PRODRUG: NOVEL APPROACHES FOR ANTIINFLAMMATORY ACTION OF NSAID’s

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Abstract

“Prodrug Approach” is a versatile approach in solving the problem associated with drug molecules. Prodrug approach have been proposed to overcome the side effects of drugs by masking the carboxylic acid group via formation of bioreversible bonds. It has been demonstrated that the production of reactive oxygen (ROS) plays an important pathogenic role in gastrointestinal ulceration. In this review goal was to develop the such prodrugs of NSAID’s which integrates the concepts of prodrug and the beneficial antioxidant effect. These newly synthesized prodrug were analyzed by NMR and IR spectroscopy. This review focuses on the prodrug approaches used to improve the GI tolerance of NSAIDs

Key words: Prodrug, Carboxylic acid, ROS, Gastrointenstinal ulceration, NSAIDs, NMR, IR spectroscopy, antioxidant.

Introduction

Numerous therapeutic drugs for treating various ailments suffer from undesirable properties after metabolism leading to drug inactivation causing pharmacological, pharmaceutical and pharmacokinetic barriers in their clinical drug application. There are various approaches from which these undesirable effects can be reduced. This can be achieved through biological, physical or chemical means.

• The biological approach is to alter the route of administration which may or may not be acceptable tonpatient.

• The physical approach is to modify the design of dosage form such as controlled drug delivery of drug.
The third and best approach in enhancing drug selectivity while minimizing toxicity, is the chemical approach for design of prodrugs.\textsuperscript{2,3,4}

Among the various approaches to minimize the undesirable drug properties while retaining the desirable therapeutic activity, the chemical approach using drug derivatization offers perhaps the highest flexibility and has been demonstrated as an important means of improving drug efficacy\textsuperscript{5}. The prodrug approach gained a lot of attention in the 1970s, as a powerful method for enhancing drug therapy. The prodrug approach was developed to overcome mainly pharmacokinetics problems of many therapeutic classes of drugs\textsuperscript{6,7}. Prodrug design can be very effective in solving many of the stability, solubility, permeability and targeting problems that plague drug discovery and development.\textsuperscript{8}. Non-steroidal anti-inflammatory drugs (NSAIDs), commonly used for the treatment of chronic inflammatory diseases suffer from several undesired side effects, the most important being gastrointestinal (GI) irritation and ulceration. The prodrug designing is one of the several strategies used to overcome this drawback. The rationale behind the prodrug concept is to achieve temporary blockade of the free carboxylic group present in the NSAIDs till their systemic absorption. In this paper, a review on the concept of prodrugs designing of NSAIDs to improve their efficacy and reduce the toxicity is being presented.\textsuperscript{9}.

**Prodrugs**

The term "prodrug" or "proagent" was first introduced by Albert to signify pharmacologically inactive chemical derivatives that could be used to alter the Physicochemical properties of drugs, in a temporary manner, to increase their usefulness and or to decrease associated toxicity. Such compounds have also been called "latentiated drugs," "bioreversible derivatives," and "congeners," but "prodrug" is now the most commonly accepted term\textsuperscript{10,11,12}. A prodrug is a pharmacological substance (drug) administered in an inactive (or significantly less active) form. Once administered, the prodrug is metabolised in vivo into an active metabolite, a process termed bioactivation. The rationale behind the use of a prodrug is generally for absorption, distribution, metabolism, and excretion (ADME) optimization. Prodrugs are...
usually designed to improve oral bioavailability, with poor absorption from the gastrointestinal tract usually being the limiting factor.\textsuperscript{13.}

According to IUPAC (International Union of pure and applied chemistry): Prodrug is defined as any compound that undergoes biotransformation before exhibiting its pharmacological effects. \textsuperscript{14.}

Prodrugs can be used to

a) Improve patient acceptability (decrease pain on injection)

b) Alter or improve absorption.

c) Alter biodistribution.

