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Research Article

Designing, Release Characteristics and *In vitro* Evaluation of Flurbiprofen Sodium Suppositories

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ABSTRACT
The present investigation was aimed to evaluate the possibility of using different suppository bases i.e. cocoa butter and different polymeric grades of PEG (4000 and 6000) for the development of rectal drug delivery system of flurbiprofen sodium, an non steroidal anti-inflammatory drug to minimize the gastric irritation of the drug upon oral administration. Suppositories were formulated by fusion method and evaluated for their physicochemical characterization followed by *in vitro* evaluation. Suppositories containing PEG 4000 showed a better permeation of drug with faster dissolution rate *in vitro* when compared with other formulations.

Keywords: Flurbiprofen sodium, Cocoa butter, PEG 4000 and 6000, *in vitro* release study.

INTRODUCTION

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 the suppositories 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 additives and its concentration. [1]

Non-steroidal Anti-inflammatory Drugs (NSAIDs) are usually good candidates for the development of controlled release preparations particularly through the rectal route to reduce or eliminate the gastrointestinal irritation. Flurbiprofen is an NSAID having prominent anti-inflammatory, analgesic and antipyretic properties. Flurbiprofen is an arylpropionic acid derivative. Similar to other NSAIDs flurbiprofen also exerts its therapeutics effects largely by its ability to inhibit the biosynthesis of prostaglandins in all cells through inhibition of cyclooxygenase, thus inhibiting the gastro-protective prostaglandin's which leads to gastric intolerance. Absorption after rectal doses may be more rapid. It is about 99 % bound to plasma proteins and has a plasma half-life of about 3 to 6 hours. It is extensively metabolized mainly by hydroxylation. Minor symptoms of ocular irritation including transient burning and stinging have been reported following the instillation of flurbiprofen sodium eye drops; there may be increased bleeding from ocular surgery and wound healing may be delayed. Local irritation may also follow rectal use and local effects including a sensation of warming or burning in the mouth may be seen after using flurbiprofen lozenges. A sensation of warming, transient burning sensation, local irritation, in conjunction with surgery there is an increase in bleeding tendency of ocular tissue. It is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis, in soft-tissue disorders such as sprains and strains, for postoperative pain, in mild to moderate pain including dysmenorrhoea and migraine, as lozenges in the symptomatic relief of sore throat, in eye drops to inhibit intra-operative miosis and to control postoperative inflammation of the anterior segment of the eye. [2-5]

The objective of the study was to develop suppository of flurbiprofen by using different type of suppository bases with a view to avoid loss of drug due to first pass effect and to uncover toxic effects and produce safe and effective dosage form and safely improve the solubility and/or absorbability of poorly soluble drug.

MATERIALS AND METHODS

Flurbiprofen Sodium was a gift sample from Sun Pharmaceutical Industries Ltd., Silvassa, Gujarat, India and FDC Limited, Jogeshwari (w), Mumbai, India, Poly ethylene glycol 4000, 6000 and 400 were purchased from Central Drug House (Pvt.) Ltd., New Delhi. Cocoa butter (B. P. grade) was purchased from Mohan Scientific & Pharmaceuticals, New Delhi. All other chemicals and reagents were used of analytical grade.

Preparation of Suppositories

The details of the formulations are given in Table 1. Accurately weighed quantities of respective suppositories bases were melted on the water bath. The finely divided drug powder and plasticizer(s) were incorporated via through mixing. The melted mass was poured into the appropriate suppository mould (1.0 g capacity). The suppositories were then refrigerated [1], they were stored at 4°C to avoid the development of cracking [6] and exposure to room temperature was limited to less than 24 h before use in *in vitro* release studies.

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Characterization of Suppositories

Subsequent to suppository development and manufacture, the finished product must undergo a number of simple tests in order to ascertain quality. Ideally, these tests should be repeated periodically during storage as well.

The visual parameters such as fissuring, pitting, fat blooming, exudation, migration of active ingredient and physical parameters such as length, width, weight variation, hardness (mechanical strength), breaking strength, liquefaction time, melting time of prepared suppositories were determined.

