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ASSESS THE SOLUBILITY OF PROPYPHENAZONE, FLURBIPROFEN, MEFENAMIC ACID, ACECLOFENAC, ASPIRIN IN VARIOUS SOLVENTS INCLUDING WATER, ETHANOL

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ABSTRACT

Significant efforts have been made to enhance the effectiveness of various pharmaceuticals. The prodrug strategy has emerged as a promising method for delivering medications with improved pharmacokinetic and pharmacodynamic characteristics. Biological evaluations, including analgesic, anti-inflammatory, and ulcerogenicity studies, were conducted on the synthesized prodrugs, revealing that all prodrugs exhibited superior activity compared to their parent compounds. Analgesic effects were assessed using the acetic acid-induced writhing test, while anti-inflammatory effects were measured through the carrageenan-induced rat paw edema model. The ulcerogenicity results indicated that all prodrugs caused less gastrointestinal irritation than the parent drugs. Mutual prodrugs of propyphenazone combined with selected NSAIDs were developed to enhance the therapeutic index by mitigating gastrointestinal irritation and bleeding. The structures of these synthesized mutual prodrugs were verified using IR, Mass, 1H NMR, and C-13 NMR spectroscopy. An in vitro hydrolysis study conducted in simulated intestinal fluid (SIF) and simulated gastric fluid (SGF) demonstrated that the prodrugs remained stable in a buffer solution at pH 1.2, indicating their stability in gastric conditions. A validated HPLC method was employed to estimate the release of free drug following hydrolysis.

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Keywords: Flurbiprofen, Validation, RP-HPLC, Prodrug, NSAIDs, Propyphenazone

1. INTRODUCTION:

In response to trauma, microbial invasion, or exposure to harmful substances, the body can undergo acute inflammation, which sets in quickly and intensifies rapidly. This type of inflammation typically lasts for a brief period, ranging from a few days to a short period. Examples of conditions characterized by acute inflammation include cellulitis or acute pneumonia. Following acute inflammation, there is a transitional phase known as subacute inflammation. This stage bridges the gap between acute and chronic inflammation and typically endures for a period of 2 to 6 weeks. During this time, the body's immune response continues to address the initial trigger and promote healing. The inhibition of cyclooxygenase (COX) enzymes plays a crucial role in reducing prostaglandin synthesis, which, in turn, alleviates inflammation, pain, and fever. However, the suppression of prostaglandin production is associated with several adverse effects, including gastrointestinal (GI) discomfort, cardiovascular complications, renal toxicity, fluid retention, and exacerbation of hypertension. Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their effects through dual inhibition

of COX enzymes, specifically COX-1 and COX-2.While COX-2 inhibition is primarily responsible for the anti-inflammatory and analgesic properties of NSAIDs, the inhibition of COX-1 contributes to GI mucosal damage, leading to complications such as ulceration, upper gastrointestinal perforation, and hemorrhage.NSAID-induced GI toxicity occurs through two primary mechanisms. The first involves direct contact between NSAIDs and the gastric mucosa, leading to localized suppression of prostaglandin synthesis in the GI tract. Additionally, the presence of the carboxyl functional group in NSAIDs contributes to local irritation and mucosal damage. While COX-2 selective inhibitors were developed to mitigate GI-related adverse effects, their use has been linked to other complications, including elevated serum potassium levels and potential hepatotoxicity.Recent studies have highlighted the role of reactive oxygen species (ROS) in the development of gastric mucosal injuries associated with NSAID therapy. The excessive generation of ROS exacerbates oxidative stress, further contributing to NSAID-induced ulcerogenicity. To overcome these challenges, the concept of mutual prodrugs has gained attention as a strategy to enhance the safety and efficacy of NSAIDs. Mutual prodrugs are designed to improve the physicochemical and pharmacological properties of parent drugs by modifying their structure to minimize direct exposure to the gastric mucosa. These prodrugs undergo enzymatic or chemical conversion at the target site, releasing the active drug in a controlled manner. Various NSAID derivatives, including ester and amide prodrugs, have been synthesized to improve solubility, bioavailability, and gastrointestinal safety. By preventing the direct interaction of the parent drug with the gastric mucosa, these prodrugs offer enhanced therapeutic benefits while reducing adverse effects. The present study is focused on the development and validation of a robust and reliable analytical method for the quantification of a mutual prodrug of Propyphenazone and Flurbiprofen. A comprehensive literature review revealed that no liquid chromatographic method has been previously reported for the estimation of this specific mutual prodrug. Therefore, this study aims to bridge this gap by establishing and validating a novel reverse-phase high-performance liquid chromatography (RP-HPLC) method to accurately quantify the prodrug in bulk and pharmaceutical formulations.