d) Alter metabolism.

e) Alter elimination. \textsuperscript{15.}

**Characteristics of Prodrugs**

- Low oral absorption properties
- Lack of site specificity
- Chemical instability
- Toxicity
- Bad taste
- Bad odour
- Pain at application site \textsuperscript{16,17,18}

**Classification of Prodrugs**

The prodrugs has classified into two broad categories: the carrier-linked prodrugs and bioprecursors. The carrier-linked prodrug consists of the attachment of a carrier group to the active drug to alter its physicochemical properties and then subsequent enzymatic or nonenzymatic mechanism to release the active drug moiety. Depending upon the nature of carrier used, the carrier-linked prodrug may further be classified into:

1. Double prodrugs, pro-prodrugs or cascade-latentiated prodrug, where a prodrug is further derivatized in a fashion
such that only enzymatic conversion to prodrug is possible before the latter can cleave to release the active drug.

2. Macromolecular prodrugs, where macromolecules like polysaccharides, dextrans, cyclodextrins, proteins, peptides, and polymers are used as carriers.

3. Site-specific prodrugs where a carrier acts as a transporter of the active drug to a specific targeted site.

4. Mutual prodrug, where the carrier used is another biologically active drug instead of some inert molecule. A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts as a promoiety for the other agent and vice versa. The carrier selected may have the same biological action as that of the parent drug and thus might give synergistic action, or the carrier may have some additional biological action that is lacking in the parent drug, thus ensuring some additional benefit. The carrier may also be a drug that might help to target the parent drug to a specific site or organ or cells or may improve site specificity of a drug. The carrier drug may be used to overcome some side effects of the parent drugs as well.19

**NSAIDS**

Non-steroidal anti-inflammatory drugs (NSAIDs) are most widely prescribed drugs for the treatment of various inflammatory disorders including rheumatoid arthritis. However, gastrointestinal, renal and cardiovascular toxicity associated with common NSAIDs limits their usefulness. All NSAIDs are believed to inhibit the biosynthesis of prostaglandins by inhibiting the group of enzymes called cyclooxygenases (COX).20,21,22 The development of a gastrointestinal tract (GIT)-safe anti-inflammatory therapy for the treatment of disease of joints presents a unique challenge. Gastric mucosal injury produced by NSAIDs is generally aggravated by the local irritation caused by acidic group of NSAIDs. Thus temporary masking of this group gives some relief to the patient from GI irritation; hence prodrug approach is the most suitable technique for this purpose. It has been more than a hundred years since Felix Hoffman, working at Bayer Industries, reported the successful synthesis of acetylsalicylic acid as the first non-steroidal anti-inflammatory drug (NSAID).
The prodrug designing is one of the several strategies used to overcome this drawback. The rationale behind the prodrug concept is to achieve temporary blockade of the free carboxylic group present in the NSAIDs till their systemic absorption.  

Present review focuses on various modifications of NSAIDs using prodrug approach, in order to reduce their gastric side effects without affecting their biological potential.  

**Prodrugs of NSAID’S:** Considerable attention has been focused on the development of bioreversible derivatives, such as prodrugs, to temporarily mask the acidic group of NSAIDs as a promising means of reducing or abolishing the GI toxicity due to the local action mechanism. Prodrugs are pharmacologically inactive derivatives of active agents, which undergo chemical and/or enzymatic biotransformation resulting in the release of active drug after administration. The metabolic product (i.e. parent drug) subsequently elicits the desired pharmacological response.  

There are different approaches of prodrugs for reduction of side effects of GI and ulcerogenicity of NSAIDs  

- Ester and Amide prodrugs of NSAIDs  
- Anhydride prodrugs of NSAIDs  
- Mutual prodrugs of NSAIDs  

**Ester and amide prodrug of NSAIDs:** Most prodrugs of NSAIDs have been prepared by derivatization of the carboxyl group. The esters have dominated prodrug research because they have the ideal characteristic of exhibiting reasonable *in vitro* chemical stability which allows them to be formulated with adequate shelf lives. In addition, by virtue of their ability to function as esterase substrates, esters are suitably labile, *in vivo*.  

