Dissolution characteristics of nicardipine hydrochloride microcapsules from hard gelatin capsules and tablets* 

Nicardipine hydrochloride microcapsules prepared by using ethylcellulose as coating material were put into hard gelatin capsules and were compressed into tablets to investigate the effect of direct tabletting agent on the release of nicardipine hydrochloride. Dissolution tests were studied in simulated gastric medium without enzyme using the USP XXII rotating basketmethod. In vitro release was evaluated by zero order, first order, RRSBW, Hixson-Crowell, Higuchi and Hopfenberg kinetic models. The release of nicardipine hydrochloride was found to be governed by the core: wall ratio, microcapsule particle size and the kind of direct tabletting agent. Release from hard gelatin capsules and tabletted microcapsules were significantly more prolonged than the respective batches of the microcapsules, but release of tabletted microcapsules was found to be low degree of drug. Therefore, direct tabletting agents such as lactose, lactose fast flo and avicel pH 101 were added to the tablets to increase the release rate of drug. It was concluded that avicel pH 101 could be used to increase dissolution rates from tabletted microcapsules.

The multiple regression technique was assumed for the analysis of experimental data. Three-dimensional response-surface graphs for percentage of nicardipine hydrochloride released as a function of percentage of drug content and dissolution time were generated.

Keywords: Nicardipine hydrochloride microcapsules; core:wall ratio; microcapsule particle size; direct tabletting agent; dissolution test; response-surface graphs

Anahtar kelimeler: Nikardipin hidrokarbon mikrokapsüller; çekirdek; ceper orama; mikrokapsül parçacık büyüklüğü; dağıtımcı ajan; çözünme hızı testi; şişeybps veya grafikerleri

Introduction

Nicardipine hydrochloride (Nd.HCl) is a new calcium channel-blocking agent, classified with the dihydrochloride derivatives (1,2). Various formulations have been proposed for the administration of Nd.HCl. Tablets, hard gelatin capsules and coated pellets have been suggested for oral release formulations (3,4). Recently, this drug was widely used for the treatment of hypertension, angina pectoris and cerebrovascular diseases but its bioavailability is very limited (15-45%) (5,6). Its elimination half-life is very short (about 1 hour) and it has some side effects such as nausea, vomiting, flushing, headache, dyspepsia, anorexia, diarrhea, probably due to rapid absorption or gastric irritation (3,7). Therefore, various sustained release formulations such as alginate beads, tablets, granules and microcapsules of Nd.HCl have been presented (8-11). In a study,

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physicochemical properties of Nd.HCl and its microcapsules have been investigated (12). Various studies concerning sustained release microcapsules formulated into tablets and capsules have been reported (13-17). A number of studies covering the effects of direct tabletting agents (DTA) such as lactose, avicel pH 101 and primojel on the tablets prepared from phenylpropanolamine hydrochloride, dihydroalazine sulfate and acetaminophen microcapsules have been reported (14,17,18).

The purpose of this investigation is to study in vitro release kinetics of ethylcellulose coated Nd.HCl microcapsules formulated into tablets and capsules. In addition, the prepared microcapsules were compressed by using different types of DTA such as lactose, lactose fast flo and avicel pH 101.

The main objective of our study was to prepare sustained action Nd.HCl microcapsules formulated into tablets and capsules in order to overcome the development of tolerance seen in conventional preparations, and to increase patient compliance. In addition, in this study it was aimed to investigated the effects of DTA on the release rate of drug.

Materials and Methods

Materials
Nicardipine hydrochloride (Yamanouchi Pharm. Co. Ltd., Japan); ethylcellulose (ethoxy number 48 and Type N-10) (Sigma, St. Louis, USA); cyclohexane (E. Merck, Darmstadt, Germany); avicel pH 101 (Marcus Hook, Pennsylvania, USA); lactose (E. Merck, Darmstadt, Germany); lactose fast flo (Seppic, Paris, France); the other chemicals used were of analytical grade.

Methods
Preparation of nicardipine hydrochloride microcapsules
The method of preparation was developed by modifying the techniques of Jansenjak et al. (1976), Sulib et al. (1976) and Sevgi et al. (1994) (19-21). The preparation of microcapsules was given elsewhere (10). Quantities of Nd.HCI and ethylcellulose used depending on the core:wall ratio 2:1, 1:1 and 1:2 are shown in Table 1. Assay of nicardipine hydrochloride
Batches of 10 mg powdered microcapsules of different core:wall ratio were extracted 10 times with 10 ml simulated gastric fluid (SGF) without enzyme (22). Nd.HCl was assayed spectrophotometrically at 239 nm. Particle size distribution
Particle size distribution of the microcapsules was determined by sieving. Hard gelatin capsules and tablets were prepared from microcapsules retained at sieves of 840-247 μm sizes and were used in the dissolution experiments.

