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Synthesis and evaluation of mutual prodrugs of some NSAIDs

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Abstract

The therapeutic efficacy of NSAIDs can be improved by reducing their gastrointestinal side effects by modifying their carboxyl group. Anti-inflammatory drugs Ibuprofen, Ketoprofen were chosen for the preparation of mutual prodrugs with paracetamol. The compounds were synthesized with the aim of achieving a synergistic effect and reducing the gastric irritation of anti-inflammatory drugs. Compounds were confirmed by characterization. The synthesis involved an esterification reaction between the carboxyl group of selected NSAIDs and the hydroxyl group of paracetamol. Mutual prodrugs were evaluated for hydrolysis study in acidic medium and phosphate buffer. Compounds were found to hydrolyze at a controlled rate in the environment, and thus this study found that a mutual prodrug approach can be effectively used to achieve the goals of enhancing the effectiveness of NSAIDs in two ways. First, by masking the carboxyl group of NSAIDs to reduce GI effects and achieve synergistic effects using paracetamol as a pro moiety. Both IP and KP prodrugs were retaining anti-inflammatory activity intact and exhibited much-reduced gastric irritant activity. Prodrug IP however, showed better activity and negligible ulcerogenic tendency than KP.

Keywords: Mutual prodrugs; NSAIDs; Paracetamol; Esters; Hydrolysis; *In vivo* evaluation

1 Introduction

Most of the NSAIDs used today are associated with some unacceptable side effects. Nonsteroidal anti-inflammatory drugs (NSAIDs) have proven problematic with common side effects such as gastrointestinal irritation and ulcers that limit their use[1].These NSAIDs are widely used to treat pain and inflammation in many conditions, including osteoarthritis (OA). and rheumatoid arthritis. (RA)[2].The main limitations of use are gastrointestinal (GI) side effects, mainly peptic ulceration, bleeding and perforation. This is due to a local effect caused by the direct contact of the drug with the gastric mucosa[3] . The carboxyl group of NSAIDs also plays an important role in the development of gastric irritation and ulcers[4].It has been reported that several methods are used to overcome side effects . effects Chemical modification of the effects of NSAIDs with retention of efficacy. The mutual prodrug concept involves the combination of two pharmacologically active compounds where one drug acts as a promoiety[3,10]. This approach has been used to minimize GI toxicity by temporarily masking the carboxyl group of NSAIDs with the phenolic hydroxyl group of paracetamol. This also increases their absorption values[5]. Prodrugs of anti-inflammatory drugs are of great interest to medicinal chemists because the carboxyl group can be easily derivatized and this can lead to the formation of versatile derivatives[6-8]. In addition, prodrugs of selected NSAID were also reported[9]. In the present work, a new series of common prodrugs of selected NSAID was developed by combining it with paracetamol as an promoiety. Thus in the present work, the carboxyl group of NSAIDs is conjugated with phenolic hydroxyl group of paracetamol through esterification reaction.

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2 Material and method

Mutual prodrugs of Paracetamol with Ibuprofen, Ketoprofen were synthesized using Steglich esterification reaction. It is a variation of an esterification with dicyclohexylcarbodiimide (DCC) as a coupling reagent and 4-dimethyl aminopyridine (DMAP) as a catalyst. The reaction mechanism involved two steps. In the first step, the carboxylic acid reacted with DCC to an O-acyl isourea, which was more reactive than the free acid and in a second step the alcohol of HMP attacks this intermediate, forming DCU and corresponding ester [16].

