol; 3.6 ml) was slowly added to methanol (10 ml) with cooling and amino acid (0.1 mol) was added to it. The mixture was refluxed for 6-8 Hrs. at 60-70 °C with continuous stirring giving crude amino acid methyl ester hydrochloride. It was re-crystallized from hot methanol by slow addition of 15-20 ml ether followed by cooling at 0 °C. The crystals were collected on next day and washed twice with ether: methanol mixture (5:1 ratio) followed by pure ether and dried under vacuum to get pure amino acid methyl ester hydrochloride (2a).

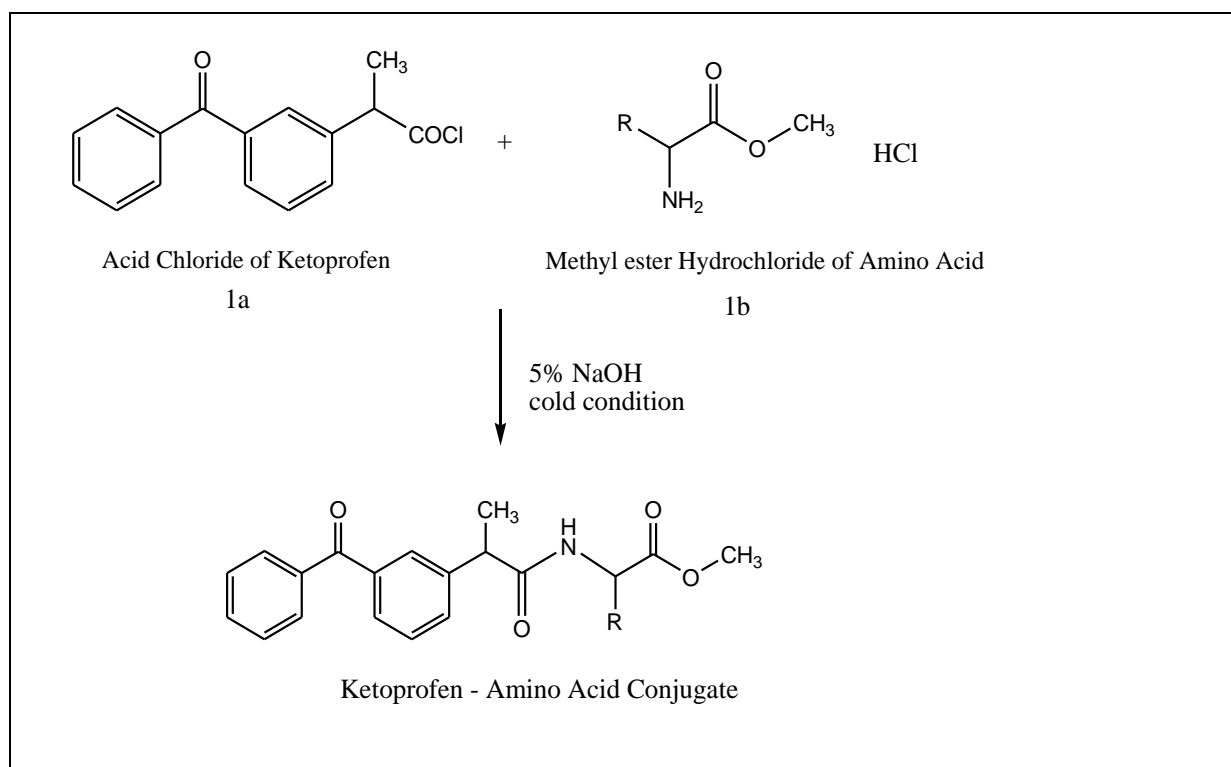
**TLC Monitoring of Methyl Ester Hydrochlorides of Amino acid (Intermediates):**

Solubility: Soluble in methanol, chloroform.

Mobile Phase used: [Ether: Methanol: chloroform (8:1:1)]

**Table 2: Physicochemical Data of reaction intermediates**

Compound	-R group	Mol. Formula	Mol. Weight	M.P. (°C)	Yield (%)	R <sub>f</sub> Value
Methyl ester hydrochloride of Glycine	-H	C <sub>3</sub> H <sub>7</sub> NO <sub>2</sub>	89.09	98-100	60.81	0.59
Methyl ester hydrochloride of Alanine	-CH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub> NO <sub>2</sub>	103.12	106-108	59.33	0.62
Methyl ester hydrochloride of Serine	-CH <sub>2</sub> OH	C <sub>4</sub> H <sub>9</sub> NO <sub>3</sub>	119.12	112-114	70.00	0.68
Methyl ester hydrochloride of Threonine	-CH(OH)-CH <sub>3</sub>	C <sub>5</sub> H <sub>11</sub> NO <sub>3</sub>	133.15	120-122	60.00	0.60
Methyl ester hydrochloride of Glutamic Acid	-(CH <sub>2</sub> ) <sub>2</sub> -COOH	C <sub>6</sub> H <sub>11</sub> NO <sub>4</sub>	161.16	154-156	51.20	0.53
Methyl ester hydrochloride of Lysine	-(CH <sub>2</sub> ) <sub>4</sub> -NH <sub>2</sub>	C <sub>7</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub>	160.21	90-92	50.00	0.61
Methyl ester hydrochloride of Arginine)	-(CH <sub>2</sub> ) <sub>3</sub> -NH-C(NH <sub>2</sub> )=NH	C <sub>7</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub>	188.23	132-134	58.29	0.66

