Preparation and Diffusional Evaluation of Sustained-Release Suppositories Containing Ibuprofen Microspheres

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INTRODUCTION

Sustained-release suppositories have been developed to sustain the effect via rectal route. There are several reports on the preparation of sustained-release suppositories using structure-altering devices and various additive substances. Nishihata et al.1 have demonstrated that a sustained-release suppository of sodium diclofenac containing lecithin as an additive in a glyceride base could be prepared. Gungor et al.2 prepared sustained release suppository formulations of tiaprofenic acid with sucrose fatty acid ester. Ohnishi et al.3 prepared double-layered suppositories of nifedipine. In this

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Sustained-release suppositories containing ibuprofen microspheres were prepared with hydrophilic polyethylene glycol (PEG) or lipophilic Witepsol bases. Microspheres were prepared by solvent evaporation method. The effect of stirring rate on the particle size and drug content of the microspheres was investigated. Decrease in particle size and drug content of microspheres was observed with an increase in stirring rate. In vitro dissolution studies were performed in phosphate buffer solution (pH 7.2) at 100 rpm. All formulations exhibited non-Fickian diffusion and first-order or Hixson-Crowell kinetics. Differential scanning calorimetric analyses showed that there were no crystal forms or decomposition products of drug in the suppositories.

This study suggested that the sustained-release ibuprofen suppositories could be prepared using PEG 400:PEG 4000 (5:95) combination with microspheres. These suppositories can be more useful for clinical use.

Key Words: Ibuprofen, microspheres, sustained-release suppository.

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Ibuprofen Mikroküreleri İçeren Sürekli-Salımlı Supozituarlar Hazırlanması ve Difüzyonal Değerlendirilmesi

Özet


Anahtar Kelimeler: ibuprofen, mikroküre, sürekli-salımlı supozituar.
solid dispersion system, polyethylene glycol (PEG) 4000 was used as a water-soluble carrier and cellulose acetate phthalate (CAP) as a poorly soluble carrier. Although there are several studies available on the use of microcapsules and micropellets for the preparation of sustained-release suppositories, only one study has been reported on the use of microspheres.

More recently, a liquid suppository dosage form of ibuprofen was presented. It was in liquid form at normal room temperature but in gel form above 30°C. However, such suppositories have some disadvantages including difficulty in packaging, protection and transport at high temperatures, i.e. above 30°C.

In this study, formulation of sustained-release suppositories using ibuprofen-ethylcellulose microspheres was attempted. Ibuprofen is a nonsteroidal antiinflammatory drug having analgesic and antipyretic effect. Ibuprofen was an appropriate candidate for sustained-release formulation because of its short half-life (1.8-2 h) and undesired gastrointestinal effects when it is administrated through oral route, such as peptic ulceration and gastrointestinal bleeding. In addition, preliminary histological examination showed that it does not exert any adverse effect on the rectal tissues. Ibuprofen has been prepared as suppository formulations using its free acid and lysinate forms. Ibrahim et al. reported that ibuprofen suppositories were more efficient than oral solutions and recommended them for counteracting gastric side effects. Ibuprofen has been prepared in microsphere form using ethylcellulose, but only thermal analysis of the matrix structure was performed on the microspheres prepared. Ethylcellulose is an inert material. By using microspheres containing inert material and drug, it may be possible to prevent undesired interactions between drug and suppository bases and other additives during production and storage. In addition, the drugs and additives may also have side effects.

In our study, solvent evaporation method was used for the preparation of ethylcellulose microspheres. Four different suppository formulations, two of them containing pure drug and PEG or Witepsol base and the other two containing microspheres and the same bases, were prepared and evaluated based on the in vitro release testing. The effect of suppository base on the diffusion mechanism was also investigated.

Differential scanning calorimetry (DSC) analyses were carried out for the determination of the crystallinity and decomposition products of ibuprofen in microspheres and in all suppository formulations.

**EXPERIMENTAL**

**Materials**

Ibuprofen (Atabay, Istanbul, Turkey), methylcellulose (Methocel A15-LV, Colorcon Ltd., England), ethylcellulose (Ethocel N-100, Hercules Powder Co., Wilmington, DE, USA), PEG 400 (Mustafa Nevzat Pharm. Co., Istanbul, Turkey), PEG 4000 (Novartis Pharm. Co., Istanbul, Turkey), and Witepsol H15 (Deva Pharm. Co., Istanbul, Turkey) were obtained from the indicated sources. All other chemicals were of the highest commercial grade and used without further purification.