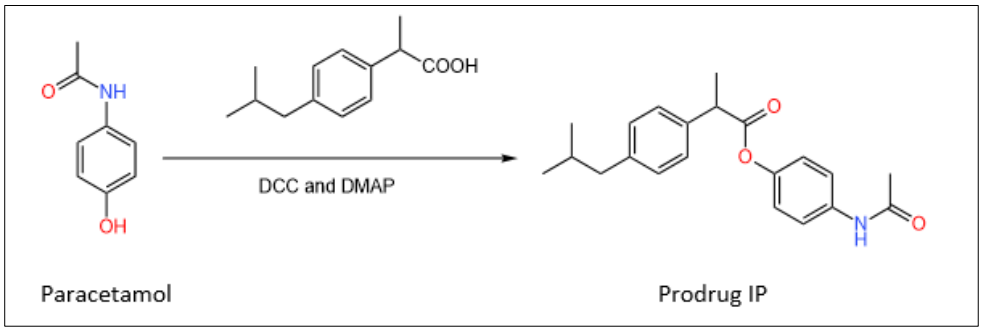

Figure 1 Synthesis of Mutual Prodrug IP

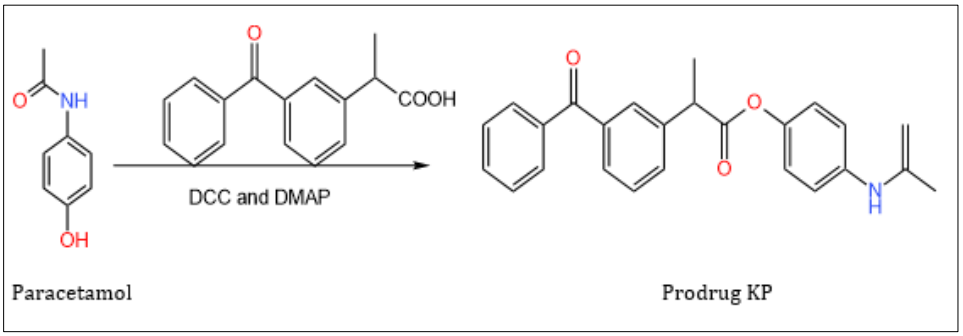

Figure 2 Synthesis of Mutual Prodrug KP

2.1 Materials

Paracetamol was obtained from Bluecross Laboratories Ltd Nashik as gift sample. Ibuprofen and ketoprofen were obtained from Holden Pharmaceuticals Sinnar,Nashik. All other chemicals and reagents are obtained from standard sources like Loba Chemie ,SD Fine, Fischer Scientific, Qualigen etc.

2.2 General Procedure

Reaction was performed by reacting 2 mmol of the selected NSAID, which was then dissolved in 20 ml DCM; 1 mmol of DCC (0.412 gm) was added to the solution, and the mixture was allowed to stir for 24 hours. DMAP (40 mg) was then added to the mixture; the mixture was then left to stir for 24 hours. 2 mmol (0.302 gm) of Paracetamol was added to the mixture, and the mixture was allowed to stir for 24 hours. Reaction was monitored by TLC using (ethyl acetate: n-hexane (70: 30) as a mobile phase.

Extraction and chromatographic separation of the synthesized ester was performed by the addition of 50 ml of distilled water to the crude mixture in a separating funnel. Organic layer was dried using $MgSO_4$. Organic layer was then evaporated under reduced pressure using the rota evaporator apparatus. Silica gel was used as a stationary phase, and the drug was eluted using the mobile phase [ethyl acetate: n-hexane (70: 30)].

The physicochemical properties were determined and shown in **Table 1**.

Table 1 Physicochemical properties of synthesized prodrugs

Prodrug Code	Molecular formula	Mol. wt.	Colour	m.p.*(℃)	% Yield	Rf value	Log P
IP	C21H25NO3	339	White	88-90	87	0.65	8.35
KP	C24H20NO4	386	White	215-217	59	0.35	9.30

2.3 *In-vitro* Hydrolysis Studies of Prodrugs

The hydrolysis of the prepared pro drugs (IP and KP) was achieved using pH of (1.2, and 7.2) which is the pH of stomach, large and small intestine of human body using UV spectrophotometer at λmax of 231 nm(IP) and 244nm(KP). It was prepared pH =1.2 from 0.1 M HCl. The hydrolysis was performed for the above pH after completion of the solution to (100 ml) using volumetric flask at temperature of (37 ± 0.1℃). The stock solution of 10 ppm from prodrugs (IP1 and KP1) is taken 2.4 ml and Acetonitrile (0.6 ml) added at pH under study. The absorbance (A0) was measured before applying the water bath at (initial Time =0) then the absorbance at time interval of (30 min) was then measured at temperature of (37℃) in a total time of (150 min) for each sample.

The blank solution which contains (0.6 ml) of Acetonitrile with (2.4 ml) of buffer solution against the sample solution.The absorbents was measured at λmax of prodrugs. Table 2 represents the results of study

2.3.1 Anti-Inflammatory Activity

The carrageenan induced rat hind paw edema method [16,17] was used to evaluate the acute anti-inflammatory activity of the prodrugs. Rats were divided into control, standard, and test groups of six animals each. Pretreatment initial paw volumes of all animals were measured using a mercury plethysmometer. The control group was given only an appropriate volume of 0.5% CMC. The standard group received Ibuprofen(50 mg/kg). To the test group, prodrugs (IP and KP) were administered orally (100 mg/kg). One hour after treatment, edema in the left hind paw of the rat was induced by injection of 0.1 mL of 1% (w/v) carrageenan solution in normal saline solution (0.9% w/v). The paw was marked with ink at the level of lateral malleolous and immersed in mercury up to this mark. The relative change in paw volume was determined by measuring the paw volume immediately after injection and at 15,30, 60, 120 min intervals following the carrageenan administration. The percent inhibition of edema, as an indication of anti-inflammatory activity was compared with the controls. The percentage inhibition of swelling was calculated using the following formula:

$$\text{Inhibition (\%)} = (Vt\text{-}Vo)\text{control} - (Vt\text{-}Vo)\text{treated} \times 100 / (Vt\text{-}Vo)\text{ control}$$

Vo and Vt relates the average volume in the hind paw of rats (n=6) before any treatment and after anti-inflammatory agent treatment, respectively.

