
Formulation, Release Characteristics and Evaluation of Nimesulide Suppositories

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Suppositories of nimesulide were formulated using cocoa butter and different polyethylene glycol (PEG) bases. PEG base suppositories showed a better permeation of drug with faster dissolution rate *in vitro* than cocoa butter base suppositories. The results of *in vivo* antiinflammatory activity of nimesulide suppositories in Wistar rats showed that suppositories of cocoa butter base exhibited better antiinflammatory activity than PEG bases.

The effect of different suppository bases on *in vitro* release of drugs has previously been described¹. Generally, drug release from a number of suppository bases depends upon the drug solubility in the base, the chemical composition of the base and drug particle size. The drug release from suppository bases is influenced by the presence of other additives in the formulation and may result in an increase or decrease in the rate of release depending on the nature of the base and that of the additive and its concentration². There are reports describing attempts at enhancing the rate of release of drug from different suppository bases by incorporation of surfactants^{1,3}.

Nimesulide is non steroidal anti inflammatory drug, (NSAID) employed in the treatment of inflammation and pain. It exhibits antipyretic and analgesic properties. Though the incidence of adverse effects are low with nimesulide, it is not totally free from side effects. The common side effects are epigastralgia, nausea, diarrhoea, vomiting, CNS effects, dizziness, headache and dermatological disorders like rash and pruritis⁴. Similar to other

NSAID's, nimesulide also exerts its therapeutic effect largely by its ability to inhibit prostaglandin synthesis through inhibition of cyclooxygenase, thus inhibiting the gastroprotective prostaglandin's which leads to gastric intolerance. Many NSAID's are formulated as suppositories which helped to circumvent the problem of gastric intolerance including indomethacin¹, ibuprofen² and oxyphenbutazone⁵. However less consideration has been given to the formulation of nimesulide in the form of suppositories except for a few reports⁶⁻⁸.

In the present investigation, an attempt was made to formulate nimesulide suppositories using water soluble as well as fatty bases. Various *in vitro* studies including permeation across synthetic membrane and dissolution studies were conducted. The prepared formulations were evaluated for antiinflammatory activity in Wistar rats using carrageenan-induced paw oedema volume method.

MATERIALS AND METHODS

Nimesulide was a gift sample from Juggat Pharma, Bangalore, India, Polyethylene glycols 1000, 4000 and 400 were procured from Ranbaxy Ltd. S.A.S., Nagar, India. Cocoa butter (B.P. grade), was obtained from the indicated sources. All other chemicals were of analytical grade and used as procured.

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TABLE 1 : TYPE AND COMPOSITION OF THE SUPPOSITORY BASES

Base Type	Composition
Polyethylene glycol's (PEG)	
PEG 'A'	PEG 1000
PEG 'B'	PEG 1000 : PEG 4000 (3:1)
Cocoa butter	

Preparation of Suppositories:

The details of the formulations are given in Table 1. Accurately weighed quantities of respective suppository bases were melted on the water bath. The finely divided drug powder (29.8 mg) was incorporated into molten base with thorough mixing. The molten mass was poured into suppository mold of 125 mg capacity. The suppositories formed were then stored in refrigerated condition; exposure to room temperature was limited to less than 24 h before use in *in vitro* release studies.

For studying antiinflammatory activity, nimesulide (3.6 mg dose calculated according to Ghosh and Schild)⁹ was mixed with melted suppository base and poured into a special mold of 125 mg capacity. For comparison, an aqueous suspension of nimesulide (3.6 mg/ml) was prepared by dispersing in 2% acacia solution. This solution was used as an oral dosage form (1 ml).

Uniformity of Weight:

Twenty suppositories were weighed and average weight was calculated. Each suppository was then individually weighed. No suppository should deviate from the average weight by more than 5% except that 2 should not deviate by more than 7.5%.

Drug Content Determination:

Nimesulide was extracted from cocoa butter suppositories and PEG suppositories by shaking 5 suppositories with 25 ml methanol in a standard flask. The extract was filtered and suitably diluted. The absorbance was measured at 300 nm using a double beam spectrophotometer (Shimadzu UV-240, graphicord, Tokyo, Japan). The blank suppository, treated in the same manner served as blank.

Melting Range:

This test is also known as macromelting range test. During this test, the time taken for the entire suppository to melt/disperse is measured when immersed in a water bath maintained at constant temperature (37° water bath). The time required for the whole suppository to melt or disperse in the surrounding water is noted¹⁰.

Breaking Strength:

Breaking strength or friability test was carried out to determine the tensile strength of the suppositories to assess whether they will be able to withstand the hazards of packing, transporting and normal handling or not¹⁰.