**Preparation of microspheres and drug content analysis**

Microspheres were prepared according to the solvent evaporation method as described below. Ibuprofen-ethylcellulose ratio was selected as 1:1 according to the results of the preliminary studies. 2 g of ethylcellulose was dissolved in 20 mL of methylene chloride and 2 g of ibuprofen was added. The polymer phase was emulsified in 250 mL of aqueous phase containing 0.25% (w/v) methylcellulose. Stirring rates (Janke and Kungel Stirring Apparatus) were set at three different constant rates, namely 500, 750 and 1000 rpm. Stirring was continued at room temperature until complete evaporation of methylene chloride. Microspheres were then collected, washed three times with deionized water, fil-
Ibuprofen content of microspheres was determined spectrophotometrically. 5 mL of phosphate buffer solution (pH 7.2) was added onto 25 mg of microspheres and shaken for 23 h. Then, 5 mL of phosphate buffer solution (pH 7.2) was added and shaken for another 1 h. After filtration, 100 µL of filtrate was diluted to 10 mL with phosphate buffer solution (pH 7.2). The absorbance of the solution was measured at 223 nm by a spectrophotometer (Shimadzu UV-Visible Recording Spectrophotometer UV-160A) against the blank, and the drug concentration was determined from the calibration curve (n=3).

Preparation and physical properties of suppositories

In order to investigate the release of ibuprofen from different suppository bases, four different suppository formulations were prepared using lipophilic Witepsol and hydrophilic PEG. Two of these formulations were prepared using ibuprofen (Witepsol suppositories and PEG suppositories) and the others were prepared using microspheres (Witepsol-MI suppositories and PEG-MI suppositories). They were prepared by fusion process in a metallic suppository mold. The base was fused at 60°C and then ibuprofen or microspheres were added to the melted base and dissolved or dispersed by stirring. They were poured into the metallic suppository mold and allowed to solidify at room temperature. Each suppository was formulated to contain 300 mg of ibuprofen.

All suppository formulations were evaluated in respect to content and weight uniformity according to BP 1998. Mechanical strength tests were also performed (Erweka hardness tester SBT). For content uniformity analysis of both lipophilic and hydrophilic suppositories, the suppository was stirred in 150 mL of phosphate buffer solution (pH 7.2) at 60°C by a magnetic stirrer. After melting or dissolving process was completed, 100 µL of sample was adjusted to 10 mL with phosphate buffer solution (pH 7.2) and drug concentration was determined as described above (n=3).

In vitro release tests

Many research groups have been examining different techniques and their applications to test for drug release from rectal dosage systems\textsuperscript{15}. In the present study, in vitro release tests were carried out according to the method reported by Asikoglu et al.\textsuperscript{16}. Dissolution medium was 150 mL pH 7.2 phosphate buffer solution at 37°C. Suppository was placed in the dissolution medium and stirred with a paddle at 100 rpm. 100 mL aliquots were taken at time intervals after initiation of the test and replaced by 100 mL of pH 7.2 phosphate buffer solution at 37°C. Aliquots were diluted to 10 mL with phosphate buffer solution (pH 7.2) and the drug concentration was determined as described above.

Kinetic analyses of dissolution data obtained from microspheres and all suppository formulations were done using zero-order, first-order, Higuchi’s square root of time and Hixon-Crowell cube-root models. The release rate constants (k) and determination coefficients (r\textsuperscript{2}) were calculated by means of a computer program\textsuperscript{17-18}.

Calculation of exponent ‘n’

Curve fitting was performed using Microsoft Excel 2000 version. The dissolution data were fitted to Peppas equation\textsuperscript{19}. Release exponent “n” was calculated.

\[
\frac{M_t}{M_\infty} = k_p t^n
\]  

where \(M_t\)/\(M_\infty\) is the fraction of drug released at time \(t\), \(k_p\) is the kinetic constant of the system, and \(n\) is the exponent characteristic of the mode transport.