2.3.2 Gastric irritant Activity

Wistar rats were divided into five groups consisting of six animals in each group. All animals fasted for 12 h before the administration of the drug.

The first group served as control and received *p.o.* administration of the vehicle (0.5% CMC) only. Group II received Ibuprofen as standard (50 mg/kg). Group III and IV received equivalent doses of prodrugs IP (200 mg/kg,) and KP (200 mg/kg) separately. All the test drugs or standard of the vehicle were administered orally to rats over a period of three successive days.All the rats fasted for 12 hrs after last dose. The animal were sacrificed with excessive anesthesia. The stomach was removed, opened along the greater curvature, and washed gently in running tap water.The tissue specimens which were prepared by embedding with paraffin.Thus formed paraffin blocks were cut by using a rotary microtome. The sections were then fixed onto glass slides, stained with eosin and evaluated [18]. The histopathological examination of gastric tissue carried out using microscope[20]. Results of samples compared with that of ibuprofen administration. For each sample, the mucosal damage was assessed according to the following scoring system:

0.0 - normal stomach; + - Mild irritation of stomach; ++ - Moderate irritation of stomach, +++ - Severe irritation of stomach

3 Results

The yields of prodrugs were good. The structures of prodrugs formed were confirmed by 1H-NMR, Mass, and FT-IR spectral methods. The purity was determined by TLC. The results of elemental analysis of synthesized prodrugs were in all case within 0.4% of theoretical values and were in confirmation of the desired structure. In both prodrugs IP and KP the IR stretching band ranging from 1740-1723 cm-1 indicated the formation of an ester linkage (C=O str.). The presence of C-O str. (ester linkage) was obtained in a range of 1020-1275 cm-1 . Presence of phenyl nucleus in the synthesized compounds was indicated by the presence of a skeletal stretching band of phenyl nucleus at 1590-1480 cm-1 . The appearance of the multiplet signal around 6.997-7.973 ppm depicted the presence of aromatic protons. In IP the Doublet signal observed in the range 1.258-1.488 ppm indicated the presence of isopropyl group -CH_3 of –CH (CH_3)2 in IP. Presence of isopropyl group (-CH of -CH(CH_3)2) is also indicated by multiplet signals around 2.414-2.449 ppm in IP Further, the elemental analysis and mass spectra also supported the formation of title compounds.

3.1 *In-vitro* Hydrolysis of Ester

One of the crucial requirements for a prodrug to be used, they should show good stability in aqueous solutions and in gastrointestinal fluid, and it should be readily hydrolyzed following gastrointestinal absorption to release the parent drug [3,12,]. Since, the carboxylic group of Ibuprofen and Ketoprofen is essential for the therapeutic action, prodrugs of prolonged action were designed in a form which the biologically active moiety can be released in its original state with time.

Therefore the release of NSAIDs from its prodrugs was studied *in-vitro* to evaluate the possible period in which the drug could be available from different prodrugs. The comparative patterns of hydrolysis of these prodrugs in 0.1N HCl and Phosphate buffer PH 7.2 are shown in the Fig. 3 and 4, respectively

