Development and Evaluation of Matrix and Two Layered Sustained Release Suppositories of Nimesulide

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Nimesulide loaded conventional suppositories, sustained release matrix suppositories and sustained release two layered suppositories were prepared using polyethylene glycol (PEG) 4000 and ethylcellulose. In vitro characteristics of these suppositories were evaluated. In comparison to conventional suppositories the release of drug from sustained release matrix suppositories was gradual and extended over a period of time. On the other hand, two layered suppositories produced an initial quick release followed by extended release of drug.

Introduction

Nimesulide is a nonsteroidal antiinflammatory drug (NSAID) administered orally or rectally twice daily for a variety of inflammatory and pain states. It has similar effectiveness as other NSAIDS in these indications but has shown superior antipyretic potency to Indomethacin, Ibuprofen, Aspirin and Paracetamol. Concomitant administration of food decreased the rate of absorption and the elimination half-life of this drug is 1.56 to 4.9 h. As with other NSAIDs the most common adverse effects are gastrointestinal disturbances, nausea and vomiting. The drug is well absorbed through rectal route and suppositories considered as an alternative dosage form to achieve systemic effect. Sustained release suppositories can provide a more convenient therapy with less risk of side effects and reduced frequency of administration.

The objective of this work is to compare the matrix and two layered suppositories with conventional suppositories for sustained release of nimesulide.

Materials and Methods

Materials

Nimesulide (Aristo Pharmaceuticals Ltd, Bombay) was obtained as a gift sample. Polyethylene glycol (PEG) 4000 (S D Fine Chem Ltd, Bombay) Ethylcellulose (BDH, Bombay) and all other analytical grade chemicals were obtained commercially and used as received.

Preparation of Suppositories

Nimesulide loaded conventional suppositories (CS) were prepared using PEG 4000 as base in a stainless steel mold of 1 g capacity by the fusion method. Sustained release matrix suppositories (SMS) were prepared using PEG 4000 and variable amount of ethylcellulose (5, 10, 15 per cent) by solid dispersion technique following the method of Ohnishi et al. Two layered sustained release suppositories (STLS) were prepared by casting SMS onto CS in the mold. The theoretical drug loading in each of the suppositories was 100 mg and in STLS the drug was distributed in 1:1 proportion in each layer. Weight and drug content of the suppositories were determined. Average of nine determinations and standard error of mean (SEm) were calculated.

Treatment of Data

In order to ascertain whether there was significant differences in the average weights and in the drug contents of the suppositories, t-test was performed. Further to find out whether the average weights and the drug contents of matrix suppositories varied significantly due to variation in the percentage of ethylcellulose, one criteria classification of analysis of variance (ANOVA) was done.

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In vitro and In vivo Liquefaction Time

In vitro and in vivo liquefaction time of the suppositories were determined following the method reported previously.

In vitro Drug Release Study

The dissolution rate of nimesulide from the formulated suppositories were measured in alkaline borate buffer (pH 8.4) as described by Chowdary et al. with little modifications. Suppositories were placed in dialysis tubing (previously soaked in water for 24 h) and then placed in 900 ml buffer solution at 37 ± 1°C in USP XXI 3 station dissolution rate test apparatus (Model DR 3 Campbell Electronics) and rotated at 50 rpm. Samples of dissolution medium (5 ml) were withdrawn at different time intervals, suitably diluted and assayed for nimesulide by measuring absorbance on double beam spectrophotometer at 230 nm (Beckman UV - visual, model DV 64).

Results and Discussion

The characteristics of nimesulide-loaded conventional suppositories (CS) and sustained release matrix suppositories (SMS) have been presented in Table 1. The average weights and the drug contents of SMS containing variable amount of ethylcellulose were apparently found to be similar to those of CS. Statistical analysis revealed that the average weights and the drug contents of different samples of CS did not differ significantly (P > 0.05, n = 9). Similar observations were noted among the samples of each of the SMS prepared with variable amount of ethylcellulose. Further, when SMS containing variable amount of ethylcellulose were compared with each other using one criteria classification of ANOVA, no significant differences were observed (F₂, 2₄ > 0.01) both in the average weights and in the drug contents. These observations indicate the simplicity and reproducibility of the method of preparation and homogeneity of the suppositories.