Thermal analysis

Thermal analyses were performed using Differential Scanning Calorimeter (SETARAM DSC92). DSC analyses were carried out on the samples of 17.7-
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37.7 mg range. All samples were scanned in aluminium pans from 25°C to 300°C, at a constant rate of 5°C min⁻¹ using nitrogen as effluent gas.

RESULTS AND DISCUSSION

It is known that particle size of microspheres depends on the stirring rate. Thus, the effects of three different stirring rates of 500, 750 and 1000 rpm on particle size and drug content were investigated (Figures 1 and 2). Microspheres prepared were sieved through combined sieve system and grouped based on particle size ranging from <125, 125-250, 250-500 and >500 µm. Approximately 87-90% of the microspheres were within the 125-500 µm range. Therefore, all subsequent studies were performed on 125-250 µm and 250-500 µm particles.

The amounts of 125-250 µm microspheres prepared at 500, 750 and 1000 rpm were determined to be 14%, 40% and 43%, respectively. On the other hand, the amounts of 250-500 µm microspheres prepared at the same stirring rates were determined to be 70%, 50% and 44%, respectively. It was found that the amount of <250 µm microspheres increased while the amount of >250 µm microspheres decreased with an increase in stirring rate (Figure 1).

The drug contents of 125-250 µm microspheres prepared at 500, 750 and 1000 rpm were 47%, 45% and 37%, respectively. The drug contents of 250-500 µm microspheres prepared at the same stirring rates were 50%, 47.5% and 40%, respectively. When the stirring rate was increased, drug content of the microspheres decreased slightly (Figure 2). Based on these present results, 250-500 µm particles prepared at 500 rpm were used in the preparation of suppository formulations since they were obtained at high yield (73%) with high drug content (50%).

The suppositories prepared were found to be in accordance with BP 1998 requirements for weight uniformity. Drug contents were homogeneous for all suppositories according to content uniformity tests. The hardness of lipophilic suppositories was almost 2 kg, but suppositories prepared using PEG 4000 were very hard (>5 kg). Therefore, combination studies were performed to decrease the hardness. As a result of these studies, PEG 400:PEG 4000 (5:95) combination was selected after preliminary studies and used in all hydrophilic suppositories. The results related to suppository properties are given in Table 1.

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Table 1. Weight variation, content uniformity and hardness of suppositories

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight variation (g)</th>
<th>Content uniformity (mg)</th>
<th>Hardness (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X ±SD</td>
<td>X ±SD</td>
<td>X ±SD</td>
</tr>
<tr>
<td>PEG Supp.</td>
<td>1.94 ±0.018</td>
<td>301.90 ±1.516</td>
<td>3.92 ±0.075</td>
</tr>
<tr>
<td>Witepsol Supp.</td>
<td>1.66 ±0.037</td>
<td>301.01 ±1.722</td>
<td>2.02 ±0.132</td>
</tr>
<tr>
<td>PEG-MI Supp.</td>
<td>1.74 ±0.107</td>
<td>299.54 ±2.118</td>
<td>3.42 ±0.116</td>
</tr>
<tr>
<td>Witepsol-MI Supp.</td>
<td>1.65 ±0.040</td>
<td>301.10 ±2.514</td>
<td>1.72 ±0.147</td>
</tr>
</tbody>
</table>

×n=20, y n=3
In vitro release tests were conducted on both microspheres and four suppository formulations as shown in Figure 3. The complete dissolution of both pure ibuprofen and PEG suppositories lasted 2 h. While 80% of pure ibuprofen was dissolved within 30 min, this value was only 40% for PEG suppositories because of the slow melting of the suppositories in the dissolution medium. However, it was observed that PEG base did not have any effect on the drug release. Ibuprofen was completely released from Witepsol suppositories in approximately 5 h. This time period was longer than that of PEG suppositories because of the lipophilicity and phase separation from the dissolution medium of Witepsol base. In this phenomenon, ibuprofen stayed in a solid form in the melted base and then separated very slowly from the base with the agitation of the dissolution medium. These results are consistent with the findings of Gjellan and Graffner.