With this aim different promoeities have been taken into consideration to design new efficacious NSAID prodrugs. In the following sections, various ester and amide derivatives of NSAIDs will be discussed. Simple ester prodrugs of NSAIDs like Ibuprofen (1), Flurbiprofen (2), Ketoprofen (3) have been synthesized and evaluated. These simple esters were synthesized using simple alcohols like ethanol, isopropyl alcohol etc. This kind of system can easily undergo enzymatic hydrolysis by the action of esterases present abundantly in the small intestine; hence stomach’s mucosa is not exposed to the free carboxylic group. Similarly, simple amide prodrugs of Ibuprofen (4), Flurbiprofen
(5), Ketoprofen (6) have also been reported, wherein simple amines were used to form amide bond with the carboxylic acid. These are more stable in stomach as amidases that bring upon the hydrolysis of amide bond are present only in intestine$^{29,30}$

![Chemical structures](image-url)
Some examples of ester prodrug is given in table 1.⁴¹
### TABLE: 1

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EXAMPLE OF PRODRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>• Benzyl ester prodrug of ibuprofen&lt;br&gt;• Alkyl ester prodrugs for improved topical delivery of ibuprofen.&lt;br&gt;• glycolamide ester prodrugs of ibuprofen.</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>• 2-(l-imidazolyl)ethyl ester of ibuprofen and flurbiprofen&lt;br&gt;• Amino-alcohol Ester Derivatives of Flurbiprofen&lt;br&gt;• n-propyl, iso-propyl, benzyl and cyclopentyl prodrugs of flurbiprofen are significantly less irritating to the gastric mucosa as compared to the parent drug, i.e., flurbiprofen.</td>
</tr>
<tr>
<td>ketoprofen</td>
<td>• 1-Ethyl and 1-Propylazacycloalkan-2-one Ester Prodrugs of Ketoprofen.&lt;br&gt;• ketoprofen-dextran ester prodrug</td>
</tr>
</tbody>
</table>

**Anhydride prodrugs of NSAIDs:**

The objective of this study was to synthesize anhydride prodrugs for carboxylic-acid-bearing agents such as non-steroidal anti-inflammatory drugs, shield the carboxylic acid group from irritative effects, and obtain sustained release patterns. Ibuprofen was used as a representative drug for anhydride derivatization. Conjugates of ibuprofen with carboxylic acid moieties of different acrylic polymers were prepared by dehydration reaction using acetic anhydride. Products were characterized by infrared spectroscopy, nuclear magnetic resonance, and scanning electron microscopy followed by preparation of microspheres with different sizes from the conjugate Eudragit® L-100-ibuprofen. The drug release was monitored by high-performance liquid chromatography. Ibuprofen was bound to the polymers via an anhydride bond in high reaction yields (75–95%) with drug loading of up to 30% (w/w). These anhydride derivatives hydrolyzed and release the drug at different periods ranging from 1 to 5 days, depending on the hydrophobicity and the cross-linking of the conjugates. The release of drug from the microspheres was correlated to their size and ranged from 2 to almost 8 days. This study demonstrates the promise of anhydride prodrug for extending drug action while shielding the carboxylic acid group.\(^{32}\)
Mutual prodrugs of NSAIDs:

Mutual prodrug is a form of prodrug in which two pharmacologically active agents are attached to each other in such a way that each drug acts as a promoiety/carrier for each other and vice versa. The association may be “synergistic” if the carrier shows the same biological action as that of parent drug or may provide “additional” benefit if it shows new pharmacological action which is lacking in parent drug. The mutual prodrug concept has shown its marked therapeutic gain in case of well-accepted and useful drugs with minor undesirable properties and in those active compounds that suffer from severe limitations, like lack of site specificity, poor bioavailability or lack of particular activity.33

