Effect of different surfactants on the release pattern of cocoa butter suppositories containing Flurbiprofen sodium

Varshney Himanshu M.1* and Tanwar Y.S.2

1Apex Institute of Pharmaceutical Sciences, Jaipur. Lecturer (Pharmaceutics), Apex Institute of Pharmaceutical Sciences, Jaipur (Raj.), 302020.

2B.N. (PG) College of pharmacy, Udaipur. Reader (Pharmaceutics), B.N. (P.G.) College of Pharmacy, Udaipur (Raj.).

Abstract

Suppositories were formulated by hot melting / fusion method and evaluated for their physicochemical characterization followed by in vitro evaluation. The present investigation was aimed to evaluating the possibility of using suppository base i.e. cocoa butter with different surfactants i.e. SLS, Span 60 and 80, Tween 60 and 80 and sodium taurocholate for the development of rectal drug delivery system of flurbiprofen sodium, an NSAIDs, to minimize the gastric irritation of the drug upon oral administration. Suppositories containing PEG 4000 with SLS showed a better permeation of drug with faster dissolution rate in vitro than other formulations.

Keywords: Flurbiprofen sodium, cocoa butter, surfactants.

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 (El-Faham et al. 1990). There are reports describing attempts at enhancing the rate of release of drug from different suppository bases by incorporation of surfactants.

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 h. It is extensively metabolized mainly by hydroxylation.

*Corresponding author: hmv_mpharm2005@yahoo.com
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 (Barar 2003, Brooks 1990, Budavari et al. 1996, Nafria 1991).

The objective of the study is to develop suppository of flurbiprofen by incorporation of suppository base and different surfactants 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, bioavailability and/or absorbability of poorly soluble drug.

Materials and Methods

Materials

Flurbiprofen Sodium was a gift sample from Sun Pharmaceutical Industries Ltd., Silvassa, Gujarat and FDC Limited, Jogeshwari (w), Mumbai, Poly ethylene glycol 400, Span 60 and 80, Tween 60 and 80 were purchased from Central Drug House (P) Ltd., New Delhi, Sodium Lauryl Sulphate was purchased from S.D. Fine Chem. Ltd., Mumbai and sodium taurocholate was purchased from Romali Chem. Ltd., Mumbai. Cocoa butter (B.P. grade) was purchased from Mohan Scientific and Pharmaceuticals, New Delhi. All other chemicals and reagents were used of analytical grade.

Preparation of flurbiprofen suppositories

The details of the formulations are given in Table 1.

<table>
<thead>
<tr>
<th>Code</th>
<th>Suppository bases* (mg)</th>
<th>Drug (mg)</th>
<th>Surfactants (0.25% w/w)</th>
<th>Plasticizer (PEG 400) %w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>F₁</td>
<td>Cocoa butter</td>
<td>100</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>F₂</td>
<td>Cocoa butter</td>
<td>100</td>
<td>SLS</td>
<td>20</td>
</tr>
<tr>
<td>F₃</td>
<td>Cocoa butter</td>
<td>100</td>
<td>Span 60</td>
<td>20</td>
</tr>
<tr>
<td>F₄</td>
<td>Cocoa butter</td>
<td>100</td>
<td>Span 80</td>
<td>20</td>
</tr>
<tr>
<td>F₅</td>
<td>Cocoa butter</td>
<td>100</td>
<td>Tween 60</td>
<td>20</td>
</tr>
<tr>
<td>F₆</td>
<td>Cocoa butter</td>
<td>100</td>
<td>Tween 80</td>
<td>20</td>
</tr>
<tr>
<td>F₇</td>
<td>Cocoa butter</td>
<td>100</td>
<td>Sod. Taurocholate</td>
<td>20</td>
</tr>
</tbody>
</table>

*Based on mould capacity

Accurately weighed quantities of respective suppositories bases were melted on the water bath. The finely divided drug powder and plasticizer(s) (20% w/w of suppositories bases) and surfactants (0.25 %
w/w of suppositories bases) were incorporated via through mixing. The melted mass was poured into the appropriate suppository mould (1.0 g capacity). The suppositories were then refrigerated (El-Faham et al. 1990), they were stored at 4 °C to avoid the development of cracking (BP, 2003) and exposure to room temperature was limited to less than 24 h before use in in vitro release studies (Figure 1).