The dissolution of the drug from Witepsol-MI suppositories was about 80% after 8 h. In pure microsphere tests, 94% of the drug was released in 8 h. The decrease in release of ibuprofen from Witepsol-MI suppositories may be due to the lipophilicity of the Witepsol base. From PEG-MI suppositories, 90% of ibuprofen was released in 8 h. It is clearly seen in Figure 3 that the PEG base did not show any significant effect on the dissolution and thus the release was almost the same as with the microspheres. Therefore, PEG combination seems to be suitable for sustained-release ibuprofen suppositories. Similarly, Ermiş and Tarmcı reported that PEG mixtures as a hydrophilic base were suitable for ketoprofen sustained-release suppositories containing hydroxypropylmethylcellulose phthalate as the inert matrix material. 100% dissolution from PEG formulation prepared with microspheres was not observed due to the low incorporation of drug in the microspheres. Nakajima et al. performed indomethacin release test carried out with indomethacin-ethylcellulose microcapsules to determine the effect of suppository bases. They found that the release was almost the same for PEG and Witepsol suppositories containing microcapsules. In our study, it was found that only lipophilic Witepsol base slightly affected the dissolution, most probably due to the fact that ibuprofen is more soluble than indomethacin. Moreover, in the study of Arra et al., the dissolution of both pure micropellets and conventional suppositories of the terbutaline sulfate were higher than of PEG suppositories prepared with micropellets. Therefore, it can be concluded that dissolution from sustained-release suppositories containing microparticulate dosage forms depends on the solubility of the drug and lipophilicity or hydrophilicity of the base used.

The dissolution data obtained were subsequently analyzed according to Eq. (1). The value of n indicates the drug release mechanism from the non-swellable and swellable spherical devices and the value of n= 0.43 indicates Fickian diffusion. Values of 0.43< n <1.0 indicate anomalous non-Fickian transport, whereas the value of n= 1.0 indicates case-II or zero-order release. It is clear from the n values shown in Table 2 that microspheres and suppositories exhibited a non-Fickian diffusion mechanism. n value was 0.273 for the ethylcellulose microspheres prepared, which is far below 0.43. Grattard et al. found that the n values for the lactase, Tempol and Tempo (small paramagnetic probes) microspheres prepared with ethylcellulose were approximately 0.26. This data fit our findings very well. Ritger and Peppas explained that the size distribution of microspheres could influence the value of n. Size of our microspheres was 250-500 µm; Grattard et al. prepared 30.2 µm microspheres. There seems to be a great difference among the prepared microspheres. Therefore, there might be another reason for the low n value. The n value of PEG-MI suppositories was 0.290, which indicates that the hydrophilic base has no effect on the dissolution from microspheres. Moreover, dissolution profiles from these microspheres and suppositories were very similar (Figure 3). The n value of only PEG suppositories was 0.767, showing the non-Fickian drug release. This type of diffusion contains Fickian and relaxation or gelation properties together, but PEG does not have these properties. The reason for the high n value could be the rapid melting of the suppository in the dissolution medium (2 h) and the linearity of the first 80% of the dissolution profile. It is known that n value
Table 2. Results of the exponent ‘n’ and dissolution kinetics of microspheres and suppository formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Peppas equation k_β</th>
<th>n</th>
<th>r^2</th>
<th>Higuchi k_H</th>
<th>k_H (min^-1/2)</th>
<th>Higuchi r^2</th>
<th>First-order k</th>
<th>First-order r^2</th>
<th>Hixon-Crowell k_Hc</th>
<th>Hixon-Crowell r^2</th>
<th>Zero-order k_β</th>
<th>Zero-order r^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG Suppl.</td>
<td>2.986</td>
<td>0.767</td>
<td>0.967</td>
<td>20.266</td>
<td>0.956</td>
<td>5.351</td>
<td>0.942</td>
<td>0.215</td>
<td>0.995</td>
<td>20.146</td>
<td>0.895</td>
<td></td>
</tr>
<tr>
<td>Witepsol Suppl.</td>
<td>17.937</td>
<td>0.305</td>
<td>0.997</td>
<td>26.778</td>
<td>0.987</td>
<td>4.551</td>
<td>0.959</td>
<td>0.657</td>
<td>0.988</td>
<td>51.182</td>
<td>0.935</td>
<td></td>
</tr>
<tr>
<td>Microspheres</td>
<td>18.578</td>
<td>0.273</td>
<td>0.961</td>
<td>35.988</td>
<td>0.917</td>
<td>3.960</td>
<td>0.958</td>
<td>1.000</td>
<td>0.920</td>
<td>55.032</td>
<td>0.810</td>
<td></td>
</tr>
<tr>
<td>PEG-MI Suppl.</td>
<td>16.082</td>
<td>0.280</td>
<td>0.949</td>
<td>32.341</td>
<td>0.901</td>
<td>3.965</td>
<td>0.925</td>
<td>0.941</td>
<td>0.886</td>
<td>51.236</td>
<td>0.789</td>
<td></td>
</tr>
<tr>
<td>Witepsol-MI Suppl.</td>
<td>4.269</td>
<td>0.495</td>
<td>0.963</td>
<td>6.281</td>
<td>0.949</td>
<td>4.328</td>
<td>0.956</td>
<td>0.462</td>
<td>0.929</td>
<td>30.060</td>
<td>0.861</td>
<td></td>
</tr>
</tbody>
</table>

