UZUN ETKİLİ SIPROFLOKSASIN FORMÜLASYONLARI VE İN VİTRO SALIM KINETIKLERİ*

SUSTAINED RELEASE FORMULATIONS OF CIPROFLOXACIN AND IN VİTRO RELEASE KINETICS*

Sevil AŞIKİ** – Özgen ÖZER** – Esra BALOĞLU**

SUMMARY

A new sustained-release dosage form of ciprofloxacin as microcapsules was prepared by means of coacervation-phase separation technique. Ethyl cellulose used as coating material. In vitro release studies for microcapsules and their formulated tablet forms were performed. Release rates were studied as a function of core-wall ratios. Dissolution patterns of the microcapsules were studied using USP XXII basket method in AGM without enzyme. Release data were examined kinetically and the ideal kinetic model was estimated for drug release. The best results for sustained action in AGM were obtained from microcapsules of 2:1 core-wall ratio.

ÖZET


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INTRODUCTION

Ciprofloxacin is a fluoroquinolone with a broad spectrum of antibacterial activity (1). It has proved to be effective in a wide range of infections including those urinary, respiratory and gastrointestinal tracts and in septicemia skin, soft tissue and bone and joint infections. It has also half-life of 4 hours (2,3). There is no recorded experience with prolonged administration of the drug in high dosage and the resultant effects of such treatment in causing toxicity or bacterial resistance (4).

Microencapsulation is now the most frequently employed method of producing sustained released form.

In this study, we planned to prepare sustained action preparation of ciprofloxacin as microcapsules and tabletted microcapsules and the influences of core : wall ratio on the release of ciprofloxacin from the microcapsules and tabletted dosage form were investigated.

The microcapsules and tablets were tested by using USP rotating basket method (5) and the dissolution results thus obtained were evaluated kinetically and the ideal method was estimated for drug release and the ideal sustained release formulation of ciprofloxacin were determined (6).

EXPERIMENTAL

Materials

Ciprofloxacin was obtained from FAKO A.Ş., Ethyl cellulose (EC), ethoxy number 48, type N-45 was purchased from Hercules and cyclohexane from E. Merck. All materials used were of analytical grade.

Method

Preparation of microcapsules

Microcapsules with core : wall ratio of 1:2, 1:1, 2:1 were prepared by the coacervation phase separation technique (7). The microcapsulation method was modified to change the temperature and the stirring rate.

Preparation of Tablets (T1, T2, T3) were prepared by direct compression. No lubricants were used.

A single-punch hand compre

Assay of Total Drug Content

Microcapsules of different c with 10 ml of AGM without AGM without enzymes. The spectrophotometrically at 278 nm

Dissolution proce

Dissolution profiles of micro 37.0 ± 0.1°C in 900 ml of method at 100 rpm. The apparatus was immersed in a cooler to ensure a well engaged and controlled at temperature.
of antibacterial activity (1).

Including those urinary, n., soft tissue and bone and here is no recorded experience and the resultant effects of such method of producing sustained preparation of ciprofloxacin as
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otating basket method (5) and cally and the ideal method was xe formulation of ciprofloxacin close (EC), etoxy number 48, e from E. Merck. All materials

e prepared by the coacervation method was modified to change

Into a 500 ml three necked flask fitted with stirrer, thermometer and a reflux, 200 ml cyclohexane was added. 4 g ethyl cellulose was added at 50 °C by continuously stirring at 300 rpm. The temperature was first raised to 70° C slowly over 20 minutes. The temperature was raised from 70° C to 80° C over a period of 75 minutes. Ciprofloxacin, the core material, was then dispersed in the polymer solution with stirring at 300 rpm for 10 minutes. The mixture was cooled to room temperature with constant stirring to solidification of the coating. Ciprofloxacin microcapsules were separated by filtration and dried at room temperature.

The microcapsules were sieved through a combined sieve set and ciprofloxacin with particle size between 840 - 476 µm were used. Microcapsules with core : wall ratio of 1:2, 1:1, 2:1 (M1, M2, M3) were prepared with the same manner.

**Preparation of Tablets**

Tablets (T1, T2, T3) were prepared from microcapsules with different core : wall ratios by direct compression. No lubricant, excipient or binder was added to the microcapsules. A single-punch hand compressor was used to press the tablets.