Table 1. Amounts of nicardipine hydrochloride and ethylcellulose used for different core:wall ratios of microcapsules

<table>
<thead>
<tr>
<th>Core:wall ratio</th>
<th>Nicardipine hydrochloride (g)</th>
<th>Ethylcellulose (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:1</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>1:1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>1:2</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

Content uniformity and microcapsule recovery
The microcapsules were weighed after being dried. Since the amount in grams of the added material was known, microcapsule recovery was determined.

Preparation of hard gelatin capsules
Nd.HCl microcapsules of different core:wall ratios and of different microcapsule sizes were filled into hard gelatin capsules (Table 2). The amount of microcapsule fed into the die corresponds to 20 mg Nd.HCl.

Table 2. Codes of Nd.HCl microcapsules formulated into hard gelatin capsules and tableted microcapsules

<table>
<thead>
<tr>
<th>Core:wall ratio</th>
<th>Particle size (μm)</th>
<th>Code</th>
<th>Hard gelatin capsules</th>
<th>Tableted microcapsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:1</td>
<td>&gt;840</td>
<td>C1(0)</td>
<td>T1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>840-476</td>
<td>C2(0)</td>
<td>T2</td>
<td></td>
</tr>
<tr>
<td>1:1</td>
<td>&gt;840</td>
<td>C3(00)</td>
<td>T3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>840-476</td>
<td>C4(0)</td>
<td>T4</td>
<td></td>
</tr>
<tr>
<td>1:2</td>
<td>&gt;840</td>
<td>C5(00)</td>
<td>T5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>840-476</td>
<td>C6(00)</td>
<td>T6</td>
<td></td>
</tr>
</tbody>
</table>

Conventional tablet | L | Tabled microcapsules
Pure drug           | N |

Preparation of tablets
Tablets were prepared from Nd.HCl microcapsules of different microcapsule sizes as coded in Table 2. Tablets of 2 kg hardness were compressed by hand using a single-punch tabletting machine. The amount of microcapsule fed into the die corresponded to 20 mg Nd.HCl. These microcapsules were tableted with different types of DTA. Lactose, lactose fast flo and avicel pH 101 were used as DTA. The amounts of lactose, lactose fast flo and avicel pH 101 were determined as 10 per cent of the microcapsule weight according to the results of preliminary experiments. Coded numbers of tableted microcapsules prepared with lactose, lactose fast flo and avicel pH 101 are shown in Table 3.

In addition, dissolution experiments were repeated using 25, 50% DTA to investigate kind and amount effect. According to kinetic evaluations highest determination coefficient results were obtained with 2:1 core:wall ratio microcapsules which have 840-476
Table 3. Codes of nicardipine hydrochloride microcapsules formulated into tabletted microcapsules with 10% direct tableting agent.

<table>
<thead>
<tr>
<th>Core:wall ratio</th>
<th>Particle size (μm)</th>
<th>Direct</th>
<th>Tableting</th>
<th>Agent (DTA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:1</td>
<td>&gt;840 840-476</td>
<td>T1A</td>
<td>T1B</td>
<td>T1C</td>
</tr>
<tr>
<td>1:1</td>
<td>&gt;840 840-476</td>
<td>T2A</td>
<td>T2B</td>
<td>T2C</td>
</tr>
<tr>
<td>1:2</td>
<td>&gt;840 840-476</td>
<td>T3A</td>
<td>T3B</td>
<td>T3C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T3A</td>
<td>T3B</td>
<td>T3C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T5A</td>
<td>T5B</td>
<td>T5C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T6A</td>
<td>T6B</td>
<td>T6C</td>
</tr>
</tbody>
</table>

Table 4. Codes of nicardipine hydrochloride microcapsules formulated into tabletted microcapsules with 25 and 50% direct tableting agent.

<table>
<thead>
<tr>
<th>Core:wall ratio</th>
<th>Particle size (μm)</th>
<th>Direct</th>
<th>Tableting</th>
<th>Agent (per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:1</td>
<td>840-476</td>
<td>25 T7A</td>
<td>25 T7B</td>
<td>25 T7C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 T8A</td>
<td>50 T8B</td>
<td>50 T8C</td>
</tr>
</tbody>
</table>

μm particle size. These microcapsules code numbers are shown in Table 4.

In vitro dissolution rate experiment

Dissolution from microcapsules were studied using the USP XXII rotating basket method (22). 900 ml of simulated gastric fluid (SGF) without enzyme were placed in the dissolution apparatus. The mesh size of the basket was 40. The water bath was maintained at 37.5±0.1°C and constant speed motor was calibrated to provide 100 rpm stirring rate throughout the test. Samples of 2 ml were removed at time intervals and 2 ml dissolution medium was added to the system. The Nd.HCl contents of hard gelatin capsules and tabletted microcapsules which contained DTA were determined spectrophotometrically at 239 nm. Commercially available tablets and pure drug were tested. All samples were run in triplicates and the means were calculated.