r^2: Determination coefficient. k: Release rate constant for respective models. MI: Microspheres.

approaches 1.0 with the linearity of the dissolution profile. For correction based on this knowledge, a simulation study was done on the 80% of the dissolution profile of the PEG suppository and it was observed that the n value increased to 0.893 from 0.767 and r^2 increased to 0.994 from 0.895 for zero-order drug release.

The Witepsol suppositories surprisingly showed a low n value (n=0.305) like microspheres. It can be explained by the slow drug diffusion from the separated Witepsol phase in the aqueous dissolution medium. Another unexpected finding for the Witepsol-MI suppository was a rise in n value to nearly 0.5. This could be non-Fickian drug diffusion, but this phenomenon is still unknown. It is thought that the restriction of the contact of microspheres with the dissolution medium by Witepsol causes a slow release at the beginning of the drug dissolution and the release profile somehow approaches linearity (Figure 3).

It is well known that Higuchi’s square root of time relationship indicates a pure Fickian diffusion controlled mechanism. None of the formulations showed Higuchi kinetics as shown in Table 2. This is a good evidence for the non-Fickian diffusion mechanism explained above. The best kinetics were observed by Hixon-Crowell model for both Witepsol and PEG suppositories (represented by an initial burst followed by a gradual increase in drug release) and by first-order model for other microspheres and suppositories prepared with microspheres (showing both the non-Fickian diffusion and proportional drug release with the reservoir). Results concerning dissolution kinetics are shown in Table 2.

Differential scanning calorimetry (DSC) is one of the thermal methods used in pharmaceutical systems for studying the physical nature of pure compounds. It has also been used to detect the presence of decomposition products formed in aminophylline suppositories prepared at high temperatures. Figures 4–6 show the thermograms of pure ibuprofen, ethylcellulose, microspheres, suppository bases and suppositories.

As shown in Figure 4, ibuprofen has a well-defined peak at approximately 78°C and ethylcellulose shows no peak at a temperature range of 25°C to 300°C. Microspheres, however, exhibit a small peak at approximately 75°C, demonstrating that they contain ibuprofen in crystalline form.

In Figure 5, Witepsol base shows a peak around 45°C and suppositories show no transition peak at temperatures between 75-78°C, which indicates the
absence of ibuprofen in crystalline form.

As shown in Figure 6, PEG 4000 or its combination shows a peak at temperatures between 67-69°C and there is no transition peak for suppositories at temperatures between 75-78°C. This indicates that ibuprofen is not present in crystalline form in suppositories and also that there is no decomposition product of the drug in all suppository formulations. On the other hand, although ibuprofen is known as thermally stable even at high temperatures, a metastable molecular dispersion could exist in the ethylcellulose microsphere and these molecules will tend to recrystallize under storage, leading to a modification of the release profiles of the suppositories.

CONCLUSION

In this study, sustained-release ibuprofen suppositories containing microspheres were prepared and investigated in terms of kinetics, diffusional behavior and DSC analysis. To our knowledge, this is the first time that microspheres have been used in sustained-release suppository formulations. According to the results of this study, type of salt and basic form of drug, suppository base and particle size of the microparticulate system must be selected carefully to prepare the sustained-release suppository dosage forms. With this kind of formulation, the undesired gastrointestinal and first-pass effects of the drug can be eliminated, and a sustained effect can be obtained. Therefore, ibuprofen suppositories prepared in this study are promising as being more useful than conventional formulations in therapy.

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