**Assay of Total Drug Content from Microcapsules**

Microcapsules of different core:wall ratios containing 250 mg ciprofloxacin extracted with 10 ml of AGM without enzyme. Samples were taken as 100 µl and added 10 ml AGM without enzymes. The ciprofloxacin quantities of microcapsules were determined spectrophotometrically at 278 nm.

**Dissolution procedures**

Dissolution profiles of microcapsules with different core:wall ratios were determined at 37 ° ± 0.1° C in 900 ml of AGM without enzyme using USP XXII rotating basket method at 100 rpm. The apparatus consists of cylindrical 100 ml round bottom flasks and immersed in a controlled temperature both maintained at 37 ° ± 0.1° C. The basket was positioned to extend to exactly 2.5 cm above the flask bottom. Basket rotation was engaged and controlled at a constant 100 rpm using a dissolution stirrer drive. The
samples were assayed from the dissolution medium by measuring the absorbance at 278 nm against a AGM blank without enzyme.

The dissolution data for three core:wall ratios of microcapsules and tabletted microcapsules were treated by converting observed drug concentrations at each sampling time to amounts dissolved and in turn to percentage dissolved.

The results were evaluated kinetically by zero , first- order , Hixon-Crowell, RRSBW , Q √t , ( Bt ) a , Higuchi and Hopfenberg equations. The release rate constants (k), correlation coefficients (r) and determination coefficients (r²) were calculated by means of a computer program (6).

Artificial gastric medium was prepared by dissolving 2 g of NaCl in 7 ml of concentrated HCl and sufficient water to make 1000 ml; the pH of this solution was 1.2.

RESULT AND DISCUSSION

Plasma elimination half-life of ciprofloxacin is 3.5 - 4.5 hours and it is easily dissolved in AGM without enzyme. Preparing microcapsules with water-insoluble coating such as EC is one way of prolonging its effect.

The recovery of ciprofloxacin from microcapsules with different core:wall ratios is shown in Table 1.

Table 1. Recovery of ciprofloxacin from microcapsules

<table>
<thead>
<tr>
<th>Core: wall ratio</th>
<th>Percentage recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:1</td>
<td>62</td>
</tr>
<tr>
<td>1:1</td>
<td>32</td>
</tr>
<tr>
<td>1:2</td>
<td>81</td>
</tr>
</tbody>
</table>

Dissolution results show decrease in dissolution rate from microcapsules with microcapsules and tablets shown in Fig. 1 and Fig. 2.
Dissolution results showed that encapsulation of ciprofloxacin resulted in a marked decrease in dissolution rate. The best results for sustained action in AGM were obtained from microcapsules with core:wall ratio of 2:1. Release of ciprofloxacin from microcapsules and tableted microcapsules prepared with different core:wall ratios were shown in Fig. 1 and Fig. 2, respectively.

Fig. 1: Release of ciprofloxacin from microcapsules with different core:wall ratios

Fig. 2: Release of ciprofloxacin from tableted microcapsules with different core:wall ratios
The release rate constants (k), correlation coefficient (r) and determination coefficients (r²) were calculated by means of a computer program (6). As for the kinetic evaluations the highest determination coefficient and best linear relation were observed from microcapsules and tableted microcapsules with 2:1 core:wall ratio by RRSBW distribution (8). Dissolution results of those were shown in Table 2.

Table 2: Dissolution kinetics of ciprofloxacin tableted microcapsules with core:wall ratio (2:1)

