Synthesis and evaluation of mutual prodrugs of non-steroidal anti-inflammatory drugs with antioxidants

ABSTRACT
Background: NSAIDs are commonly used alone or in combination with other drugs. These drugs have major side effects like gastrointestinal irritation due to the presence of the carboxylic group in the structure. Therefore, mutual prodrugs of NSAIDs with antioxidants were synthesized toward a pharmacological objective of improving each drug's efficacy, optimizing delivery, and lowering toxicities. Method: The synthesize compounds were assigned for physical constant determination, λ max, Rf and further subjected for spectral analysis like infrared spectroscopy, nuclear magnetic resonance spectroscopy and mass spectroscopy. Algesic activity was performed by using the hot plate method. Carrageenan-induced rat paw oedema method of winter et al was used for evaluation of an anti-inflammatory activity. Invitro and invivo bioavailability studies were carried out for synthesized products. Results: The structures of 17a,17b, 19a, 19b, 21a, 21b were confirmed by IR, NMR and Mass spectral data. The synthesized mutual prodrugs (17a-b), (19a-b) and (21a-b) showed significant analgesic and anti-inflammatory activity as compared to standard compounds. The results showed that the free drug IBU, MEF and INDO and their mutual prodrugs (17a-b), (19a-b) and (21a-b) gives plasma concentration increase sharply within 1 hr after administration, but in free drug decrease rapidly with time and in mutual prodrugs plasma concentration was maintained for a long time. Conclusion: On the basis of the above observations, it is concluded that these mutual prodrugs conjugates can be successfully applied to attain the goal of minimizing gastrointestinal toxicity without loss of the desired anti-inflammatory and analgesic activity of the drug. The pharmacokinetic studies showed greater bioavailability as compared to parent’s compounds.

Keywords: NSAIDs; Mutual prodrugs; Antioxidants; Spectroscopy; Anti-inflammatory; Bioavailability

INTRODUCTION
The concept of “mutual prodrug” is relatively new in medicinal chemistry, pharmaceutics, and drug delivery. A mutual prodrug is a form of the prodrug in which two pharmacologically active agents are attached to each other in such a way that each drug acts as a carrier for the other [1]. Inflammation may be defined as the series of changes that occur in living tissues followed by injury. The injury which is responsible for inflammation may be brought about by a verity of conditions such as: physical agents like mechanical trauma, ultra-violet or ionizing radiation; chemical agents like organic and inorganic compounds, the toxins of various bacteria; intracellular replication of viruses; hypersensitivity reactions like reaction due to sensitized lymphocytes with a specific antigen material viz., inhaled organic dust or invasive bacteria; and necrosis of tissues whereby inflammation is induced in the surrounding tissues [2]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used drugs. Since the introduction of NSAIDs in the market, enormous literature has been published regarding their side effects such as nephrotoxicity, haemorrhages and the most serious GIT ulceration [3]. These side effects are due to the presence of carboxylic group (-COOH) in the structure which is significantly ionized at the physiological pH of the stomach [4]. The local generation of various “reactive oxygen species” (ROS) plays a significant role in the formation of gastric ulceration associated with NSAID therapy. These observations indicate that antioxidants may be used to prevent NSAIDs induced gastrointestinal toxicity. Algesic activity was performed by using the hot plate method. Carrageenan-induced rat paw oedema method of winter et al was used for evaluation of an anti-inflammatory activity. Invitro and invivo bioavailability studies were carried out for synthesized products. Results: The structures of 17a,17b, 19a, 19b, 21a, 21b were confirmed by IR, NMR and Mass spectral data. The synthesized mutual prodrugs (17a-b), (19a-b) and (21a-b) showed significant analgesic and anti-inflammatory activity as compared to standard compounds. The results showed that the free drug IBU, MEF and INDO and their mutual prodrugs (17a-b), (19a-b) and (21a-b) gives plasma concentration increase sharply within 1 hr after administration, but in free drug decrease rapidly with time and in mutual prodrugs plasma concentration was maintained for a long time. Conclusion: On the basis of the above observations, it is concluded that these mutual prodrugs conjugates can be successfully applied to attain the goal of minimizing gastrointestinal toxicity without loss of the desired anti-inflammatory and analgesic activity of the drug. The pharmacokinetic studies showed greater bioavailability as compared to parent’s compounds.

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Keywords: NSAIDs; Mutual prodrugs; Antioxidants; Spectroscopy; Anti-inflammatory; Bioavailability
MATERIALS AND METHODS

Materials
The chemicals used in the present work were AR grade and LR grade, purchased from Loba, Merck and Fisher scientific fine chemicals. Mefenamic acid was obtained as a gift sample from the Blue Cross Laboratories Limited, Nashik. Ibuprofen and Indomethacin were gifted by the Zim Laboratories, Kalmeshwar, and Nagpur.