Permeation Studies:

A simple assembly was used for the release studies. The suppository to be tested was placed in a glass tube open at both ends. To one end of which a sigma membrane (soaked overnight in buffer solution) was stretched and securely fastened with a rubber band. The tube was hung in a vertical position into a 250 ml beaker containing 100 ml phosphate buffer (pH 7.4±0.1) with PEG 400 (20% v/v), such that the lower end of the tube was 3 cm from the bottom of the beaker. The beaker was then placed in a thermostatically controlled magnetic stirrer (37±0.1°) and the solution agitated using a magnetic stirrer. Phosphate buffer containing 20% v/v PEG 400 (5 ml) was placed inside the tube over the suppository at the beginning of experiment. Samples of 5 ml were withdrawn from the solution in the beaker at regular time intervals and were replaced by fresh buffer samples kept at the same temperature. Drug concentrations for these samples were determined spectrophotometrically at 401 nm.

In vitro Dissolution Studies:

The USP XXI Dissolution Apparatus I was used for dissolution studies. The dissolution medium was 250 ml phosphate buffer (pH 7.4±0.1) with 20% v/v PEG 400 kept at 37±0.1°. The suppository was placed in the metal basket which was then spun at 50 rpm. Samples of 5 ml were withdrawn at regular time intervals for spectrophotometric estimation of nimesulide concentration. Samples, which had been withdraw, were replaced by same volume of fresh buffer solution. The materials used did not interfere with the assay procedure for the drug.

Antiinflammatory Activity:

Screening for antiinflammatory activity was carried

out by carrageenan-induced paw oedema method in male Wistar rats. The animals were divided into five groups of 6 animals each. Group 1 received no treatment and served as control. Group 2 received the drug by oral route and served as a standard. Animals in Group 3,4, and 5 received treatments with cocoa butter suppositories, PEG 'A' Suppositories and PEG 'B' suppositories, respectively. After 30 min 0.1 ml of 1% carrageenan in saline was injected by subplantar route into the right hind paw. The volume of the paw was measured immediately with the help of a pletysmometer. This reading was assigned as zero h volume. The volume of the right hind paw was again measured after three hour and designated as 3rd h volume. The paw volume were measured subsequently at 1.0, 1.5, 2.0, 2.5, 3.0, 4.0 and 5.0 h. Swelling in case of animals treated with drug was compared with that of control and the percentage inhibition of oedema was calculated using the formula:

$$\text{Per cent reduction of oedema} = \frac{C-T}{C} \times 100$$

Where C is mean volume of oedema for control

T is mean volume of oedema for treated group

RESULTS AND DISCUSSION

The prepared suppositories showed a fair uniformity of drug content of 95 to 98%. The melting range of various suppositories was found to be in the range of 20-25 min. The breaking strength of the prepared suppositories was 0.5 kg/cm².

The permeation patterns of nimesulide from the three different suppository bases were studied (Figure 1). It was observed that permeation was more rapid from PEG 'B' base followed by PEG 'A' base and cocoa butter base. These studies were primarily aimed to obtain the release pattern of the formulations. Dissolution pattern of the drug from different bases was compared with the drug powder and are shown in Figure 2. Suppositories prepared with PEG 'B' base showed maximum release of the drug followed by suppositories prepared with PEG 'A' base and suppositories prepared with cocoa butter base. PEG bases are water soluble hence they dissolved more rapidly in the dissolution medium releasing the drug in to the dissolution medium. On the other hand, the hydrophobic nature of drug and its high affinity for the fatty base (cocoa butter), the release rate from this base less. This may be due to two reasons. Firstly though the cocoa butter can melt easily at 37° (melting range 33.5-35°)¹¹ it may

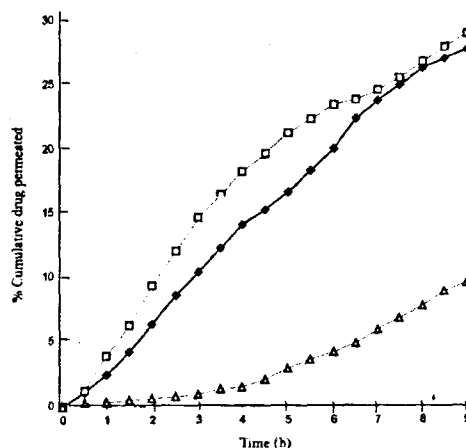


Fig. 1 : Permeation of Nimesulide From Different Suppositories Across Sigma Membrane