Visual characterization

The randomly selected suppositories (six suppositories from each batch) were cut longitudinally and examined with the naked eye (subjective evaluation) to assess the verified the homogenicity of surface appearance and color of suppositories by

i. Absence of fissuring.
ii. Absence of pitting.
iii. Absence of fat blooming.
iv. Absence of exudation.
v. Absence of migration of the active ingredients.

This last test is best accomplished by taking a longitudinal section of the suppository to verify the homogeneity of the active ingredient(s) within the mass. [7]

Length and Width

The width and length of the randomly selected suppositories (six suppositories from each batch) were measured for their physical dimension. After that the same number of suppositories were selected and cut longitudinally and the surface was examined with the naked eye (subjective evaluation) for the homogeneity. [8]

Fig 1: Breaking Strength

Breaking strength

The breaking strength or crushing strength was determined for measuring fragility or brittleness of suppositories, which assess whether the suppositories will be able to withstand the hazards of packing, transporting and normal handling or not. [8-9] A plastic disc was fixed horizontally on to one end of the iron rod to which weight are applied and other end had been reduced to sharp point. The sample suppository was placed between the metal plate and the sharp end of the iron rod and placing 600 g weights on to the pan. After 1min time intervals, 200 g weights are added, and the weight at which the suppository collapses in the breaking point, or the force that determined the fragility of brittleness characterization of the suppositories. (Fig. 1) [10]

Mechanical strength (Hardness)

The physical characteristic such as mechanical strength (hardness test) was determined. The hardness of a cylindrical portion (9.6 mm thickness) of suppository, which was obtained by cutting the middle portion of the suppository, was measured in its diameter direction with a Monsanto hardness tester. [11]

Weight variation

Twenty suppositories were weighed and average weight was calculated. Each suppository was then individually weighed by using digital balance. [8] Not more than 2 of the individual masses deviate from the average mass by more than 5% and non deviate by more than twice that %. [12]

Friability

Twenty suppositories were weighted and placed in the plastic chamber of Roches Friabilator. The chamber was then rotated for 4 minutes at 25 rpm (a total of 100 revolutions). During each revolution suppositories fall from a distance of 6 inches. After 100 revolutions the suppositories were removed and weighed again.

$$\text{Friability (\%)} \quad W_i W_r / W_i \times 100$$

Where, W_i was the initial weight of the suppositories before friability testing, W_r was the weight of suppositories after the testing. [10]

Melting point

The melting time is a critical factor in the determination of the release rate of the active ingredient(s) from the suppository. This test is also known as macro melting range test. During this test, the time taken for the entire suppository to melt or disperse is measured when immersed in a water bath maintained at constant temperature (37°C $\pm$ 1°C). The time required for the whole suppository to melt or disperse in the surrounding water was noted. [8-9, 11-13]

Table 1: Code and composition of the Formulations

Code	COMPOSITION		
	Suppository bases	**Drug**	**Plasticizer**
F1	PEG 4000 (83% w/w)	Flurbiprofen sodium (7% w/w)	PEG 400 (10% w/w)
F2	PEG 6000 (83% w/w)	Flurbiprofen sodium (7% w/w)	PEG 400 (10% w/w)
F3	Cocoa butter (83% w/w)	Flurbiprofen sodium (7% w/w)	PEG 400 (10% w/w)

Liquefaction or softening time

This important element indicates the physical behavior of a suppository subjected to its maximum functional temperature (37°C). [7] It consists of a U-tube partially sub merged in a constant temperature water bath. A constriction on one side holds the suppository in place in the tube. An iron rod is placed on the top of the suppository and the time for the rod to pass through to the constriction is recorded as the "softening time". This can be carried out at various temperatures from 35.5 to 37°C, as a quality control check and can also be studied as a measure of physical stability over time.