There are so many methodologies followed to synthesize mutual prodrug depending upon the functional group attached to parent drug or carrier drug. Among them some are given below:

- Esterification
- Amidation
- Using spacer technique
- Azo linkage for example Sulfasalazine
- Enzymatic Regioselective methodology
- Elaborate protection/deprotection and separation strategies
- Multi-step chemical reaction synthesis

Objective/ Reasons of Mutual Prodrug:

Mutual prodrug design is really no different from the general drug discovery process, in which a unique substance is observed to have desirable pharmacological effects, and studies of its properties lead to the design of better drugs. The main objectives of a mutual prodrug designing are:

- To bring both active drugs to their respective active sites.
- To provide the desired pharmacological effects while minimizing adverse metabolic and/or toxicological events.
To improve the clinical and therapeutic effectiveness of those drugs which suffer from some undesirable properties that otherwise hinder their clinical usefulness.

To avoid the practice of clinically co-administering two drugs in order to enhance pharmacological activity or prevent clinical side effects. Simultaneous administration does not guarantee equivalent absorption or transportation to site of action. So, mutual prodrug concept is useful when two synergistic drugs need to be administered at the same site at the same time. Mutual prodrugs are synthesized toward a pharmacological objective of improving each drug's efficacy, optimizing delivery, and lowering toxicities. Some examples of mutual prodrugs of NSAIDs will given in table 2.

<table>
<thead>
<tr>
<th>THERAPEUTIC AREA</th>
<th>EXAMPLE OF MUTUAL PRODRUG</th>
<th>PURPOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-steroidal Anti-Inflammatory Drugs (NSAIDS)</td>
<td>• Benorylate (Mutual prodrug of paracetamol and aspirin). 35</td>
<td>For Reduction of Gastro-intestinal side effects and ulcerogenicity of NSAIDs</td>
</tr>
<tr>
<td></td>
<td>4-biphenylacetic acid and quercetin tetramethyl ether (BPA-QTME). 36</td>
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<td></td>
<td>Chlorzoxazone esters of acidic NSAIDs. 37</td>
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<td></td>
<td>Indomethacin–flavonoid Mutual prodrug. 38</td>
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<td></td>
<td>Aminoalcohol ester analogues of Indomethacin. 39</td>
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<td></td>
<td>Coupling with amino acids. 40-41</td>
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<tr>
<td></td>
<td>Paracetamol (acetaminophen) esters of some acidic NSAIDs. 42</td>
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<td></td>
<td>Naproxen propyphenazone mutual prodrugs. 43</td>
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<td></td>
<td>Mutual prodrugs of NSAIDs and natural antioxidants. 44</td>
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<tr>
<td></td>
<td>Conjugation of NSAIDs with H2</td>
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</table>
Chemically coupling a nitric oxide (NO) releasing moiety to the parent NSAID \(^4\) to show additional Antiarthritis activity.

### Non-steroidal Anti-inflammatory Drugs (NSAIDs)

<table>
<thead>
<tr>
<th>Non-steroidal Anti-inflammatory Drugs (NSAIDs)</th>
<th>• Glucosamine conjugate prodrug of NSAIDs. (^4)</th>
<th>To show additional Antiarthritis activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-steroidal Anti-inflammatory Drugs (NSAIDs)</td>
<td>• Colon-specific mutual prodrug of 5-aminosalicylic acid (5-ASA) and sulfapyridine. (^4)</td>
<td>To enhance site-specific delivery of NSAIDs</td>
</tr>
<tr>
<td></td>
<td>• Aceclofenac colon specific mutual amide prodrug. (^4)</td>
<td></td>
</tr>
</tbody>
</table>

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**Benorylate (Mutual prodrug of paracetamol and aspirin).**