**STEP 03: Synthesis of Conjugates of Ketoprofen with methyl esters of amino acids** <sup>[1, 20]</sup>**Procedure:**

Ice cold, aqueous sodium hydroxide solution (5%) was taken in 250 ml beaker and methyl ester of amino acid hydrochloride (0.05 mol) was added to it. The reaction mixture was mechanically stirred for 30 min at room temperature, after which the beaker was transferred to an ice bath kept on mechanical stirrer, maintaining the temperature at 10 °C. Ketoprofen acid chloride (0.01 mol; 2.73 gm) was added in small portions with continuous stirring for 7-8 Hrs. The solid that separated out was filtered off. The crude prodrug was recrystallised from methanol.

**TLC Monitoring of all synthesized conjugates:**

**Solubility:** Soluble in chloroform, methanol.

Mobile Phase used: [Chloroform: Methanol (9:1)]

**Table 3: Physicochemical Data of final compounds**

Compound	-R group	Mol. Formula	Mol. Weight	M.P. (°C)	Yield (%)	R <sub>f</sub> Value
Ketoprofen (Pure)	---	C <sub>16</sub> H <sub>14</sub> O <sub>3</sub>	254.30	92-96	---	0.63
Glycine Conjugate of Ketoprofen	-H	C <sub>19</sub> H <sub>19</sub> NO <sub>4</sub>	325.36	104 – 106	62.48	0.67

Alanine Conjugate of Ketoprofen	-CH <sub>3</sub>	C <sub>20</sub> H <sub>21</sub> NO <sub>4</sub>	339.39	84 – 86	80.07	0.63
Serine Conjugate of Ketoprofen	-CH <sub>2</sub> OH	C <sub>20</sub> H <sub>21</sub> NO <sub>5</sub>	355.38	74 – 76	52.42	0.66
Threonine Conjugate of Ketoprofen	-CH(OH)- CH <sub>3</sub>	C <sub>21</sub> H <sub>23</sub> NO <sub>5</sub>	369.41	106 – 108	62.78	0.77
Glutamic Acid Conjugate of Ketoprofen	-(CH <sub>2</sub> ) <sub>2</sub> - COOH	C <sub>22</sub> H <sub>23</sub> NO <sub>6</sub>	397.42	81 – 82	81.40	0.81
Lysine Conjugate of Ketoprofen	-(CH <sub>2</sub> ) <sub>4</sub> - NH <sub>2</sub>	C <sub>23</sub> H <sub>28</sub> N <sub>2</sub> O <sub>4</sub>	396.48	80 – 82	64.00	0.74
Arginine Conjugate of Ketoprofen	-(CH <sub>2</sub> ) <sub>3</sub> - NH- C(NH <sub>2</sub> )=N H	C <sub>23</sub> H <sub>28</sub> N <sub>4</sub> O <sub>4</sub>	424.49	78 – 80	66.09	0.53

## RESULT AND DISCUSSION

### [A] synthetic aspect

Amino acid conjugates of ketoprofen were synthesized by adopting very much easy route of synthesis. Conjugating NSAID'S with various amino acids provides a new way for drugs having poor physicochemical properties like solubility and partition coefficient.

The Synthesis of Conjugates of ketoprofen with amino acids involves following three steps:

- 1) Synthesis of Acid Chloride of Ketoprofen
- 2) Synthesis of Methyl ester hydrochlorides of Amino acids
- 3) Synthesis of Amino Acid conjugates of Ketoprofen

The first step is the activation step where the carboxylic acid group of ketoprofen is converted to carbonyl chloride group in the presence of Thionyl chloride & chloroform. In the second step corresponding amino acids are esterified with methanol to give methyl ester of amino acids for protection of carboxylic acid group of amino acid & this will be helpful for the coupling of acid chloride of ketoprofen & methyl ester of amino acid. Due to this protection –NH<sub>2</sub> group is only available to react with -COCl group of Acid chloride of ketoprofen.

### [B] Characterization of compounds

Structures of synthesized compounds were confirmed by IR, NMR & Mass Spectral analysis.