Kinetic evaluation of dissolution rate results

The data obtained from Nd.HCl microcapsules formulated into tablets and capsules were evaluated kinetically by zero order, first order, RRSBW, Higuchi, Hopfenberg equations (23-29). The release rate constants (k), correlation coefficients (r) and determination coefficients (r²) were calculated by means of a computer program (30). The results of dissolution studies obtained were compared and evaluated kinetically and the most convenient model for the release of Nd.HCl was determined. Mathematical evaluations

In order to explain the variation in % release of Nd.HCl from capsules and tablets, a multiple linear regression model has been assumed. This model was in the form of:

\[ y = \alpha + \beta_1 x + \beta_2 \log x + e \]  

(Eq. 1)

where, \( y \) is the observed % release of drug, \( e \) is the error term, \( \alpha \), \( \beta_1 \) and \( \beta_2 \) are the coefficients to be estimated. \( x \) and \( \log x \) are % drug content and logarithm of time, respectively.

SPSS statistical analysis package has been used for statistical evaluations of the experimental data (31).

Results and Discussion

In this investigation ethylcellulose with a viscosity of 10cp was chosen as the wall material and the coacervation phase separation method was employed. Ethylcellulose was selected as the wall material for its widely usage in suspension formulations and as wall material in tablets and has no side effects (32,33).

Particle sizes of the microcapsules were determined by sieve analysis. Since particle size is one of the important factors in affecting the release profiles of microcapsules (17-19), three different particle sizes: 476-247 μm; 840-476 μm; >840 μm were separated and 840-476 μm; >840 μm used for the release rate experiments. 476-247 μm microcapsules were not used, because of their low recovery.

Since the amount of the active substance in the particles changes depending on particle size and core:wall ratio, recovery was measured in all the microcapsule formulations prepared (Table 5) and it was low in microcapsules with core:wall ratio 1:2 compared to 1:1 and
2.1. As the amount of ethylcellulose was increased, the amount that adheres to the glassware and to the filter paper increased, thus the recovery reduced.

Table 5. Recovery of microcapsules prepared using 10cp ethylcellulose

<table>
<thead>
<tr>
<th>Core:wall ratio</th>
<th>Total summation</th>
<th>Particle size (µ)</th>
<th>% Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;840</td>
<td>840-476</td>
<td>476-247</td>
</tr>
<tr>
<td>2:1</td>
<td>94.41</td>
<td>39.27</td>
<td>58.95</td>
</tr>
<tr>
<td>1:1</td>
<td>95.87</td>
<td>17.99</td>
<td>75.62</td>
</tr>
<tr>
<td>1:2</td>
<td>77.50</td>
<td>20</td>
<td>74.83</td>
</tr>
</tbody>
</table>

The calibration equation of $y = 0.0506x + 0.036$ (r=0.99) was used for the determination of the Nd.HCl ($y = \text{absorbance}; \ x = \text{concentration \ µg/ml}$). The sensitivity was found within the range of 2.5-15 µg/ml. Analysis of variance which belongs to the correlation between x and y is given in Table 6. As a result lack of fit test is found to be insignificant.

Table 6. Analysis of variance

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>DF</th>
<th>SS</th>
<th>MS</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>1</td>
<td>0.84005</td>
<td>0.84005</td>
<td>2896.72</td>
</tr>
<tr>
<td>Error</td>
<td>16</td>
<td>0.00467</td>
<td>0.00029</td>
<td>0.00029</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>0.84473</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p<0.01 %CV=3.77

The most frequently used dosage forms for microencapsulated products have been suspension, gel and hard gelatin capsule. Only a few investigations of tablet formulations from microcapsules have been reported by using DTA (16-18,34). Therefore the purpose of this investigation was to compress the respective batches of microcapsules into their tablets and study the release kinetics of the drug from them.

Dissolution results obtained from gelatin capsules are shown in Fig.1. The in vitro drug release was sustained from 30 minutes to 5 hours. Tableted microcapsules were prepared in order to obtain a better sustained action than hard gelatin capsules. Dissolution results of tablets prepared from microcapsules are shown in Fig.2. Although drug release was sustained to 8-9 hours, the amount of drug release was found very low (20-46%). Therefore, in order to increase the drug release, 10% of DTA such as lactose, lactose fast flo and avicel pH 101 were added to the tablets. These disintegrants were chosen because of their easily dispersability and freely solubility in water.

