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Formulation and evaluation of co-prodrug of flurbiprofen and methocarbamol

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ABSTRACT

The current work envisages synthesis of an ester prodrug of flurbiprofen whereby its carboxylic group was condensed with a skeletal muscle relaxant methocarbamol, with the aim of synergistic activity of two drugs, avoid flurbiprofen mediated gastro-intestinal damage and minimize the ulceration tendency of flurbiprofen. The synthesized prodrug was characterized and confirmed by physicochemical and spectroscopic studies. Solubility and partition coefficient studies indicated an increased lipophilicity and thus better suitability for oral administration than the parent drugs and the protein binding studies revealed a low protein binding capacity of the mutual prodrug. Subsequently, *in-vitro* hydrolysis was studied in different pH, simulated gastric fluid, simulated intestinal fluid and plasma and quantitative evaluation was performed by high performance liquid chromatography. It was found that the prodrug remained unhydrolyzed in the stomach after absorption however, underwent rapid cleavage by the esterases in blood to give the parent drug. Furthermore, the mutual ester prodrug was evaluated for its anti-inflammatory, analgesic, skeletal muscle relaxation, ulcerogenic and total acid content activity and was found to possess comparable activity with that of the parent drugs. Microscopic structures of the stomach tissues revealed significant reduction in gastric ulcer formation of mice gastric mucosa as compared to parent carboxylic acid drug.

1. Introduction

NSAIDs are a vast group of medications that are highly praised nowadays for their triple action: analgesic, antipyretic and anti-inflammatory activities. The nonsteroidal anti-inflammatory drugs are the most widely prescribed and used drugs for rheumatologic as well as nonrheumatologic conditions, which include acute and chronic pain [1], biliary, ureteric colic [2], dysmenorrhea [3], fever, and other applications [4]. In other words, NSAIDs help to relieve pain, lower high body temperature or fever and reduce inflammation. These are more prescribed than

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opioids because of no narcotic effect and dependence risk. NSAIDs block the production of substances in the body called prostaglandins that play a role in pain, inflammation, fever, and muscle cramps and aches. At low doses, NSAIDs work essentially as pain relievers while at higher doses they can actually reduce the body's inflammatory response to tissue damage as well as relieve pain.

Almost all NSAIDs on long-term treatment inhibit the enzyme cyclo-oxygenase (COX) and production of prostaglandins [5]. Continuous intake of NSAIDs results in irritation of the gastric mucosa and enhances ulceration by blocking protective action of the prostaglandins on gastric mucosa, causing ulcer formation not only in the stomach but also in the lower part of the esophagus and also in the duodenum. In general, the properties of NSAIDs that contribute to ulcerogenesis can be divided into two categories: topical irritancy and the suppression of prostaglandin synthase activity. In addition, NSAIDs tend to damage the mucosa due to the presence of acid in the stomach and in the duodenum and in some cases due to the presence of *Helicobacter pylori* (*H. pylori*) [6]. The gastrointestinal side effects of NSAIDs are generally attributed to direct and/or indirect mechanisms. The direct contact effect results usually from a local irritation produced by the acidic group of the NSAIDs and local inhibition of prostaglandin synthesis in the GI tract. The indirect mechanism is due to a generalized systematic action occurring after prior absorption.

Prodrugs, the pharmacologically inactive derivatives of active drugs, are designed to maximize the amount of active drug that reaches its site of action, through manipulation of the physicochemical, biopharmaceutical or pharmacokinetic properties of the drug. Prodrug synthesis is one of the approaches to modify chemical and physical parameters of parent drugs to overcome their limitations [7]. At the same time, biotransformation of a prodrug to its parent compound at its target site of activity may be used to achieve rate-controlled and time-controlled drug delivery of the actives [8]. The prodrug approach has the ability to keep promising new drug candidates alive through development and to improve the safety and efficacy of existing drug products. It is a very fruitful area of research and its introduction in human therapy has given successful results in improving the clinical and therapeutic effectiveness of drugs with undesirable side-effects [9–11].