**[C] Solubility and partition coefficient study**

Solubility and Partition coefficient study showed the improved solubility and partition coefficients of conjugates than the parent drug ketoprofen. Serine conjugate of ketoprofen showed highest solubility in water (0.209 mg/ml) and its partition coefficient is 2.13 in octanol: water system

**[C] in-vitro hydrolysis study**

In-Vitro hydrolysis study of synthesized compounds was carried out in 0.05 M hydrochloric acid buffer (pH 1.2, ionic strength 0.5) and 0.05 M phosphate buffer (pH 7.4, ionic strength 0.5). During hydrolysis study in hydrochloric acid buffer, it was observed that the release of free parent drug is very slow, indicating that amino acid conjugates of ketoprofen were stable at pH 1.2. All the conjugates were show fast release of free parent drug in phosphate buffer. The kinetic treatment data of hydrolysis study along with  $t_{1/2}$  values are presented in Tables 11-18. The plots of time vs. log concentration of prodrug remaining showed that conjugates followed first order hydrolysis kinetics with half lives ranging from 3.50 to 8.60 hrs (at pH 1.2 Buffer) & 1.46 to 2.23 hrs (at pH 7.4 Buffer) respectively. The plots were presented in Fig 8-9.

**DISCUSSION**

The term conjugation is used to describe compounds, which undergo biotransformation, before exerting their pharmacological action. In the present study conjugates in the form of esters and amides were synthesized by linking various amino acids with Ketoprofen as per the procedures described in schemes. The parent drug Ketoprofen is practically insoluble in water, and literature revealed that the conjugates with amino acids improve the water solubility. The compound P 03 (Serine conjugate of ketoprofen) has maximum water solubility i.e. 0.209 mg/ml. A drug's partition coefficient is a measure of its distribution in a lipophilic/ hydrophilic phase system, and is indicative of its ability to penetrate biological multiphase system. The values of partition coefficient range from 2.13 to 2.92 in octanol/ water system, 1.08 to 1.67 in octanol/ hydrochloric acid (pH 1.2) system and 3.05 to 5.25 in octanol/ phosphate buffer (pH 7.4) system. IR and NMR spectra confirmed the structure of the compounds. IR spectra exhibited characteristic absorption bands of N-H stretching, C=O stretching and C-H stretching functional groups vibrations., all conjugates showed IR absorption frequency for N-H stretching in between 3500 to 3100  $\text{cm}^{-1}$ , C-H stretching in between 3000 to 2850  $\text{cm}^{-1}$  and C=O stretching in between 1750 to 1730  $\text{cm}^{-1}$  for Ester Carbonyl and 1685 to 1620  $\text{cm}^{-1}$  for amide carbonyl, 1450 to 1375 for asymmetric bend of  $\text{CH}_3$ .



The hydrolysis studies conducted at selected pH values (1.2 and 7.4) at  $37 \pm 1$  °C provide useful information of stability of the compounds in the gastrointestinal tract. Graphs were plotted with time in hours on X-axis Vs. log of amount remaining (a-x) on Y-axis. Whole kinetic hydrolysis studies were carried out in two systems that are 0.05 M HCl buffer (pH 1.2) and 0.05 M phosphate buffer (pH 7.4). From the pH rate profile it was found that all the synthesized compounds, are stable at low pH value (pH 1.2), while undergo hydrolysis as the pH is increased (pH 7.4). This indicates that the synthesized compounds will be hydrolysed and subsequently absorbed through intestine. At pH 1.2 the  $t_{1/2}$  of the compounds were in between 3.50 to 8.60 hrs, while at pH 7.4 the  $t_{1/2}$  were in between 1.46 to 2.23 hrs., the in vitro hydrolysis data are shown in Table 11-17 and half life of the synthesized compounds are given in Table - 18 for pH 1.2 and pH 7.4.

## CONCLUSION

The conjugates of Ketoprofen were synthesized using simple synthetic route in good yields (P 01 = 62.48%, P02 = 80.07%, P03 = 52.42 %, P04 = 62.78%, P05 = 81.40%, P 06 = 64%, P07 = 66.09%) and their structures were confirmed by spectral analysis (IR, NMR & Mass). All conjugates have more water solubility than parent compound, the compound P 03 (Serine conjugate of ketoprofen) have highest solubility in water. The partition coefficients of the synthesized compounds found more in octanol/ phosphate buffer (pH 7.4) as compared to octanol/ water and octanol/ Hydrochloric acid buffer (pH 1.2).

Kinetics of Hydrolysis of synthesized conjugate showed that they were chemically stable with lower value (pH 1.2), while they showed significant hydrolysis at pH 7.4. The half-life ranges in between 3.50 to 8.60 hrs for pH 1.2 while 1.46 to 2.23 hrs for pH 7.4. The compounds were found to stable at acidic pH as there was little hydrolysis of the synthesized compounds into parent compound.

The present research work aimed for improving physicochemical properties of poor bioavailable drug ketoprofen. It is a BCS Class II drug having low water solubility and high permeability; so by conjugating ketoprofen with various amino acids like serine, Threonine, Glutamic acid, Arginine etc. Solves the problem of poor water solubility of ketoprofen and this approach can be used for enhancing solubility behavior of drugs in future studies.

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