<table>
<thead>
<tr>
<th>Dissolution kinetics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Bt)^2</td>
<td>A = 0.704</td>
</tr>
<tr>
<td></td>
<td>B = 4.578 x 10⁻⁴</td>
</tr>
<tr>
<td></td>
<td>r = 0.996</td>
</tr>
<tr>
<td></td>
<td>r² = 0.982</td>
</tr>
<tr>
<td>First Order</td>
<td>k₁ = 0.137 hr⁻¹</td>
</tr>
<tr>
<td></td>
<td>r = 0.987</td>
</tr>
<tr>
<td></td>
<td>r² = 0.974</td>
</tr>
<tr>
<td>Zero Order</td>
<td>k₀ = 17.961 hr⁻¹</td>
</tr>
<tr>
<td></td>
<td>r = 0.963</td>
</tr>
<tr>
<td></td>
<td>r² = 0.928</td>
</tr>
<tr>
<td>Hixson-Crowell</td>
<td>r = 0.981</td>
</tr>
<tr>
<td></td>
<td>r² = 0.962</td>
</tr>
<tr>
<td>RRSBW</td>
<td>β = 0.766</td>
</tr>
<tr>
<td></td>
<td>r = 0.997</td>
</tr>
<tr>
<td></td>
<td>r² = 0.994</td>
</tr>
<tr>
<td>Q vt</td>
<td>k = 2.950</td>
</tr>
<tr>
<td></td>
<td>r = 0.991</td>
</tr>
<tr>
<td></td>
<td>r² = 0.982</td>
</tr>
<tr>
<td>Higuchi</td>
<td>r = 0.994</td>
</tr>
<tr>
<td></td>
<td>r² = 0.987</td>
</tr>
<tr>
<td>Hopfenberg spherical</td>
<td>k = 6.084 x 10⁻⁴</td>
</tr>
<tr>
<td></td>
<td>r = 0.981</td>
</tr>
<tr>
<td></td>
<td>r² = 0.965</td>
</tr>
<tr>
<td>Hopfenberg cylindrical</td>
<td>k = 8.192 x 10⁻⁴</td>
</tr>
<tr>
<td></td>
<td>r = 0.977</td>
</tr>
<tr>
<td></td>
<td>r² = 0.954</td>
</tr>
<tr>
<td>Hopfenberg slab</td>
<td>k = 1.197 x 10⁻³</td>
</tr>
<tr>
<td></td>
<td>r = 0.963</td>
</tr>
<tr>
<td></td>
<td>r² = 0.928</td>
</tr>
</tbody>
</table>

Fig. 3: RRSBW dissolution kinetics of active ingredient dissolve in microcapsules with core:wall ratio of 2:1.

Table 3: Dissolution from microcapsules with core:wall ratio and the process. It could also be observed that the release could sustain the release of the active ingredient.
determination coefficients (6). As for the kinetic
relation were observed core:wall ratio by RRSBW
Table 2.
d microcapsules

Graphically RRSBW distribution gave a straight line with a slope of $\beta = 0.766$ and the
time $t = 367$ min when the active ingredient was dissolved 63.2%.

![Graph](image)

Fig 3: RRSBW distribution of tableted microcapsules with 2:1 core wall ratio

Determination coefficient ($r^2$), slope ($\beta$) and the time at which 63.2 percent of the
active ingredient dissolved ($\tau$) are calculated and are shown in Table 3.

**Table 3: Dissolution rate parameters of RRSBW distribution**

<table>
<thead>
<tr>
<th></th>
<th>$r^2$</th>
<th>$\beta$</th>
<th>$\tau$</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>0.819</td>
<td>0.846</td>
<td>25 min.</td>
</tr>
<tr>
<td>M2</td>
<td>0.890</td>
<td>1.303</td>
<td>20 min.</td>
</tr>
<tr>
<td>M3</td>
<td>0.985</td>
<td>0.510</td>
<td>326 min.</td>
</tr>
<tr>
<td>T1</td>
<td>0.980</td>
<td>0.570</td>
<td>212 min.</td>
</tr>
<tr>
<td>T2</td>
<td>0.953</td>
<td>0.846</td>
<td>131 min.</td>
</tr>
<tr>
<td>T3</td>
<td>0.993</td>
<td>0.766</td>
<td>367 min.</td>
</tr>
</tbody>
</table>

Dissolution from microcapsules and tableted microcapsules are mainly governed by the
core:wall ratio and the release appears to proceed by diffusion which is a purely physical
process. It could also be expected that the microcapsules and tableted microcapsules
should behave like plastic matrices (9, 10). It was shown that when compared to
microcapsules in tableted microcapsules, ciprofloxacin release is prolonged by
compression.

As a result, $t_{50}$ percent values of microcapsules and tableted microcapsules are longer
then uncapsulated ciprofloxacin. This shows that the microcapsules and prepared tablets
could sustain the release of ciprofloxacin.
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