Numerous carriers and encapsulation techniques have been evaluated for preparation of microcapsules with sustained-release properties. However, literature survey revealed that most of the drugs used were relatively water-insoluble. While water insoluble compounds have inherent sustained-release properties when incorporated in a polymer matrix and are relatively easy to encapsulate, preparation of sustained release microcapsules of water-soluble pharmaceuticals pose a great challenge (3). Among the various methods developed for formulation of microspheres, the solvent evaporation method has gained much attention due to its ease of fabrication without compromising the activity of the drug (4).

Ropinirole hydrochloride is a selective non-ergoline dopamine D2 receptor agonist indicated for use in treating Parkinson’s disease. It is a potent drug with a dose of 2 mg to be administered 3–4 times daily. It is a highly water-soluble drug (133 mg mL\(^{-1}\)) with plasma half-life of 6 h (5). It is also soluble in dichloromethane (DCM), methanol, ethanol, etc. Results from efficacy and safety trials showed that adding extended release ropinirole to the patients on levodopa therapy reduced the amount of “off” time experienced by the patient (6).
patient. The on-off phenomenon associated with the Parkinson’s patient may also be due to fluctuation of the drug plasma concentration. Microsphere based drug delivery system of ropinirole hydrochloride will thus offer an accurate and more reliable drug release over a prolonged period under such circumstances. Parkinsonism therapy involves variable dosing of ropinirole hydrochloride and thus a number of extended release tablets having different strengths (2, 4, 6 and 8 mg) have been developed as per requirement. This leads to increased developmental cost, which would be avoided in the case of microsphere based drug delivery as the dose could be titrated as per need and requirement.

The emulsion-solvent evaporation technique has been used successfully in the preparation of microspheres made from several biocompatible polymers such as polymethacrylate, albumin, waxes, polylactic-co-glycolic acid (PLGA), chitosan, etc. (6–8). Oil-in-water emulsions are preferred for preparation of microspheres of water-insoluble drugs over water-in-oil emulsions due to the simplicity of the process. In the present investigation, a polar organic solvent in oil system was used for preparation of ropinirole hydrochloride microspheres. Ethylcellulose, a water-insoluble polymer, in combination with polyethylene glycol 6000, a plasticizer and release modifier, were used as encapsulation materials.

Besides developing a microsphere-based controlled drug delivery system of ropinirole hydrochloride, another important objective was to determine the influence of process variables such as selection of internal and external phases, surfactant, stirring speed, etc., on microsphere characteristics, such as drug incorporation, shape and in vitro drug release rate. Extended-release tablet of ropinirole hydrochloride based on the matrix type system may lead to dose dumping and gastric irritation associated with matrix polymer.

EXPERIMENTAL

Materials

Ropinirole hydrochloride was obtained as a gift sample from Lupin Research Park, India. Ethylcellulose (EC) was obtained as a gift sample from Colorcon Asia Ltd., India. All other chemicals and reagents used were of analytical grade.

Formulation optimization

Based on preliminary trials, a 2-factor 3-level full factorial design was employed to design controlled release microspheres of ropinirole hydrochloride. This design was suitable for exploring quadratic response surfaces and constructing second-order polynomial models. The two independent formulation variables analyzed during the study were the ratio of drug/ethylcellulose ($X_1$) and the portion of polyethylene glycol (PEG) in ethylcellulose ($X_2$) (Table I). All other independent variables were kept constant.

<table>
<thead>
<tr>
<th>Variables levels</th>
<th>Low (-1)</th>
<th>Medium (0)</th>
<th>High (+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug/ethylcellulose ($X_1$)</td>
<td>1:1</td>
<td>1:2</td>
<td>1:3</td>
</tr>
<tr>
<td>PEG portion in EC (%) ($X_2$)</td>
<td>0</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>
throughout the process. Dependent variables investigated were the encapsulation efficiency ($EE$) ($Y_1$) and the time taken for 100% of the drug to be released ($Y_2$) (Table II) (9).

**Methods**

Weighed amounts of ropinirole hydrochloride, ethylcellulose and PEG 6000 were dissolved in ethanol in three different beakers separately using a magnetic stirrer (Remi, 2MLH, India). PEG solution was then added to ethylcellulose solution and mixed for 15 minutes. To the resulting solution of polymers, drug solution was added and mixed. This solution was then added in a thin stream to a beaker containing a mixture of 90 mL light liquid paraffin, 10 mL $n$-heptane and 2% ($V/V$) Span 80 in liquid paraffin under stirring at 500–700 rpm with a mechanical stirrer. Stirring was continued for 2 h at room temperature until ethanol evaporated completely and microspheres were formed. The formed microspheres were initially filtered through a nylon cloth and then finally filtered through Whatman no. 1 filter paper. The microspheres were washed 4–5 times with a total volume of petroleum ether of 50 mL. The product was then dried at room temperature for 24 hours. All batches were prepared in triplicate. This method was developed on the basis of practical observations, which are discussed in the later part by carrying out certain modifications to the existing methods (10, 11).