![Suppository mold used in formulating an open position, allowing removal of the finished hard suppositories after cooling.](image)

**Figure 1.** Suppository mold used in formulating an open position, allowing removal of the finished hard suppositories after cooling.

**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 homogeneity of surface appearance and color of suppositories by Absence of fissuring, Absence of pitting, Absence of fat blooming, Absence of exudation, 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 (Banker et al. 1996).

**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 (Moorthi et al. 2005).

**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 (Moorthi et al. 2005, Gulzar et al. 2000). 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. At 1-minute 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 (Kanig et al. 1991) (Figure 2).

Figure 2. Breaking strength of prepared suppository

Mechanical strength (Hardness)

A 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 (Dorle et al. 2003).

Weight variation

Twenty suppositories were weighed and average weight was calculated. Each suppository was then individually weighed by using digital balance (Moorthi et al. 2005). 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 % (USP, 1990).

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.

\[
\text{Friability (\%) = } \frac{W_i - W_r}{W_i} \times 100
\]

Where, \( W_i \) was the initial weight of the suppositories before friability testing, \( W_r \) was the weight of suppositories after the testing (Kanig et al. 1991).

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 ± 1°C). The time required for the whole suppository to melt or disperse in the
surrounding water was noted (Moorthy et al. 2005, Gulzar et al. 2000, Dorle et al. 2003, Gowthamarajan et al. 2002).

Liquefaction or softening time

This important element indicates the physical behavior of a suppository subjected to its maximum functional temperature (37 °C) (Banker et al. 1996). It consists of a U-tube partially submerged 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 (Kanig et al. 1991). In this, to measures the time necessary for 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 (Banker et al. 1996).

Content uniformity

Content uniformity test was determined by spectrophotometric method. The suppository was individual melted, dissolved in 100 ml of PBS in separate volume flask and the solution was filtered using 0.45 μm membrane. After suitable dilution, the absorption was measured using thermospectronic UV-1 at a wave length of 247 nm (Moorthy et al. 2005, Gulzar et al. 2000, Dorle et al. 2003).

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°C ± 1°C for a period of 220 minute. All different time intervals 5 ml of the sample was taken and filtered. The dissolution medium was the replaced by 5 ml of fresh dissolution fluid to maintain a constant volume. The samples were filtered through 0.45 μmembranes, diluted suitably and assayed at 247 nm using a UV-visible spectrophotometer (Thermospectronic UV-1) (BP 2003, Hanaee et al. 2004).

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 and 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 suppository base i.e. 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.
The width and length of the randomly selected suppositories was found to be good homogeneity. 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 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 with or without surfactants containing flurbiprofen sodium can be arranged in the order of F1 > F2 > F4 > F6 > F5 > F7 > F3. 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 97.89 to 99.66 % per suppository.

Table 2. Visual characterization of the formulations

<table>
<thead>
<tr>
<th>Code</th>
<th>Fissuring</th>
<th>Pitting</th>
<th>Fat blooming</th>
<th>Exudation</th>
<th>Migration of active ingredient</th>
<th>Length (cm)</th>
<th>Width (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F₁</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2.18±0.004</td>
<td>0.96±0.005</td>
</tr>
<tr>
<td>F₂</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2.18±0.006</td>
<td>0.96±0.005</td>
</tr>
<tr>
<td>F₃</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2.18±0.004</td>
<td>0.96±0.005</td>
</tr>
<tr>
<td>F₄</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2.18±0.008</td>
<td>0.96±0.004</td>
</tr>
<tr>
<td>F₅</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2.18±0.006</td>
<td>0.96±0.004</td>
</tr>
<tr>
<td>F₆</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2.18±0.006</td>
<td>0.96±0.004</td>
</tr>
<tr>
<td>F₇</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>2.18±0.006</td>
<td>0.96±0.004</td>
</tr>
</tbody>
</table>