Fig.1. Dissolution profiles of pure drug (N) and nicardipine hydrochloride microcapsules formulated into hard gelatin capsules

![Fig.1](image1)

Fig.2. Dissolution profiles of commercial tablet (L) and nicardipine hydrochloride tabletted microcapsules

![Fig.2](image2)

In a previous study, 50% lactose, primojel and avicel pH 101 have been added as DTA to phenylpropanolamine hydrochloride tablets prepared from microcapsules. Also in this study it has been shown that lactose prolonged the release of phenylpropanolamine hydrochloride more than avicel pH 101, whereas, primojel released the active principle more rapidly than avicel pH 101 (17). In a similar study dihydralazine sulphate, 50% lactose and 25 and 50% avicel pH 101 have been added and it has been observed that 50% lactose prolonged the release of dihydralazine sulphate more than 50% avicel pH 101, whereas 50%
avicel pH 101 released the active principle more quickly than the 25% direct tableting agent (18). In other studies, the absence or presence of 0.75% magnesium stearate as lubricant has not effected the release from HPMC K15M matrices of promethazine HPMC matrix tablets (35) and 75% lactose or calcium phosphate have been added to HPMC matrix tablets of promethazine hydrochloride resulted in an increase in release rates for active substance (36).

In the present study by adding lactose to the tablets coded as T3A and T4A, drug release was determined as 65-70%, but sustained action range was found very low (Fig.3). Although a good sustain action was observed in codes T5A and T6A, drug release reached to only 50-60%. Drug release was also very low in comparison to the other two tablets (T1A, T2A).

![Fig.3. Dissolution profiles of tabletted microcapsule prepared by adding 10% lactose](image)

Dissolution by adding both 10% lactose fast flo and avicel pH 101 resulted in a good sustained action but the drug amount obtained was very low (<50%) (Figs, 4,5).

![Fig.4. Dissolution profiles of tabletted microcapsules prepared by adding 10% lactose fast flo](image)

![Fig.5. Dissolution profiles of tabletted microcapsules prepared by adding 10% avicel pH 101](image)

According to the obtained results, it was considered to increase the amount of DTA than 25 and 50 per cent of DTA were added to the tablets prepared from microcapsules with 2:1 core:wall ratio and particle size 840-476 μm (Table 4) and dissolution studies were repeated. A satisfactory sustained action was obtained (7 hours) and drug release was increased to 83% in T8C (Fig.6). Drug release of the commercial tablets was 30-60 minutes.

![Fig.6. Dissolution profiles of tabletted microcapsules prepared by adding 25 and 50% direct tableting agent](image)

At the end of the dissolution experiments, the tabletted microcapsules used in this study did not disintegrate. This physical property suggests that the release of Nd.HCl from tabletted microcapsules is through passive diffusion (37).

According to the kinetic evaluations, the RRSBW distribution was found to be most suitable for defining the release from gelatin capsules and tabletted microcapsules. RRSBW
kinetic profiles of prepared formulations are illustrated in Fig. 7. For the ideal gelatin capsule and tabletted microcapsule, the shape parameters (β) were found as 0.889 and 1.34 respectively, t_{63.2%} values were 169.89 and 260.55 min.

![Graph](image)

Fig. 7. RRSBW distributions of ideal gelatin capsule (C1) and tabletted microcapsule (T8C)

In conclusion, if nicardipine hydrochloride microcapsules are to be prepared in gelatin capsule form, we suggest the microcapsules to be prepared in the form of core:wall 2:1 and particle size >840 μm (as coded C1). If they are to be prepared in the form of a tablet, the microcapsules with a core:wall ratio 2:1 and particle size 840-476 μm by adding 50% avicel pH 101 is suggested (T8C).

The dissolution results obtained at 6-7 hours were evaluated mathematically. For this, the multiple regression model given in Eq. 1 was fitted. The estimated model was found to be the best y=-58.371+0.309x+35.459 log t (Eq. 2) fitted one for % release of drug from gelatin capsules and tabletted microcapsules without DTA. A three-dimensional response-surface graph for percentage of Nd.HCl released as a function of percentage of drug content and dissolution time was generated by using Eq. 2 in order to enable selection of optimum formulation (Fig. 8) (p<0.001).

![Graph](image)

Fig. 8. The response-surface graph for percentage nicardipine hydrochloride released from the hard gelatin capsules and tabletted microcapsules as a function of percentage drug content and dissolution time

In order to investigate the effect of the drug content and the time on the % drug release of the tablet formulations prepared with DTA, multiple regression model given in Eq. 1 has been fitted similar to the one obtained for formulations. The estimated model which is in the form of:

\[ y = -18.069 - 0.067x + 23.71 \log t \quad \text{(Eq. 3)} \]

![Graph](image)

Fig. 9. The response-surface graph for percentage nicardipine hydrochloride released from tabletted microcapsules prepared by adding 10% direct tablettling agent as a function of percentage drug content and dissolution time

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References


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