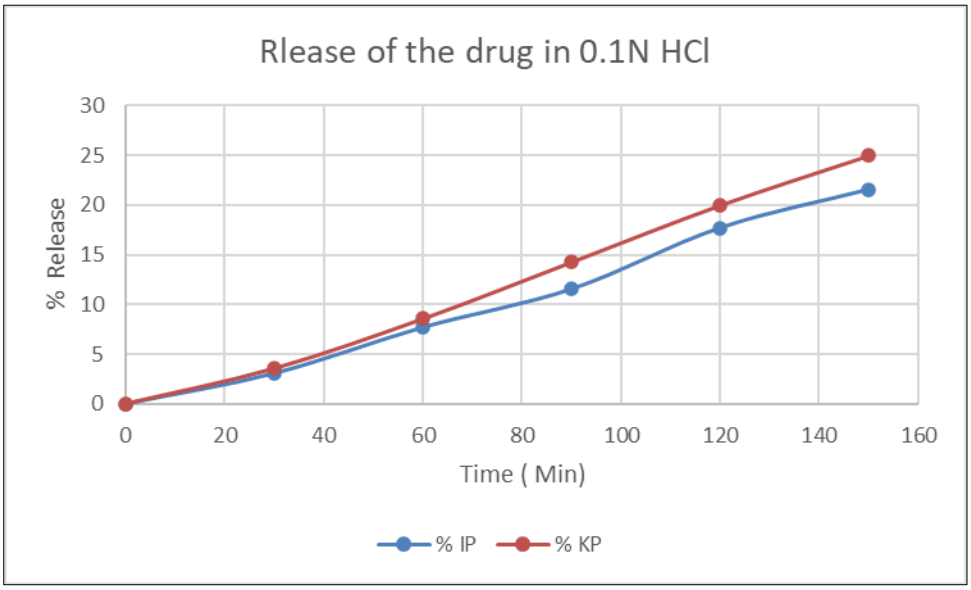

Figure 3. Comparative pattern of hydrolysis of IP and KP prodrugs in 0.1N HCl

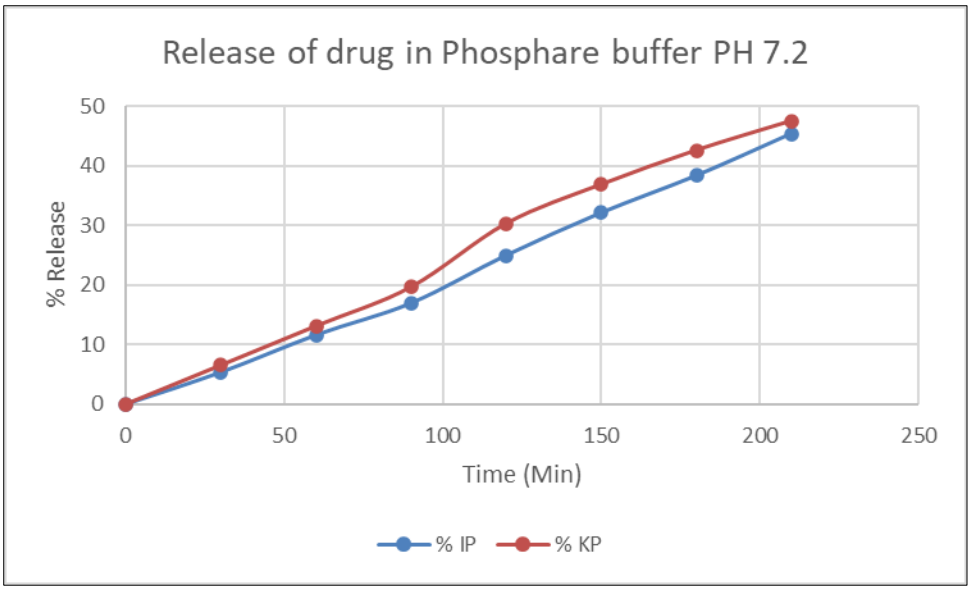

Figure 4. Comparative pattern of hydrolysis of IP and KP prodrugs in phosphate buffer (pH-7.2)

The amount of prodrugs IP and KP hydrolysed in 0.1N HCl (pH-1.2) was found as 9 % and 8% respectively in 1hr and that in Phosphate buffer (pH-7.2) was found as 45.53% and 47.54% respectively in 7 hrs. The results of the hydrolytic kinetics study revealed that both followed first order kinetics. But these prodrugs showed negligible hydrolysis in acidic medium (pH 1.2) for 1 h. From these results, this is confirmed that the release of drugs occurred predominantly at higher pH of the intestine. This may be because ester hydrolysis is a reversible reaction in acidic pH, and alkaline pH it is irreversible and complete [3,14] .

The predominant hydrolysis of prodrugs at pH 7.2 indicates the potential of the prodrug to reduce the gastric complications caused by direct contact of the free carboxyl group of the drug to the gastric mucosa. Kinetic parameters for hydrolysis of mutual prodrugs at 37 ℃ are shown in Table 2. The corresponding half-lives for IP and KP were found to be 6.48 and 5.84 hrs (in .1N HCl, pH 1.2) and 4 and 3.5 hrs (in Phosphate buffer, pH 7.2) respectively.