Identification and Characterization Methods
The synthesized compounds were scaled for yield and purified by recrystallization with a suitable solvent system. The purified compounds were assigned for physical constant determination, λ max, Rf and further subjected for spectral analysis like infrared spectroscopy, nuclear magnetic resonance spectroscopy and mass spectroscopy.

Synthetic procedure
Step-1
Synthesis of antioxidant chloroacetyl derivative (15a-b)
A mixture of an appropriate antioxidant (0.01 mol), triethylamine (0.01 mol) in dichloromethane (25 ml) was cooled in an ice salt mixture to -10°C. To this reaction mixture, chloroacetyl chloride (0.01 mol) in chloroform (25 ml) was added dropwise with constant stirring over a period of 1 hr, maintaining the temperature constant. The reaction mixture was stirred further for 5 hr at room temperature on the magnetic stirrer, washed with 5% HCl (3× 50 ml), 5% sodium hydroxide (3× 50 ml), and finally with brine solution (2×25 ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain the semisolid residue. All the mutual prodrugs were synthesized by the above procedure. The final products were recrystallized from petroleum ether and ethyl acetate.

Step-2
Synthesis of NSAIDs (ibuprofen, mefenamic acid, indomethacin) - antioxidant mutual prodrugs (17a-b, 19a-b, 21a-b)
A mixture of an appropriate antioxidant chloroacetyl derivative (0.01 mol), NSAIDs (Ibuprofen, mefenamic acid or indomethacin) (0.01 mol), triethylamine (0.01 mol), sodium iodide (0.01 mol) in DMF (25 ml) was stirred overnight at room temperature. The reaction mixture was poured into finely crushed ice with stirring and extracted with chloroform (4×25 ml). The combined organic layer was washed with 2% sodium thiosulphate (3×50 ml), 5% HCl (3×50 ml), 5% sodium hydroxide (3×50 ml) and finally with brine solution (2×25 ml). The organic layer was dried over anhydrous sodium sulphate, filtered and the solvent was removed under reduced pressure to obtain the semisolid residue. All the mutual prodrugs were synthesized by the above procedure. The final products were recrystallized from petroleum ether and ethyl acetate.

2.2. Pharmacological studies
All the experimental procedures and protocols used in this study were reviewed and approved by the Institutional Animal Ethical Committee (IAEC) of the College, constituted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiment on Animals (CPCSEA), Government of India.

2.2.1 Analgesic activity
Analgesic activity was performed by using the hot plate method [7,8]. Swiss albino mice of either sex was divided into ten different groups each containing six animals, the animals were marked on tails individually. Food was withdrawn 12Hrs prior to drug administration till the completion of an experiment. The animals were weighed and numbered appropriately. These animals were treated with control, standard, and synthetic mutual prodrug (17a-b), (19a-b) and (21a-b) orally. At 0 min and after 90 min behavioural changes count like jumping and paw licking. The percentage inhibition in analgesic activity was evaluated using the following formula.

\[
\% \text{ inhibition} = \frac{1-(\text{before treatment}/\text{after treatment})}{\text{x} \ 100}
\]

Anti-inflammatory activity
Carrageenan-induced rat paw oedema method was used for evaluation of an anti-inflammatory activity [7,9]. Male or female Wistar rats with a body weight between 100-200 g were used. The animals were starved overnight. These animals were treated with control, standard, and synthetic mutual prodrug (17a-b), (19a-b) and (21a-b) orally. Thirty minutes later, the rats were challenged by subcutaneous injection of 0.05 ml of 1% solution of carrageenan into the plantar side of the left hind paw. The paw volume was measured by venire calliper scale immediately after injection i.e., 0 hours and 5 hrs. The percent inhibition of rat paw edema was calculated by the following formula-

\[
\% \text{ inhibition} = \frac{1-(a-x/b-y)}{x \ 100}
\]

Where, a = Paw volume of test group after 5 hrs of injecting carrageenan; x = Paw volume of test group before injecting carrageenan; b = Paw volume of the control group after 5 hrs of injecting carrageenan; y = Paw volume of control group before of injecting carrageenan.
Ulcerogenicity activity

The animals were dosed orally. The control, test and standard drug were administered orally for four days in 1% tween 80 solution and they were having free access to water and food during this period. On fifth day (24 Hrs after the last dose) the rats were scarified after ether anesthesia and stomach was removed. The stomach was filled with 1.5 ml of 2% buffer formalin for 10 min. and then it was opened along the greater curvature, wash with warm water and examine under a 3-fold magnifier. The lengths of the longest diameter of the lesions were measured by scoring method [7].