**Effect of process parameters**

*Viscosity of external phase.* – In the preparation of microspheres, heavy liquid paraffin was initially employed as an external phase. Then light liquid paraffin alone and then along with $n$-heptane were tried. $n$-Heptane was incorporated as a viscosity reducing agent and its effect on formation of microspheres was studied.

---

### Table II. Composition of ropinirole microspheres prepared as per $3^2$ factorial design

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Variable levels in coded form</th>
<th>$EE$ (%) ($Y_1$)</th>
<th>$DL$ (%) ($Y_2$)</th>
<th>$T_{100}$ (h) ($Y_2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$X_1$</td>
<td>$X_2$</td>
<td>$EE$ (%) $Y_1$</td>
<td>$DL$ (%) $Y_2$</td>
<td>$T_{100}$ (h) $Y_2$</td>
</tr>
<tr>
<td>F1</td>
<td>$-1$</td>
<td>$+1$</td>
<td>$37.5 \pm 0.8$</td>
<td>$18.6 \pm 0.5$</td>
</tr>
<tr>
<td>F2</td>
<td>$-1$</td>
<td>$0$</td>
<td>$38.2 \pm 0.9$</td>
<td>$19.2 \pm 0.5$</td>
</tr>
<tr>
<td>F3</td>
<td>$-1$</td>
<td>$-1$</td>
<td>$41.7 \pm 0.7$</td>
<td>$20.9 \pm 0.9$</td>
</tr>
<tr>
<td>F4</td>
<td>$0$</td>
<td>$+1$</td>
<td>$56.9 \pm 0.7$</td>
<td>$14.2 \pm 0.7$</td>
</tr>
<tr>
<td>F5</td>
<td>$0$</td>
<td>$0$</td>
<td>$58.8 \pm 1.0$</td>
<td>$14.7 \pm 0.2$</td>
</tr>
<tr>
<td>F6</td>
<td>$0$</td>
<td>$-1$</td>
<td>$60.3 \pm 0.9$</td>
<td>$20.1 \pm 0.4$</td>
</tr>
<tr>
<td>F7</td>
<td>$+1$</td>
<td>$+1$</td>
<td>$77.0 \pm 0.7$</td>
<td>$19.3 \pm 0.4$</td>
</tr>
<tr>
<td>F8</td>
<td>$+1$</td>
<td>$0$</td>
<td>$78.7 \pm 1.0$</td>
<td>$19.7 \pm 0.3$</td>
</tr>
<tr>
<td>F9</td>
<td>$+1$</td>
<td>$-1$</td>
<td>$79.4 \pm 0.8$</td>
<td>$19.8 \pm 1.0$</td>
</tr>
</tbody>
</table>

$^a$ Mean ± SD, $n = 3$.

Encapsulation efficiency ($EE$) is the percentage of encapsulated drug.

Loading efficiency ($DL$) is the concentration of the drug in the formulation.
Organic solvent as internal phase. – In the present study, dichloromethane, methanol, ethanol and combination of these solvents were employed as internal phases. Effect of internal solvent on formation of microspheres was studied by analyzing the shape, surface morphology and release profile.

Surfactant. – Selection of the dispersing agent was based on solubility criteria in the external phase. Literature survey revealed the use of Span 80 and Tween 80 for preparation of microspheres (12, 13).

Stirring speed. – Microspheres of ropinirole hydrochloride were prepared at different stirring speeds and the effect on encapsulation efficiency, size of microspheres and drug release from microspheres was observed.

Characterization of microspheres

Product yield. – The yield of microspheres of various batches was calculated using the mass of the final product after drying with respect to the initial total mass of the drug and polymer used for preparation of microspheres.

Encapsulation efficiency and loading efficiency. – About 11.4 mg of ropinirole hydrochloride equivalent to 10 mg ropinirole base was weighed accurately and transferred to a 50-mL volumetric flask to which 20 mL methanol was added and sonicated for 15 min. Final volume was made with mobile phase (methanol/0.05 mol L⁻¹ ammonium acetate, pH 7.0; 80:20, V/V). The formed solution was filtered through Whatman filter paper. One mL of this solution was withdrawn and further diluted up to 10 mL with the mobile phase. An aliquot was used for the determination of drug concentration by HPLC (Perkin Elmer series 200, USA) using a UV detector kept at 250 nm (14). Concentration of the drug in stock solution was calculated using the calibration curve.