The half-lives and the rate constants for prodrug hydrolysis Table 2 indicated that esterification of the carboxylic group of Ibuprofen and Ketoprofen rendered its prodrugs more stable at pH 1.2, but less stable at pH 7.2

Table 2 Kinetic parameters for hydrolysis of mutual prodrugs IP and KP at 37 ℃

Prodrug code	$K_{obs\,(a)}$	$t_{1/2}$ (h)$_a$	$K_{obs\,(b)}$	$t_{1/2}$ (h)$_b$
IP	0.1069	6.48	0.1785	3.88
KP	0.1186	5.84	0.1771	3.91

a In 0.1N HCl (pH-1.2), b In Phosphate buffer (pH- 7.2)

3.2 Pharmacological activity

3.2.1 Anti- inflammatory

Anti- inflammatory screening of the synthesized compounds was performed by following the carrageenan induced paw oedema method[17] in albino rats (120- 160 g), in this method Ibuprofen (50mg/kg) was used as standard drug for the comparison. Drug and test compounds were given orally by preparing suspension in 0.5 % CMC. Injection of carrageenan was done by preparing fresh aqueous suspension (1% w/v, 0.1 ml). The suspension was injected in right hind paw of each rat. Mercury displacement(plethysmograph) equipment was used for this method.

Purpose and Rationale

This method is most commonly used among other methods because this technique is based on the ability of anti-inflammatory agents to inhibit the oedema produced in hind paw of rat after injection.

Procedure

- The animals were divided into groups, 6 rats in each group. One group of animals allotted to control and one group for standard drug (Ibuprofen). Rest of the groups was allotted to the test compound.
- Ibuprofen and test compound were given orally by preparing with 0.5% CMC suspension to group (standard, control and test compound respectively).
- After 30 min, 0.1mL of 1% freshly prepared carrageenan suspension in 0.9% NaCl solution was injected subcutaneously into the planter aponeurosis of the right hind paw and volume was measured.
- The paw volume was measured again after 2h and 4h, the mean increase in the paw volume in each group was calculated.
- The paw volume was measured by a plethysmometer apparatus. The difference in volume given the amount of oedema developed.
- The percent inhibition value calculated by formula given below
  % anti-inflammatory activity = [1-Dt / Dc]*100

Dt and Dc are paw volumes of oedema is tested and control groups respectively

Table 3 Anti-inflammatory effect of synthesizes compounds on carragenan - induced paw edema in rats using Ibuprofen as standard drug (50 mg/kg)

Treatment	**Increase in Paw volume (ml) (% inhibition of paw oedema)**			
	15 min	**30 min**	**60 min**	**120 min**
Vehicle (0.5 % CMC)	0.21 ± 0.011	0.21 ± 0.112	0.21 ± 0.87	0.22 ± 0.49
Carragenan	0.35 ± 0.161	0.44 ± 0.554	0.48 ± 0.11	0.48 ± 0.248
Ibuprofen (50 mg/kg)	0.22 ± 0.241 (37.1%)	0.24 ± 0.687 (45.5%)	0.24 ± 0.65 (50%)	0.23 ± 0.877 (52%)
Compound IP (100 mg/kg)	0.33 ± 0.147 (6.28 %)	0.36 ± 0.11 (17%)	0.28 ± 0.99 (40%)	0.25± 0.365 (46.87 %)
Compound KP (100 mg/kg)	0.32 ± 0.119 (7.1%)	0.30 ± 0.21 (31.6%)	0.25 ±0.331 (46.6%)	0.23 ± 0.888 (50.6%)