Table 3. Physico-chemical characterization of the formulations

<table>
<thead>
<tr>
<th>Code</th>
<th>Weight variation (mg)</th>
<th>Friability (%)</th>
<th>Hardness (kg/cm²)</th>
<th>Breaking strength (cm)</th>
<th>Liquefaction time (min.)</th>
<th>Melting time (min.)</th>
<th>Drug Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F₁</td>
<td>1.1458±0.024</td>
<td>0.54±0.02</td>
<td>1.5</td>
<td>335±13.78</td>
<td>1.59±0.0005</td>
<td>27:52±0:022</td>
<td>99.12</td>
</tr>
<tr>
<td>F₂</td>
<td>1.1419±0.028</td>
<td>0.46±0.05</td>
<td>1.5</td>
<td>338±8.1649</td>
<td>1.56±0.0017</td>
<td>27:45±0:0107</td>
<td>99.66</td>
</tr>
<tr>
<td>F₃</td>
<td>1.501±0.021</td>
<td>0.51±0.02</td>
<td>1.5</td>
<td>335±10.954</td>
<td>1.38±0.0117</td>
<td>25:53±0:0562</td>
<td>98.46</td>
</tr>
<tr>
<td>F₄</td>
<td>1.1525±0.026</td>
<td>0.48±0.03</td>
<td>1.5</td>
<td>332±9.8319</td>
<td>1.52±0.0217</td>
<td>27:18±0:3125</td>
<td>99.51</td>
</tr>
<tr>
<td>F₅</td>
<td>1.1520±0.026</td>
<td>0.52±0.02</td>
<td>1.5</td>
<td>320±3.1623</td>
<td>1.45±0.0167</td>
<td>27:03±0:2524</td>
<td>98.94</td>
</tr>
<tr>
<td>F₆</td>
<td>1.1502±0.024</td>
<td>0.51±0.03</td>
<td>1.5</td>
<td>327±5.1639</td>
<td>1.50±0.0122</td>
<td>27:11±0:0651</td>
<td>97.89</td>
</tr>
<tr>
<td>F₇</td>
<td>1.1542±0.008</td>
<td>0.53±0.03</td>
<td>1.5</td>
<td>318±5.1639</td>
<td>1.44±0.0121</td>
<td>26:57±0:1875</td>
<td>99.55</td>
</tr>
</tbody>
</table>

The release profile from different suppositories formulations are shown in Figure 3. Percentage cumulative drug releases from suppositories of cocoa butter and with different surfactants were found to be 62.994, 63.617, 65.942, 66.986, 69.873, 70.958 and 73.314 % respectively at the end of 220 minutes. It was found that the SLS should maximum release of flurbiprofen from suppositories followed by cocoa butter and with different surfactants. This might be due to the fact that a surfactant with high HLB value like SLS (HLB=40) is hydrophilic. So it enhances the moisturizing of lipid excipients by the dissolution medium.
Figure 3. In vitro dissolution of Flurbiprofen sodium from different suppositories

- Cocoa butter base (F1); - Base + SLS (F2); - Base + Span60 (F3); - Base + Span80 (F4); - Base + Tween60 (F5); - Base + Tween80 (F6); - Base + Sod. taurocholate (F7)

Conclusion

The type of the surfactant employed for the preparation of suppositories of flurbiprofen sodium, influenced the release of the drug during the dissolution studies and dependent upon the condition. it may be concluded that the addition of surface active agents into the formulation enhanced the drug release and with respect to surfactant, can be arranged as- SLS > Span 80 > Tween 80 > Tween 60 > Sodium taurocholate > Span 60 > cocoa butter.

References


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