Estimation of in vitro liquefaction time showed that about 80 per cent of suppository mass from all the suppositories (CS, SMS, STLS) were liquefied within 30 min and 100 per cent suppository mass liquefied within 70 min. No palpably core was noticed at any stage. The in vitro liquefaction times were 50 to 65 min. Thus, in vitro liquefaction time was in conformity with the in vivo results.

The release profile of nimesulide from CS and SMS containing 5, 10 or 15 per cent of ethylcellulose have been shown in Figure 1. While 90 per cent of nimesulide was released in about 156 min from CS, about 82, 70 and 45 per cent drug were released from SMS containing respectively 5, 10 and 15 per cent ethylcellulose at 8 h. In order to ascertain the effect of ethylcellulose on drug release from SMS, one criterion classification of analysis of variance (ANOVA) was done. By using data in the form of per cent nimesulide released from three different batches of each formulation, ANOVA was calculated at 1st, 3rd, 5th and 7th h and was used as a representative of the entire dissolution profile. At all the time studied the calculated F values for SMS prepared with variable amount of ethylcellulose exceeded the tabular F value at the 0.95 level (Table 2). This revealed that ethylcellulose significantly influenced release of the drug from SMS. Lesser the percentage of ethylcellulose, faster was the release of the drug. It, thus, becomes obvious that if the amount of

<table>
<thead>
<tr>
<th>Average weight, g</th>
<th>Matrix suppositories containing ethylcellulose, per cent</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Average weight, g</td>
<td>0.984</td>
<td>0.969</td>
</tr>
<tr>
<td>SEₜₜ</td>
<td>0.006</td>
<td>0.007</td>
</tr>
<tr>
<td>Statistics*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Drug content, mg</td>
<td>100.23</td>
<td>100.34</td>
</tr>
<tr>
<td>SEₜₜ</td>
<td>0.051</td>
<td>0.072</td>
</tr>
<tr>
<td>Statistics**</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

* NS = Not significant; P > 0.05
**NS = Not significant; F₂, 2₄ value, obtained from one criteria classification of analysis of variance, was less than tabular F₂, 2₄ value at 0.01 level
Table 2 — Effect of ethylcellulose on the release of nimesulide from sustained release matrix suppositories

<table>
<thead>
<tr>
<th>Ethylcellulose, per cent</th>
<th>Percent nimesulide released at, h</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>10.17 (2.54)</td>
</tr>
<tr>
<td>10</td>
<td>16.10 (1.22)</td>
</tr>
<tr>
<td>15</td>
<td>21.19 (1.72)</td>
</tr>
</tbody>
</table>

Statistics

* Significant, calculated $F_{2\alpha}$ values exceeded the tabular $F_{2\alpha}$ value at 95% per cent level.

Figures in parentheses are standard deviations.

eethylcellulose is reduced to zero per cent, the release of the drug will coincide with that from CS. Thus, release of the drug can be controlled by varying the amount of ethylcellulose in SMS.

The release profile of nimesulide from STLS has been shown in Figure 2. From the release profile it appeared that there was no difference in the release of the drug at 1<sup>st</sup> h. However, one criteria classifications of ANOVA revealed that significant difference existed in release at 1<sup>st</sup>, 3<sup>rd</sup>, 5<sup>th</sup> and 7<sup>th</sup> h taken as a representative of the entire dissolution profile. As SMS containing variable amount of ethylcellulose was casted on the same amount of CS, it should be expected to have some amount of initial drug release. However, release of drug occurs concomitantly from the composit of CS and SMS and, thus, significant differences were observed during the entire dissolution profile.

Comparison of drug release from SMS and STLS indicated that while SMS provide a gradual release of the drug, STLS provided an initial higher release followed by gradual release of the drug over the entire period studied.

In conclusion, STLS designed in this study could be a useful dosage form for nimesulide as CS could provide an initial higher release to achieve minimum effective drug concentration and the casted
SMS would provide gradual release which in turn could be controlled by varying the amount of ethylcellulose.

References