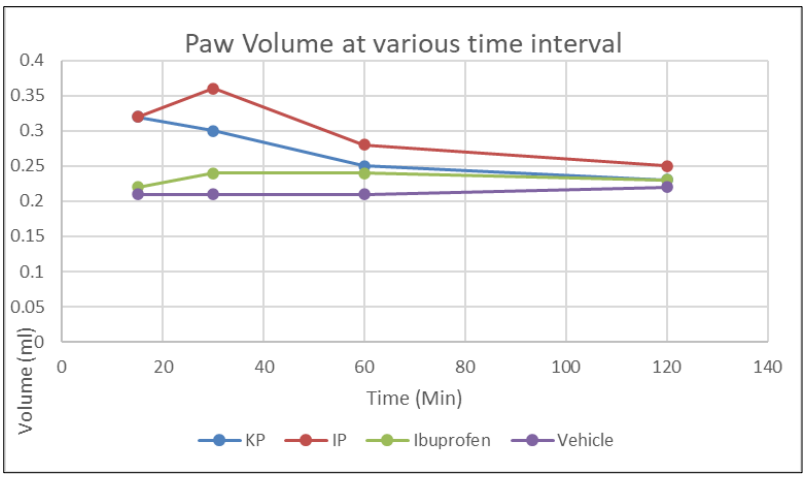

Figure 5 Paw volume at various time intervals

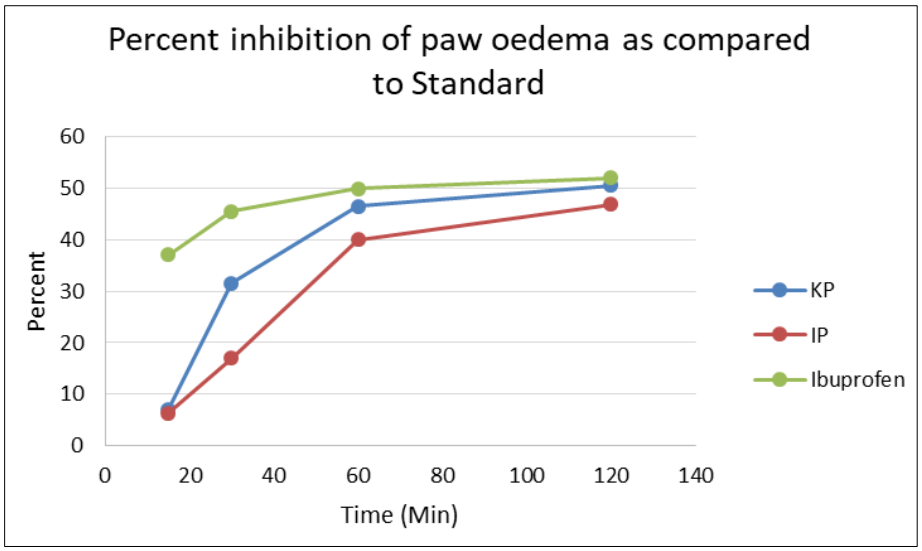

Figure 6 Percent inhibition of paw oedema

Gastric irritant Activity

Gastric irritation test was performed according to the method of Kunchandy *et al* [19]. Wistar rats were divided into three groups consisting of six animals in each group. All animals fasted for 12 h before the administration of the drug.

The first group served as control and received *p.o.* administration of the vehicle (0.5% CMC) only. Group II received Ibuprofen only. Group III, IV received equivalent doses of prodrugs IP, KP, separately. All the test drugs or standard of the vehicle were administered orally to rats over a period of three successive days.All the rats fasted for 4 h after last dose. The animal was sacrificed with excessive anesthesia. The stomach was removed, opened along the greater curvature, and washed gently in running water. The gastric mucosa of the rat was examined with tissue sampling[18,20] using a microscope and compared with that after ibuprofen administration. For each stomach, the mucosal damage was assessed according to the following scoring system: 0.0 - normal colored stomach; + - Mild effect; ++ Moderate ; +++ - Severe effects; Following are the results obtained after study.

Table 4 Gastric irritation study results

Observations	Vehicle	Ibuprofen	Test IP	Test KP
Mucosal desquamation	-nil	+++	+	++
Infilteration cells inflammatory propria	-nil	++	+	++
Odema in lamina propria	-nil	++	++	+

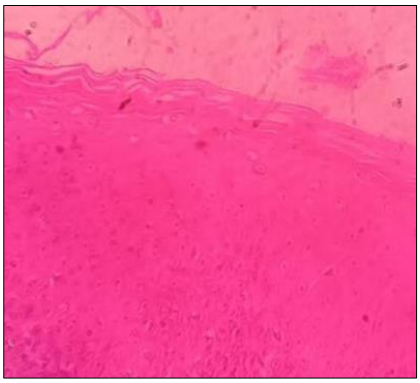

Figure 7 Histopathological examination (Vehicle)

Inference: Normal mucosal anatomy; no infiltration of inflammatory cells and no oedema was observed.

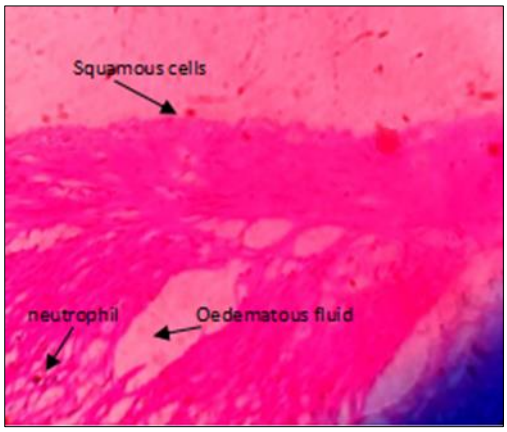

Figure 8 Histopathological Examination (Ibuprofen)

Inference: Severe desquamation in mucosal layer was observed. Severe infiltration of inflammatory cells and Accumulation of oedemateous fluid in lamina propria was moderately observed.