The softening test measures the liquefaction time of rectal suppositories. [10] In this, to measures the time necessary for

Table 2: Physical characterization of the Formulations

Code	Fissuring	Pitting	Fat blooming	Exudation	Migration of active ingredient	Length (cm)	Width (cm)
F_1	No	No	No	No	No	2.18±0.006	0.96±0.004
F_2	No	No	No	No	No	2.18±0.006	0.96±0.007
F_3	No	No	No	No	No	2.18±0.004	0.96±0.005

Table 3: Physico-Chemical Characterization Of The Formulations

Code	Weight variation (mg)	Friability (%)	Hardness (kg/cm2)	Breaking strength (gm)	Liquefaction time (min.)	Melting time (min.)	Drug Content (mg)
F_1	1.4395±0.017	0.45±0.03	3.5	855±10.488	2:58±0:3125	42:28±0:3711	99.5±0.724
F_2	1.4117±0.02	0.48±0.04	3.5	765±10.954	3:45±0:0707	50:48±0:5930	98.27±0.695
F_3	1.1458±0.024	0.54±0.02	1.5	335±13.78	1:59±0:0005	27:52±0:022	96.68±0.689

a suppository to liquefy under pressure similar to those found in the rectum in the presence of phosphate buffer pH 7.4 (5.0 ml) surrounding the water at body temperature. [7]

Content uniformity

Content uniformity test was determined by spectrophotometric method. The suppository was individually melted, dissolved in 100 ml of phosphate buffer saline (PBS) in separate volume flask and the solution was filtered using 0.45 µm membrane. After suitable dilution, the content was measured by using thermospectronic UV-1 at a wave length of 247 nm. [8-9, 11]