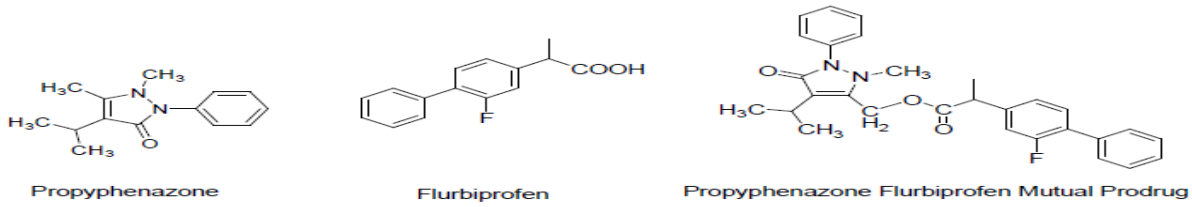

Figure 2: Chemical Structure of Drugs and Prodrug

2. MATERIALS AND METHODS

Materials

Instruments

Digital melting point apparatus was used to determine melting points (mp). An FT-IR (Alpha Model) spectrophotometer from Bruker was used to record IR spectra using the KBr disc technique. Deuterated DMSO ([D6] DMSO) was used as the solvent to record 1 H spectra at a frequency of 400 MHz on a Bruker Advanced- II 1HNMR spectrometer at room temperature. The internal standard TMS is used to measure chemical shifts in ppm. Mass spectra were recorded using a Shimadzu LC-MS 8040. The investigation employed a stationary phase Shimadzu C18 Shim-pack Gist (250 x 4.6m, 5 mm) column and an HPLC instrument of Shimadzu manufacture with a UV detector (Software: Lab Solutions). Additional instruments included a vacuum pump filtration assembly (Rocker 300), a sonicator water bath (Janki Impex), an analytical weighing balance (Mettler Toledo), a UV-Visible spectrophotometer Shimadzu 1900, and a Ph meter.

Chemicals & Apparatus

Propyphenazone was provided as a gift sample by Stellence Pharmscience (P) Ltd, located in Bangalore, Karnataka. Other initial substances and chemicals were bought from reputable suppliers, including Sigma-Aldrich and Merck, and were used as-is without additional purification. Flurbiprofen was procured from Sigma-Aldrich in Mumbai. Methanol, acetonitrile (ACN), and high-performance liquid chromatography (HPLC)-grade water were obtained from Fine Chem in Mumbai, India. Analyticalgrade glacial acetic acid and ortho-phosphoric acid were sourced from Rankem Laboratories Private Ltd in Thane, Maharashtra, India. A 0.45 µm pore size membrane filter and a 0.22 µm test filter paper were purchased from Pall India Private Ltd in Andheri, Mumbai, India.

Solubility Study

A study was conducted to assess the solubility of Propyphenazone, Flurbiprofen, Mefenamic acid, Aceclofenac, Aspirin, and Salicylic acid in various solvents including Water, Ethanol, Dichloromethane, Methanol, and Acetonitrile. To determine the solubility of each substance, 10 mg of the drugs were placed in a 100 ml volumetric flask. Solvents were then gradually added in 0.1 ml increments at room temperature, while agitating the mixture for a few minutes until the drug completely dissolved. The quantity of solvent needed to achieve full dissolution was noted, and the resulting solubility information for each substance is detailed in the table.

Table 1: Solubility data

Descriptive term	**Part of solvent required per part of solute**
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

3. RESULTS AND DISCUSSION

Solubility Study

Table 2 : Solubility study data

Name of API	**Water**	**Methanol**	**Acetonitrile**	**Dichloromethane**
Propyphenazone	Practically insoluble	Very soluble	Freely Soluble	Very soluble
Mefenamic Acid	Practically insoluble	Very soluble	Very soluble	Freely Soluble

Flurbiprofen	Practically insoluble	Very soluble	Very soluble	Very soluble
Aspirin	Practically insoluble	Very soluble	Freely Soluble	Very soluble
Aceclofenac	Practically insoluble	Soluble	Very soluble	Freely Soluble
Salicylic acid	Practically insoluble	Soluble	Freely Soluble	Freely Soluble

4. CONCLUSION

The Investigation appears to contain a solubility comparison of various APIs (Active Pharmaceutical Ingredients) in different solvents. Based on this data, we can conclude that methanol is the most effective solvent among the ones listed, as all APIs exhibit high solubility in it. Acetonitrile and dichloromethane also show good solubility for most APIs, whereas water proves to be the least effective solvent, with all APIs being practically insoluble in it. This information is crucial for pharmaceutical applications, as solvent selection plays a key role in drug formulation and dissolution behavior.

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