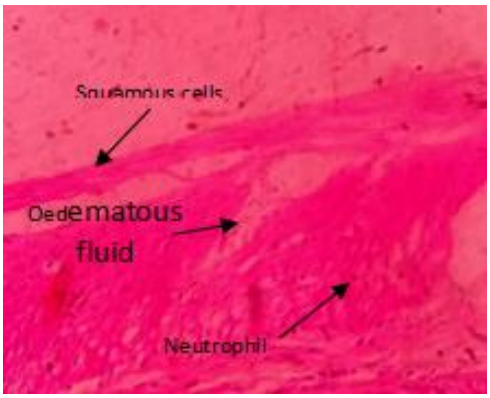

Figure 9 Histopathological Examination (IP)

Inference: Mild desquamation in mucosal layer was observed. Mild infiltration of inflammatory cells and moderate accumulation of oedemateous fluid in lamina propria was observed

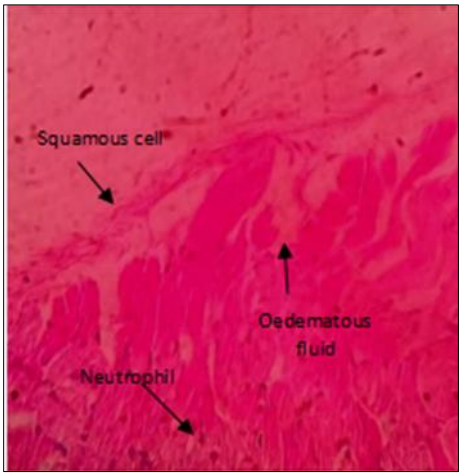

Figure 10 Histopathological Examination (KP)

Inference: Moderate desquamation in mucosal layer was observed. Moderate infiltration of inflammatory cells and mild accumulation of oedemateous fluid in lamina propria was observed.

4 Discussion

This work proposed an approach to overcome the unacceptable properties of existing drugs by designing mutual prodrugs. The synthesis of mutual prodrugs of paracetamol was achieved using known anti-inflammatory drugs. The target compounds IP and KP were successfully synthesized and characterized by converting selected anti-inflammatory drugs (ibuprofen, ketoprofen) to the corresponding esters with paracetamol. The phenolic OH of paracetamol acts as a masking agent for the carboxyl group of selected NSAIDs. The progress of the reaction was monitored by TLC using ethyl acetate and n hexane in a ratio of 7:3. The synthesized compounds were purified by recrystallization. All spectral data are in good agreement with the synthesized compounds. Infrared spectra showed C=O extending in the characteristic band region 1716-1747 cm-1 and C-O extending in the range 1225-1232 cm-1, which confirmed the formation of esters. Chemical changes in the 1H NMR spectra of the synthesized compounds show that the absence of the carboxylic acid proton peak indicates successful reaction. Mass spectra of the prepared derivatives, whose initial peak corresponds to the molecular weight of the mentioned compounds. A hydrolytic kinetic study of the prodrugs was determined at acidic and basic pH to determine the fate of the prodrugs[15,16]. From the existing literature, it seems that an important condition for the successful use of prodrugs is the acid stability of the compounds to avoid direct contact with the gastric mucosa and local inhibition of prostaglandins[13,14] . The synthesized prodrug derivatives were evaluated in an appropriate acidic and basic pH value. The result of the UV analysis of the kinetics of hydrolysis showed that the prodrug derivatives chemically decompose with first-order kinetics and thus quantitatively transform into the parent drug. All synthesized prodrug derivatives showed high stability under acidic conditions; this indicates that after oral administration the compounds passed through the stomach unhydrolyzed. Conversely, the ability of prodrugs to hydrolyse at basic pH indicates their susceptibility to hydrolysis in intestinal fluid. *in-vivo* evaluation of synthesized prodrugs revealed improvement in the therapeutic index of parent drugs.

5 Conclusion

Studies have shown that a mutual prodrug approach can be successfully applied to achieve the goal of increasing the therapeutic efficacy of selected NSAIDs in two ways; Firstly, by masking the carboxyl group by converting them to esters, and secondly by using known NSAIDs to achieve a synergistic effect. Based on observations, it is concluded that both IP and KP prodrugs were retaining anti-inflammatory activity and reduced gastric irritant activity , but prodrug IP, however, showed less gastric irritation and negligible ulcerogenic tendency than KP and hence it could be considered as a better mutual prodrug among the two. Therefore, a mutual prodrug approach allows the medicinal chemist to improve the clinical and therapeutic efficacy of a drug that has undesirable properties that prevent its clinical use.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

In present work animal studies are carried out at Pharmacology Department of Bhupal Nobles Institute of Pharmaceutical Sciences, Udaipur, Rajasthan, India, with permission from Institutional Animal Ethics Committee (IAEC) which functions based on the guidelines of CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals, http://cpcsea.nic.in).

References

[1] R.B. Silverman, Prodrugs and drug delivery systems, in The Organic Chemistry of drug design and drug action, J. Hayhurst (Ed.), Elsevier Academic Press: San Diego, 2004, pp 497–544.