The number of ulcers is noted and the severity recorded with the following scores: 0 = no ulcer; 1 = superficial ulcers; 2 = deep ulcers and 3 = perforation.

An ulcer index UI was calculated by the following formula:

\[ UI = UN + US + UP \times 10 - 1 \]

Where, UN = average of number of ulcers per animal; US = average of severity score and UP = percentage of animals with ulcers

In-vitro bioavailability studies

The in-vitro drug release study of mutual prodrugs was carried out using dissolution apparatus (Paddle assembly). 20 mg of the drug was placed separately in dissolution test apparatus containing 900 ml of dissolution media of pH 1.2 (HCl buffer) and pH 7.4 (Phosphate buffer) and stirred at 100 rpm at 37±0.1°C over a period of 12Hrs. An aliquot of 5 ml of the samples were withdrawn at each time interval (0, 2, 4, 6, 8, 10, and 12Hrs) and replaced with equal volume of fresh dissolution medium. The samples withdrawn at each time interval were filtered and analyzed by given HPLC method. The amount of drug released from the mutual prodrug at different time intervals and percentage release were calculated according to the method.

In-vivo bioavailability studies

The prepared Std. and mutual prodrugs were administered orally to Wistar rats (150-250g) after overnight fasting. The blood samples were collected from the retrobulbar plexus into anticoagulant-treated polypropylene tubes from 0 Hr to 6 Hrs after drug administration. Blood samples collected were centrifuged immediately to separate the plasma. The plasma samples collected were stored at -20°C.

Preparation of biological Samples

To 1000 µl of plasma samples in a polypropylene tube were added 5 ml of HPLC grade Methanol. After vortex mixing for 10 min at room temperature, the samples were centrifuged at 5000 rpm for 10 min. The upper organic layer was transferred to a glass container and evaporated inside a vacuum oven at 40°C. The drug residue was dissolved in 1 ml of the mobile phase. The mixture was sonicated well for 10 minutes and 20 µl of this solution was injected into HPLC. The plasma samples were then processed for determination of % drug release by using the above HPLC methods.

RESULTS AND DISCUSSION

Synthetic Studies

The physicochemical properties of synthesized mutual prodrugs are depicted in Table 1