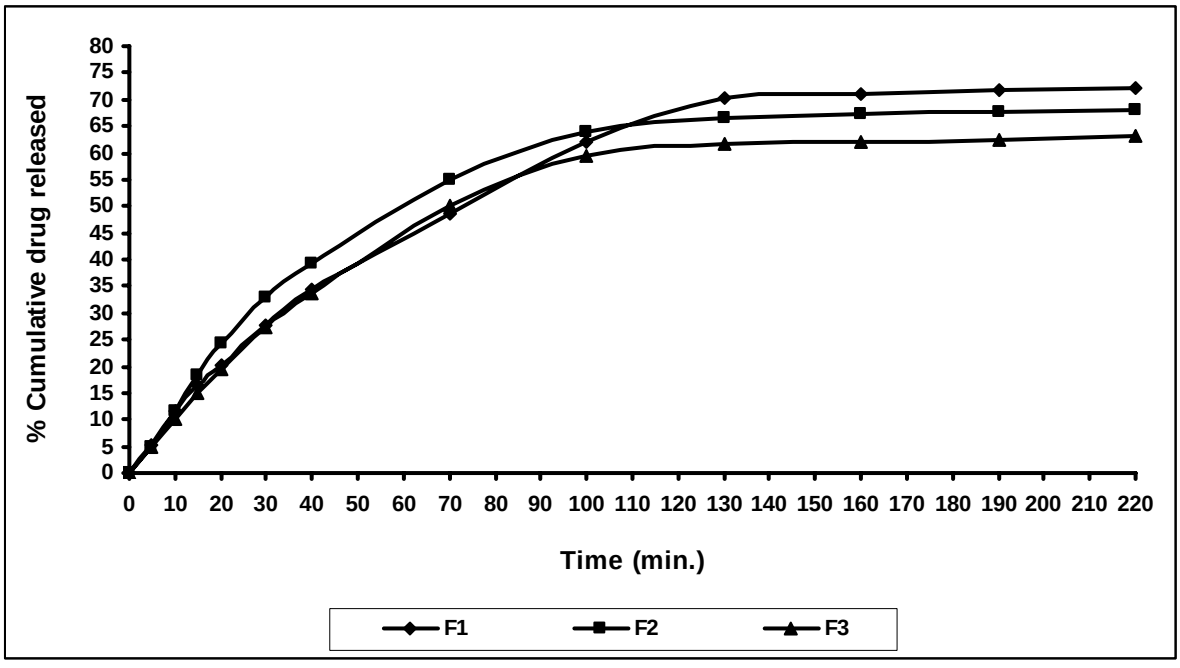
Dissolution study

The USP basket method was employed for all the *in vitro* dissolution studies (USP-XXVI, Veego Scientific, Mumbai). In this method 900 ml of Phosphate buffer solution pH 7.4 was used as the dissolution medium. The rate of stirring was 100 rpm. The suppositories were placed in basket and the temperature of the dissolution medium was maintained at $37^oC \pm 1^oC$ for a period of 220 minute. All different time intervals 5 ml of the sample was taken and filtered. The dissolution medium was replaced by 5 ml of fresh dissolution fluid to maintain a constant volume. The samples were filtered through 0.45 µ membrane, diluted suitably and assayed at 247 nm using a UV-visible spectrophotometer (Thermospectronic UV-1). [6, 14]

RESULT AND DISCUSSION

Flurbiprofen is an analgesic and non-steroidal anti-inflammatory drug usually employed in rheumatic disorder. It is rapidly eliminated from the blood after dosing administration. It has a plasma half life of 5.5 h to maintain the therapeutic plasma levels. The drug must be administered at least twice a day. In the usual oral administration of NSAIDs, the tablets and capsules have let to peptic ulceration and anorexia. Its physicochemical characteristics (weak acid) are responsible for the adverse effect on the gastro intestinal tract resulting in an increased incidence of gastric irritation.

Suppositories of flurbiprofen sodium were prepared by fusion method employing different bases such as PEG 4000, PEG 6000 and cocoa butter. The results of visual and physicochemical characterization are shown in Table 2 and 3. All the formulations were found to have homogeneous drug distribution with content uniformity, weight uniformity and sufficient mechanical strength to withstand abrasive forces causing disintegration of drug loaded formulation.



-♦- PEG 4000 base (F1); -■- PEG 6000 base (F2); -▲- Cocoa butter base (F3);

Fig. 2: *In vitro* Dissolution of Flurbiprofen sodium from different suppositories

The width and length of the randomly selected suppositories was found to be good homogenicity. The crushing or breaking strength was determined for measuring fragility or brittleness of the suppositories, which assess whether the suppositories will be able to withstand hazards of packaging, transporting and normal handling or not. The formulated rectal suppositories were smooth and fine in texture with mechanical strength (hardness) i.e. all the formulae could tolerate less than 5.0 kg. The weight variations were conformity with the British Pharmacopoeia for each formula, with standard deviation of less than 5 %. The friability was found to be within acceptable limits (less than 1%). With respect to melting range, the suppositories or different bases containing flurbiprofen sodium can be arranged in the order of PEG 4000 > PEG 6000 > cocoa butter. The liquefaction time was studies as a measure of physical stability over time. The estimation of drug content in the formulation revealed that the drug was distributed uniformity with low coefficient of variations, indicating batch to batch consistency. Considering the drug content uniformity test, the difference between mean of each formula and the theoretical values was less than 10%. All standard deviation were less than 5%. The drug content of all the formulations was determined spectrophotometrically at 247 nm. It varied from 96.68 to 99.50 mg per suppository.

The release profile from different suppositories formulations are shown in Figure 2. Percentage cumulative drug release from suppositories of cocoa butter, PEG 6000, and PEG 4000 were found to be 62.99, 68.14 and 72.184 %, respectively at the end of 220 minutes. It was found that the PEG 4000 base should maximum release of flurbiprofen from suppositories followed by PEG 6000 and cocoa butter. PEG base are water soluble, hence, they are dissolved more rapidly releasing the drug into 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°C (melting range 33.5-35°C). It may 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 favored into aqueous medium of pH 7.4.

CONCLUSION

The type of the base employed for the preparation of suppositories of flurbiprofen sodium, influenced the release of the drug during the dissolution studies and dependent upon the condition. They can be arranged in order of release rate as- PEG 4000 > PEG 6000> Cocoa butter. It would be better if the suppositories are prepared sustained release of drug for a longer period of time is desired with PEG bases, whereas suppositories prepared with cocoa butter would be a better choice for fast release action of drug.

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