[2] Bhosale D,Bharambe S,Gairola N and Dhaneshwar S,(2006 June) Mutual produg concept: fundamentals and applications,IJPS 68(3), 286-294

[3] Olhan S, Nanda S,Pathak D.P,Jagia M.(2011,3March),Mutual prodrugs-A SWOT Analysis, IJSPR, 2(4), 719-729

[4] Kankanala, K., Billur, R., Reddy, V. R., Mukkanti, K., & Pal, S. (2012). TFAAH3PO4mediated rapid and single-step synthesis of mutual prodrugs of paracetamol and NSAIDs. Green Chemistry Letters and Reviews, 5(3), 421– 432. doi:10.1080/17518253.2012.657251

[5] Kawai, S.; Kojima, F.; Kusunoki, N. Recent advances in nonsteroidal anti-inflammatory drugs. Allergol Int 2005, 54 (2), 209-215.

[6] Kean, W. F.; Buchanan, W. W. The use of NSAIDs in rheumatic disorders 2005: a global perspective. Inflammopharmacol 2005, 13 (4), 343-370.

[7] Velingkar,V. and Yadav,J.M..(2014) Synthesis,characterization, release kinetics, pharmacological screening and insilico ADME prediction of mutual prodrugs of aceclofenac, JOCPR, 6(7), 2664-2672

[8] V.L. Campo, I. Carvalho, Prodrugs: principles, design and therapeutic application, Curr. Methods Med. Chem. Biol. Phys. 2 (2008) 187–214.

[9] Functional group approach to prodrugs: Prodrugs of alcohols and phenols, in Prodrugs: challenges and rewards, V.J. Stella, R.T. Borchardt, M.J. Hageman, R. Oliyai, H. Maag, J.W. Tilley (Eds), Springer Press/AAPS Press: New York, 2007; Part 2, pp 31–99.

[10] Stella VJ, Charman WN, Naringrekar VH (May 1985). Prodrugs. Do they have advantages in clinical practice?. Drugs. 29 (5): 455–73.

[11] Mahfouz, N. M.; Omar, F. A.; Aboul-Fadl, T. Cyclic amide derivatives as potential prodrugs II: N-hydroxymethylsuccinimide-/isatin esters of some NSAIDs as prodrugs with an improved therapeutic index. Eur J Med Chem 1999, 34 (7), 551-562.

[12] Redasani, V. K.; Bari, S. B. Synthesis and evaluation of mutual prodrugs of ibuprofen with menthol, thymol and eugenol. Eur J Med Chem 2012, 56, 134-138.

[13] Omar, F. A. Cyclic amide derivatives as potential prodrugs. Synthesis and evaluation of N-hydroxymethylphthalimide esters of some non-steroidal anti-inflammatory carboxylic acid drugs. Eur J Med Chem 1998, 33 (2), 123-131.

[14] Redasani, V. K.; Bari, S. B., Synthesis and evaluation of glyceride prodrugs of naproxen. Open J. Med. Chem. 2013, 3, 87-92

[15] Mishra A, Veerasamy R, Jain PK, Dixit VK and Agrawal RK: Synthesis, characterization and pharmacological evaluation of amide prodrugs of Flurbiprofen. J. Braz. Chem. Soc. 2008; 19:89-100.

[16] Sucheta, Nanda S and Pathak DP: Synthesis, pharmacological activity and hydrolytic behaviour of mutual prodrugs of ibuprofen. Int J Pharm Sci & Res 2014; 5(10): 4509-21. doi: 10.13040/IJPSR.0975-8232.5(10).4509-21.

[17] Winter CA, Risley EA and Nuss GW: Carrageenaninduced edema in hind paw of the rat as an assay for antiinflammatory drugs. Proceedings of the Society for Experimental Biology and Medicine 1962; 111: 544-47.

[18] Sudesh Gyawali1, Gulam Muhammad Khan2, Shreekrishna Lamichane3, Jaya Gautam4, Saurav Ghimire5, Rashmi Adhikari6, Reshma Lamsal7 ;Evaluation of Anti-Secretory and Anti-Ulcerogenic Activities of Avipattikar Churna on The Peptic Ulcers in Experimental Rats

[19] Journal of Clinical and Diagnostic Research, 2013,7(6), 1135-1139.

[20] Kunchandy J, Khanna S and Kulkarni SK: Effect of α2 agonists clonidine, guanfacine and HT 920 on gastric acid secretion and ulcer in the rats. Archives Internationales de pharmacodynamie et de therapie 1984; 275: 123-28.

[21] E. Shaker a, H. Mahmoud , S. Mnaa. Anti-inflammatory and anti-ulcer activity of the extract from Alhagi maurorum (camelthorn). Food and Chemical Toxicology, 2010, 48, 2785-2790.