<table>
<thead>
<tr>
<th>Com p. Code</th>
<th>IUPAC names</th>
<th>Mol. Formula</th>
<th>Mol. Wt. (g/mol)</th>
<th>m.p. (°C)</th>
<th>b. p. (°C)</th>
<th>% Yield</th>
<th>Rf Value</th>
<th>λmax (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17a</td>
<td>2-Isopropyl-5-methylcyclohexyl-2-[2-(4-isobutylphenyl) propanoyloxy] ethanoate</td>
<td>C_{23}H_{36}O_{4}</td>
<td>402.56</td>
<td>45-47</td>
<td>230-232</td>
<td>54.82</td>
<td>0.692</td>
<td>260</td>
</tr>
<tr>
<td>17b</td>
<td>4-Formyl-2-methoxyphenyl-2-[2-(4-isobutylphenyl) propanoyloxy] ethanoate</td>
<td>C_{23}H_{26}O_{6}</td>
<td>398.44</td>
<td>-</td>
<td>200-203</td>
<td>43.65</td>
<td>0.649</td>
<td>249</td>
</tr>
<tr>
<td>19a</td>
<td>2-Isopropyl-5-methylcyclohexyl2-[2,3-dimethylphenyl] amino]benzoyloxy ethanoate</td>
<td>C_{27}H_{28}NO_{4}</td>
<td>437.57</td>
<td>40-43</td>
<td>222-225</td>
<td>36.39</td>
<td>0.851</td>
<td>279</td>
</tr>
<tr>
<td>19b</td>
<td>4-Formyl-2-methoxyphenyl-2-[2,3-dimethylphenyl] amino]benzoyloxy ethanoate</td>
<td>C_{23}H_{24}NO_{6}</td>
<td>433.45</td>
<td>101-105</td>
<td>237-240</td>
<td>46.82</td>
<td>0.736</td>
<td>237</td>
</tr>
<tr>
<td>21a</td>
<td>2-Isopropyl-5-methylcyclohexyl-2-[1-[(4-hlorophenyl) carbonyl]-5-methoxy-2-methyl-1H-indole-3-</td>
<td>C_{33}H_{28}C_{11}NO_{6}</td>
<td>554.07</td>
<td>48-51</td>
<td>211-214</td>
<td>36.61</td>
<td>0.933</td>
<td>269</td>
</tr>
</tbody>
</table>
The IR spectra of synthesized compounds were recorded on FT-IR 8400S Shimadzu, and absorbance peaks are recorded using KBr pellets. This is further supported by NMR and MASS studies. The ester derivatives of the mutual prodrug was successfully prepared by developed process and further recrystallized by using petroleum ether and ethyl acetate and checked the purity by thin layer chromatographic techniques. The title compounds were further characterized by Rf value, melting point, λ max, FTIR, NMR and MS. Infrared spectra for the synthesized compounds were recorded using SHIMADZU-FTIR 8400 spectrophotometer. ¹H NMR spectra of the synthesized compounds were taken using Bruker ACF-300 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. In FTIR spectra of comp. (17a) the stretching at about 2960 cm⁻¹ indicates the presence of C-H bond in the aromatic ring. The stretching at about 2850 cm⁻¹ shows the presence of C-H bond. Due to presence of ester O=C-O group in 17a stretching vibration is shown at 1746.42 cm⁻¹. The bending vibration at about 1453 cm⁻¹ indicates the presence of O-H bond. The C-O stretching vibrations is present at about 1150.46 cm⁻¹. A stretching vibration at 1044 cm⁻¹ indicate the presence of C-C group. In FTIR spectra of comp. (19b) the stretching at 3341.44 cm⁻¹ indicate -OH stretching. Aromatic -CH stretching is present at 2945.10 cm⁻¹. The stretching at 2720.41 cm⁻¹ indicates C-H stretching. The ester functional group O=C-O is present at about 1783.07 cm⁻¹. The C-C group is shown at about 1516.70 cm⁻¹. The bending at 1386.72 cm⁻¹ shows the C-H bend. The peak at 1290.29 cm⁻¹ indicates the presence of C-O stretching. The vibration at 1203.50 cm⁻¹ indicates the presence of C-C stretching. The deformation at 1154.32 cm⁻¹ shows –NH group. The vibration at 828.37 cm⁻¹ shows –CH bend out of plane. ¹HNMR spectra of comp. (17a) shows broad doublet peak at 7.1-7.2ppm indicating the presence of 4 protons of aromatic ring. A cluster of triplet peaks at 4.7-4.8ppm shows the presence of –CH₃ protons of cyclohexane ring. A cluster of quartet peak at 3.8ppm indicates the –CH₂ protons of ester linkage. A doublet peak at 2.4-2.5ppm shows the presence of –CH₂ protons attached to the aromatic ring. A broad multiplet at 2.2-2.3ppm indicates the presence of –CH₂ protons attached to the cyclohexane ring. A broad triplet peak at 1.6-1.7ppm shows the presence of –CH₂ protons adjacent to aromatic ring. A sharp doublet peak at 1.5ppm indicates –CH₂ protons adjacent to benzylc protons. A cluster of broad peak at 1.3-1.4ppm indicates –CH₂ protons attached to cyclohexane ring. A broad triplet peak at 1.1-1.2ppm shows the –CH₃ protons adjacent to cyclohexane ring. A broad multiplet peak at 0.9-1ppm shows the –CH₃ protons. A sharp multiplet at 0.8ppm again shows the –CH₃ protons. A broad multiplet peak at 0.7ppm shows the–CH₂ protonspec. (19b) shows a sharp peak at 10ppm indicating the presence of CH proton of –CH₂=O group. A broad multiplet peak at 7.3-7.5ppm shows the presence of three protons of aromatic ring. A broad multiple peak at 6.9-7.2ppm indicates the four protons of aromatic ring. A sharp peak at 4.7ppm shows the –NH protons. A sharp doublet peak at 3.8-4ppm shows the –CH₂ protons ester group. A doublet peak at 2.9ppm shows the –CH₂ protons of –O-CH₂ group. A sharp peak at 2.3ppm shows the –CH₃ protons attached to the aromatic ring. A sharp doublet peak at 2.1ppm indicates the –CH₃ protons attached to the aromatic ring. Mass spectra of comp. (17a) show a small peak at m/z 426.3 which is the molecular ion peak indicating the molecular weight of the compound. 426 is an even number which indicates the absence of N. S. A sharp peak at m/z 160.1 is the base peak. Mass spectra of comp. (19b) show a small peak at m/z 488.3 which is the molecular ion peak indicating the molecular weight of the compound. A sharp peak at m/z 224.1 gives the base peak.