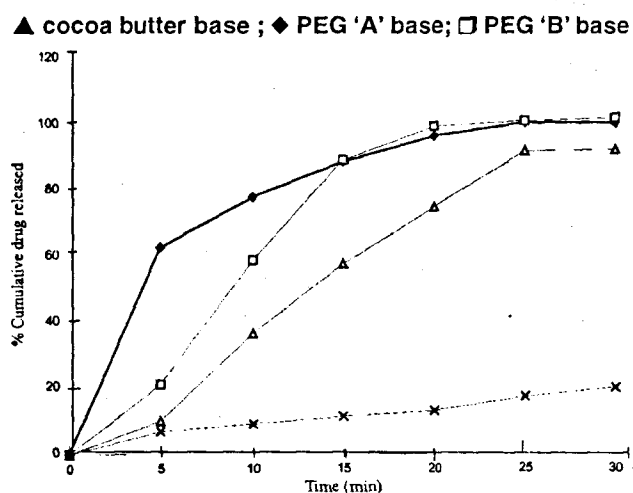


Fig. 2 : *In vitro* Dissolution of Nimesulide From Different Suppositories

x : Cocoa butter base; Δ PEG 'A' base; ■ PEG 'B' base; ± Nimesulide powder

not readily disperse the drug throughout the dissolution medium because of high affinity of drug towards the fatty base and secondly drug partitioning may not be favoured into aqueous medium of pH 7.4.

Inflammation is a protective response of the tissues to irritation or injury. One of the reasons for the inflammation is due to the synthesis of prostaglandins in the body. Inflammation may be acute or chronic. The classic signs of inflammation have long been recognised, the tissue becomes red, swollen, tender, or painful, there is local heat and the patient may be febrile. Loss of organ function occurs during chronic inflammation¹². The inflammatory reactions are readily produced in Albino rats in the

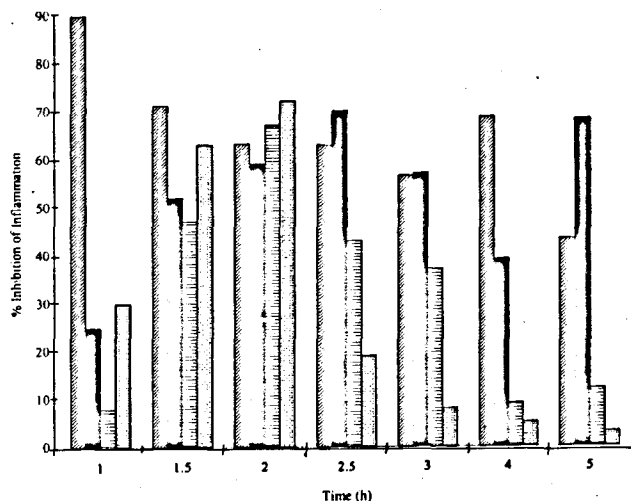


Fig. 3 : Antiinflammatory Activity of Nimesulide suppositories Prepared With Different Bases

▨ Standard ▣ Cocoa ▤ PEG 'A' ▥ PEG 'B'

form of paw oedema with the help of irritants or inflammagens such as formaldehyde, carrageenan, bradykinin, histamine, mustard or egg white. Nimesulide is a selective inhibitor of prostaglandin synthesis but appears to exert its therapeutic effect by variety of other mechanisms that include inhibition of platelet activating factor (PAF), tumor necrosis factor-alpha (TNF alpha), proteinase and histamine etc.,

From figure 3, it can be observed that the per cent inhibition of inflammation at 3 h was in the rank order of cocoa butter suppositories (54.5%)> standard formulation (53.4%)>PEG 'A' base (35.1%)>PEG 'B' base (8.1%). These results reveal that, in contrary to the slow release of drug *in vitro* from the fatty base due to hydrophobicity of the drug, the drug will partition readily into the rectal fluids *in vivo* and hence showed better antiinflammatory activity than that from PEG bases. However, from figure 3, it can also be observed that the PEG bases showed optimum antiinflammatory activity in early hours with shorter duration of action compared to cocoa butter base. This can be explained by the solubility of PEG bases in

aqueous rectal fluids thereby leaving the drug free for absorption and showed faster anti inflammatory activity than cocoa butter base. The onset of action was faster from the oral route with a short duration of action compared to the suppositories.

In conclusion, nimesulide can be formulated in the form of suppositories and the selection of the base is dependent upon the condition and severity of inflammation. It would be better if the suppositories are prepared with PEG bases to treat an acute inflammation, whereas suppositories prepared with cocoa butter would be a better choice in the treatment of chronic inflammation where a sustained release of drug for a longer period of time is desired.

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