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Short Communication

Mutual Prodrugs of Piroxicam

Mohd Imran[1] and Mohammad Asif[2]*

[1]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Northern Border University, Rafha, Saudi Arabia*

[2]*Department of Pharmaceutical Chemistry, Himalayan Institute of Pharmacy Research, Dehradun, India*

***Corresponding Author:** Mohammad Asif, Professor, Department of Pharmaceutical chemistry, Himalayan Institute of Pharmacy Research, Dehradun, India.

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Most of the drug molecules in present use are linked with some intolerable physicochemical or biopharmaceutical factors. Non-steroidal anti-inflammatory drugs (NSAIDs) have possibility of common adverse effects like dyspepsia or acidity and ulceration that limits their uses [1]. These NSAIDs are commonly used in the treatment of pain and inflammation in various conditions like osteo/rheumatoid arthritis (OA/RA) [2]. Progression in the side effects of gastrointestinal tract (GIT) mainly stomach ulceration, bleeding and damage of stomach mucus membrane are the main limitation in use. This is due to local effect applied by direct contact of drug with gastric mucosa [3]. The enolic hydroxyl group of piroxicam and free acidic group of aryl propionic acids plays a key role in sustaining the efficiency and making the gastric ulceration as well [4]. There are several advances reported that are used to overcome the side effects of NSAIDs by chemical derivatization with retention of effectiveness. Mutual prodrug concept involves the conjugation of two biologically active drugs in which individual drug acts as promoiety. This concept has used for reduced GI toxicity by temporarily masking enolic group of piroxicam with acidic group of other NDAIDs drugs and also enhance their absorption5. Prodrugs of piroxicam is of intense attention for medicinal chemist as the enolic hydroxyl group can be derivatized simply and could results in expanded derivatives like ampiroxicam, one of the extensively used drug [6-8]. Several prodrugs of selected NSAIDs were also reported [9,10]. A new series of mutual prodrugs of piroxicam is designed by combine it with well-known NSAIDs like aceclofenac, ibuprofen, mefenamic acid and naproxen as active promoieties. The enolic hydroxyl group of piroxicam is conjugated with acidic group of propionic acid derivatives to get esters.

Synthesis of piroxicam prodrugs

Mutual prodrug ester derivatives, piroxicam-aceclofenac ester (PA), piroxicam-ibuprofen ester (PI), piroxicam-mefenamic acid ester (PM) and piroxicamnaproxen ester (PN) (Figure 1) were synthesized by first converting the promoieties having acidic group into corresponding acid chlorides and followed by reaction with hydroxyl group of piroxicam (Scheme 1).

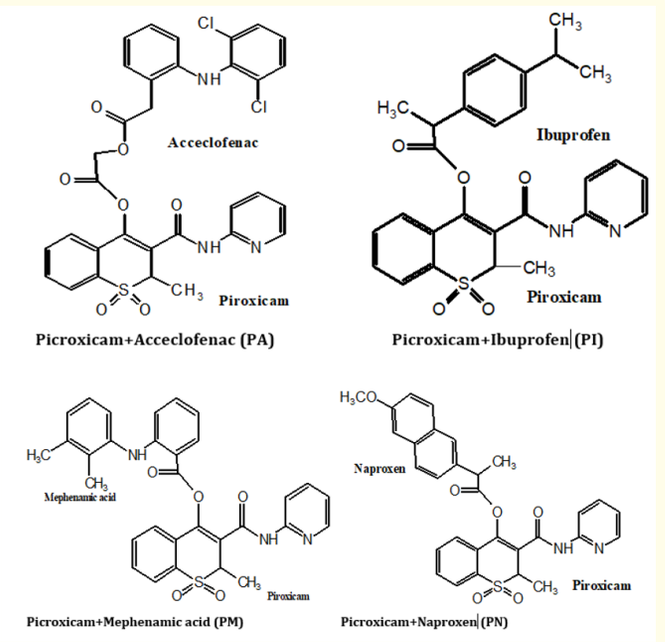
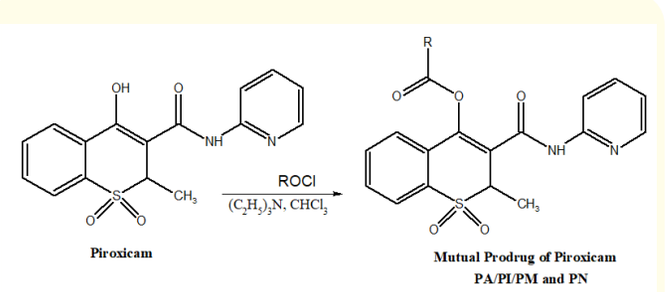


Figure 1: Structure of mutual prodrugs of Piroxicam.



Scheme 1: RCOOH=NSAIDs (Aceclofenac/Ibuprofen/ Mefenamic acid/ Naproxen).

$$RCOOH \xrightarrow[Heat]{SOCl_2,\ CHCl_3} RCOCl$$

This approach in overcoming the disagreeable properties of accessible drugs by designing the mutual prodrugs. The synthesis of mutual prodrugs of piroxicam was get with well-known NSAIDs. The targeted prodrugs PA/PI/PM and PN (Figure 1) were formed (Scheme 1) successfully by altering the selected NSAIDs (aceclofenac, ibuprofen, mefenamic acid and naproxen) to their own acid chlorides by using thionyl chloride. These NSAIDs act as masking agent for enolic hydroxyl group of piroxicam. The acid chlorides were then coupled with piroxicam through enolic hydroxyl in presence of chloroform and triethylamine. The necessary precondition for success in the use of prodrugs is that the masked drugs should be acid stable to avoid the direct contact effects with the gastric mucosa as well as the local inhibition of the prostaglandins (PGs) [11]. These piroxicam prodrug derivatives were expected across the suitable clinical range having acidic, neutral and alkaline pH values. The hydrolysis kinetics result showed that prodrugs of piroxicam undergo chemical degradation with first order kinetics, and consequently quantitatively changed to parent drug. All these prodrugs showed high stability in acidic condition; this indicates that the drugs passed unhydrolyzed through the stomach on oral use [12]. The degradation capacity of prodrugs at neutral and alkaline pH is an indication of their susceptibility for hydrolysis.

The mutual prodrug approach can be successfully applied in attaining the goal of enhancing the therapeutic values of piroxicam; masking of enolic hydroxyl group through acids and converting them to esters and using the NSAIDs for getting the synergistic effects (anti-inflammatory and gastro-protective effects). Mutual prodrug approach gives an opportunity to medicinal chemist for improving the clinical and therapeutic values of a drug that is suffering from unwanted properties hampering its clinical values.

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