**Mutual prodrugs of tolmetin with paracetamol**
Mutual prodrugs of aspirin with salicylamide

![Chemical structure of aspirin]

Mutual prodrug of flurbiprofen with a histamine H2 receptor antagonists

![Chemical structure of flurbiprofen]

Ester prodrug 2-[N-[3-(3-(1-piperidinomethyl)phenoxy)propyl]carbamoylmethylthio]

Ethyl 1-(p-chlorobenzoyl)-5-methoxy-2-methylindol-3-acetate of an H2-antagonist and indomethacin

NO RELEASING NSAIDS (NO-NSAIDS)

Another widely explored and promising approach towards the development of GIT-sparing NSAIDs is the linking of an NO releasing moiety to these compounds. The rationale behind developing this class of drugs is that, NO by maintaining gastric mucosal blood flow and preventing leucocyte adherence to the vascular endothelium of the splanchnic circulation (one of the earliest events following NSAID administration) may counteract the detrimental effect of COX-1 suppression so that mucosal injury does not occur. The general structural features of NO–NSAIDs enable a large number of variations within the linking spacer and the NO-donating moiety. Owing to the ease of
formation of these nitrate esters, several derivatives could be prepared for a given spacer. Till date, a significant amount of work on NO–NSAIDs and other related compounds has been reported.

Some example of NO-NSAIDS are given in table 3.

**Table-3**

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>EXAMPLES</th>
<th>PURPOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO-NSAIDS</td>
<td>• 3-(nitroxymethyl)phenyl 2-acetoxybenzoate (NCX-4016) (^{52,53})</td>
<td>greater anti-inflammatory and analgesic activities than aspirin</td>
</tr>
<tr>
<td></td>
<td>• 4-nitroxybutyl 2-acetoxybenzoate (NCX-4215) (^{54,55})</td>
<td>did not produce macroscopically visible histological damages in the stomach when administered up to 300 mg/kg, whereas 100 mg/kg aspirin produced widespread hemorrhagic damage</td>
</tr>
<tr>
<td></td>
<td>• S-Nitrosothiol esters of diclofenac (^{56,57})</td>
<td>anti-inflammatory and analgesic properties possessing a markedly enhanced gastric safety profile</td>
</tr>
<tr>
<td></td>
<td>• Ester derivatives of aspirin, ibuprofen and indomethacin with O(2)-acetoxyethyl 1-[N-(2-hydroxyethyl-N-methylamino]diazenium Diolate (^{58})</td>
<td><em>in vivo</em> ulcer index (UI) assay showed that aspirin derivative, ibuprofen derivatives and indomethacin derivatives were significantly less ulcerogenic when compared to the parent drugs, aspirin, ibuprofen and indomethacin at eqimolar doses.</td>
</tr>
</tbody>
</table>
Conclusions

In spite of extensive efforts in the direction of separation of therapeutic effect of NSAIDs from their GI toxicity, the search for an ideal prodrug with a superior therapeutic advantage for clinical use still remains unmet. Further, research is needed to design and identify prodrugs, which would be appropriate for clinical use in terms of stability, metabolism, toxicology and side effects. Instead of synthesizing new compounds which is a time consuming and too
costly an affair, the designing of derivatives of existing clinically used NSAIDs is definitely an interesting and promising area of research. Moreover, as the metabolic profile of the liberated parent drug (after cleavage of the derivative in the body) would be already known, it could be advantageous to design derivatives of parent NSAIDs. Synthesis of prodrugs of NSAIDs is not only an effective way of overcoming the GI toxicity but could also be used for combining other pharmacological properties or incorporating a chemical moiety for an added beneficial effect (like development of NO-NSAIDs,\textsuperscript{59,60} conjugation with H2 receptor antagonist\textsuperscript{61} or an analgesic agent\textsuperscript{60} and incorporating anticholinergic activity for reducing gastric acid secretion.\textsuperscript{62-67}

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