### Pharmacological studies

The synthesized mutual prodrugs (17a-b), (19a-b) and (21a-b) showed significant analgesic and anti-inflammatory activity as compared to standard compounds. The ulcer indexes of synthesized mutual prodrugs were less as compared to standard drugs indicates that all synthesized mutual prodrugs have less gastric irritation as side effect of NSAIDs as compared to parent molecules.

![Figure 1: Analgesic activity of synthesized mutual prodrugs.](image-url)
Note: Analgesic activities of the test compounds were compared w.r.t control. Data are expressed as % Analgesic activity ± S.E.M. (n=6) and analyzed by one-way ANOVA followed by Bonferroni t test to determine the significance of the difference between the control group and rats treated with the test compounds. The difference in results were considered significant when P < 0.05. All statistical calculations were carried out using Graph Pad® Prism 5.0 (USA) statistical software.

![Graph showing analgesic activity](image)

**Figure 2: Anti-inflammatory activity of synthesized mutual prodrugs.**

Note: Anti-inflammatory activities of the test compounds were compared w.r.t control. Data are expressed as % anti-inflammatory activity ± S.E.M. (n=6) and analyzed by one-way ANOVA followed by Bonferroni t test to determine the significance of the difference between the control group and rats treated with the test compounds. The difference in results were considered significant when P < 0.05. All statistical calculations were carried out using Graph Pad® Prism 5.0 (USA) statistical software.

![Graph showing anti-inflammatory activity](image)

**Figure 3: Ulcergenicity activity of synthesized mutual prodrugs.**

Ulcerogenic activities of the test compounds were compared w.r.t control. Data are expressed as Ulcer index ± S.E.M. and analyzed by one-way ANOVA followed by Dunnett’s t test to determine the significance of the difference between the control group and rats treated with the test compounds. The difference in results were considered significant when P < 0.05. All statistical calculations were carried out using Graph Pad® Prism 3.0 (USA) statistical software.

![Graph showing ulcerogenic activity](image)
Pharmacokinetic studies
The synthesized mutual prodrug on administration should undergo drug release in the biological media followed by absorption of the drug into the systemic circulation before eliciting their action. The rate and the extent of drug release will decide the intensity and duration of the drug action in the system. The in-vitro drug release profile of mutual prodrug (17a-b), (19a-b) and (21a-b) are given in figures 18-23, shows a pH-dependent drug release behaviour. At pH 7.4 the drug release followed a sustained release pattern over a period of 12 hrs. At pH 1.2 drug releases were seen to be comparatively slower. This confirms that the release of IBU, MEF and INDO should occur predominantly at higher pH of the intestine. It indicates that these prodrugs are stable at acidic pH and their carboxylic acid group was masked which one was responsible for gastric irritation. Therefore, these synthesized mutual prodrugs may have fewer ulcerogenic side effects.

![Figure 1: In-vitro release of drugs in buffer solution at pH 1.2 and pH 7.4](image)

A comparative in-vivo bioavailability study between the free drug IBU, MEF and INDO and its mutual prodrugs (17a-b), (19a-b) and (21a-b) was carried out. The plasma concentration of IBU, MEF and INDO over time after oral administration of free drug and its mutual prodrugs are shown in Figure 24-29. The results showed that the free drug IBU, MEF and INDO and their mutual prodrugs (17a-b), (19a-b) and (21a-b) gives plasma concentration increase sharply within 1 hr after administration, but in free drug decrease rapidly with time and in mutual prodrugs plasma concentration was maintained for a long time. This indicates that the mutual prodrugs have better bioavailability as compared to the free drugs.

![Figure 2: Plasma concentration of drugs after oral administration of the free drug and mutual prodrug in Wistar rats](image)
of free drug and mutual prodrug (19a); 19b: Plasma concentration of MEF after oral administration of free drug and mutual prodrug (19b); 21a: Plasma concentration of INDO after oral administration of free drug and mutual prodrug (21a); 21b: Plasma concentration of INDO after oral administration of free drug and mutual prodrug (21b) Each value is the mean ± S.D, n=6.

CONCLUSION

The ester derivatives of a mutual prodrug of ibuprofen, mfenamic acid and indomethacin with antioxidants menthol and vanillin were successfully synthesized by using the mentioned synthetic scheme and the purity and homogeneity of the synthetic compounds were determined by sharp melting point and good percentage yield. On the basis of the above observations, it is concluded that these mutual prodrugs conjugates can be successfully applied to attain the goal of minimizing gastrointestinal toxicity without loss of the desired anti-inflammatory and analgesic activity of the drug. The pharmacokinetic studies showed greater bioavailability as compared to parent’s compounds.

REFERENCES