The aim of designing a mutual prodrug is to overcome limitations of a parent drug that would otherwise hinder its clinical use. Gastric mucosal injury produced by NSAIDs is generally aggravated by the local irritation caused by acidic group of NSAIDs [12,13]. The temporary masking of this group may offer relief to the patient suffering from GI irritation; hence, prodrug approach is the most suitable technique for this purpose. The current work deals with a potent anti-inflammatory drug associated with GI irritation, flurbiprofen, which was selected as a model drug for carboxylic acid derivatization. Another drug, methocarbamol, is also clinically prescribed for painful spasms associated in GI disorders as skeletal muscle relaxant [14]. The rationale of this work was to couple flurbiprofen with methocarbamol to achieve reduced GI irritation and related side effects along with a synergistic effect of both actives. Generally, these two drugs are prescribed in combination; however, this combination often reveals the side effects associated with each other. Coupling of both compounds as a hybrid drug or through a spacer known as a mutual prodrug can result in a potent anti-inflammatory compound with reduction of the main adverse local effects related to the activity of the NSAID and skeletal muscle relaxant.

2. Materials and methods

2.1. *Materials*

NSAID flurbiprofen and skeletal muscle relaxant methocarbamol were kindly provided by Sun Pharma, Mumbai and Synthochem Pvt. Ltd., Hyderabad. The other reagents and solvents used were of analytical/spectroscopic/HPLC grade as needed. The reactions were monitored by TLC on precoated silica G plates using iodine vapor as detecting agent. Melting points were recorded using capillary tube method. IR spectra were obtained by a Shimadzu IR spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded using DMSO on a Bruker-300 AVANCE instrument. Chemical shifts are expressed as δ (ppm). HPLC analysis, i.e. *in-vitro* hydrolysis studies, were carried out using a Jasco HPLC system using mobile phase acetonitrile:water (80:20) and detection wavelength 228 nm with flow rate 1 ml/min. The protocol for the animal experiments performed was approved by the IAEC (Institutional Animal Ethics Committee) as registered under the Committee for the Purpose of Control and Supervision of Experiments on Animals (Reg.No.988/C/06/CPCSEA); approval number (BVCPK/CPSCEA/IAEC/01/08). Activities were carried out at the Department of Pharmacology, Bharati Vidyapeeth College of Pharmacy, Kolhapur.

2.2. *Synthesis of prodrug*

The reaction for synthesis of prodrugs involved two steps. The first step consisted of acid chloride formation and the second step gives formation of mutual prodrug (Fig. 1). Acid chloride formation is initiated by reacting flurbiprofen with thionyl chloride. The acid chloride of flurbiprofen was synthesized by reacting with excess thionyl chloride and refluxed for 30 min in RBF. After completion of the reaction, the mixture was cooled to room temperature and the excess of the thionyl chloride was removed from the reaction mixture. The product (acid halide derivative of flurbiprofen) was collected and then washed with water.

In the second step, the acid chloride of flurbiprofen was treated with the other drug methocarbamol to form the mutual prodrug. A three-necked flask with a sealed stirrer was fitted with a reflux condenser and a dropping funnel. 0.77 mol of methocarbamol, 0.84 mol of pure dimethyl aniline and 100 ml of anhydrous ether was placed in the flask. The stirrer was set in motion and the mixture was heated to gentle reflux on a water bath. 0.79 mol of redistilled acid chloride of flurbiprofen was run at such a rate that moderate refluxing continued after heating was removed. When two-third of the acid chloride was introduced, the dimethyl aniline hydrochloride commenced to crystallize and then the mixture was refluxed vigorously. Subsequently, it was cooled on an ice bath and after the refluxing ceased, the remainder of the acid chloride was added. The mixture was then heated on a water bath for 1 h. It was cooled