Surface morphology. – Shape and surface morphological examination of drug microspheres was done by scanning electron microscopy (SEM). Dried samples were coated with platinum using an auto fine coater (JFC 1600, Jeol, Japan). These samples were observed under different magnifications with an analytical scanning electron microscope (Jeol-JSM 6360A).

Differential scanning calorimetry. – The possibility of any interaction between ropinirole hydrochloride and polymer was studied by differential scanning calorimetry (DSC), which was performed using a Shimadzu-thermal analyzer DT 40, Japan. Thermograms were obtained at a scanning rate of 10 °C min⁻¹ conducted over a temperature range of 30–300 °C in a liquid nitrogen environment (flow rate 10 mL min⁻¹).

Micromeretic properties of microspheres. – Angles of repose of different formulations were calculated according to the fixed funnel standing method (15). Bulk density and tapped density were measured in a 10-mL graduated cylinder using a bulk density apparatus (15). Carr’s compressibility index of microspheres was computed (15).

Particle size and particle size distribution. – The particle size distribution of different batches of microspheres was determined by optical microscopy. The projected diameter of microspheres was determined using an image analyzer (Labomed, India) that consisted of an optical microscope linked to a computer and digital camera. The digitized images captured were analyzed with image analyzing software (Digipro version 2, Labomed, India).
In vitro drug release and kinetics. – In vitro release of ropinirole from the microspheres was performed in a modified USP type I dissolution apparatus, in which the basket was covered with nylon cloth (0.15 mm), at a speed of 50 rpm (15, 16). The dissolution medium was 500 mL of citrate buffer (pH 4.0) at 37.0 ± 0.5 °C. The aliquots of samples were analyzed by HPLC at 250 nm. Cumulative percentage drug release was calculated and the data was then fitted into various mathematical models. There are several models of the drug dissolution profiles where the amount of the drug dissolved from the system is a function of time \( t \). Quantitative interpretation of the values obtained in the dissolution is facilitated by the usage of mathematical equations (17). Models with major appliance and best describing drug release phenomena are the Higuchi model, zero-order model, Weibull model and Korsmeyer-Peppas model. The criteria for choosing the "best model" to study drug dissolution/release phenomena are based on the use of the \( R \) value; the "best" model would be the one with the highest adjusted \( R \) (19).

Regression analysis. – Targeted response parameters were statistically analyzed by applying one-way ANOVA at 0.05 level in the Design-Expert® 7.1.6 demo version software (Stat-Ease Inc., USA). Individual response parameters were evaluated using the \( F \)-test and quadratic models of the form given below were generated for each response parameter using multiple linear regression analysis:

\[
Y = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_1 X_2 + b_4 X_2 + b_5 X_2^2
\]

where \( Y \) is the level of the measured response, \( b_0 \) is the intercept, \( b_1 \) to \( b_5 \) are the regression coefficients, \( X_1 \) and \( X_2 \) stand for the main effects, \( X_1 X_2 \) is the interaction between the main effects, \( X_1^2 \) and \( X_2^2 \) are the quadratic terms of the independent variables that were used to simulate the curvature of the designed sample space. A backward elimination procedure was adopted to fit the data to the quadratic model. The quadratic models generated from the regression analysis were used to construct 3-dimensional graphs, in which the response parameter \( Y \) was represented by a curved surface as a function of \( X \). The effects of independent variables on the response parameters were visualized from the contour plots (18, 19).

RESULTS AND DISCUSSION

Process parameters. – Only heavy liquid paraffin was initially used as a dispersion medium to generate the emulsion; however, serious agglomeration was observed during the process. The high viscosity (110–230 mPa s) of heavy liquid paraffin may have forced the droplets of organic polymer solution to coalesce, or may have prevented the droplets from separating following collision during the stirring procedure. Light liquid paraffin has comparatively low viscosity (25–80 mPa s) and so it was tried instead of heavy liquid paraffin. This resulted in sticking of the formed microspheres to the walls of the beaker. To overcome this problem, part of liquid paraffin was replaced by \( n \)-heptane. It was observed that addition of \( n \)-heptane reduced the viscosity of the dispersion medium and the small viscosity differences between the internal and external phases increased the stability of the emulsion system and sticking was prevented. In addition, the specific gravity
of the internal phase was somewhat lower than that of the oil phase. A reduction in the specific gravity of the oil phase due to replacement by heptane may have prevented the emulsion from creaming. A 90:10 ratio of light liquid paraffin to heptane was found to be satisfactory in preventing agglomeration during the stirring process, which resulted in increased production yield (Table III) as well as in obtaining perfectly smooth spherical microspheres (Fig. 1a).

DCM was initially employed as polar internal organic solvent phase for preparation of microspheres because it is a good solvent for most polymers and drugs. However, it was observed that the microparticles obtained were not spherical in shape, as shown in Fig. 1b. To solve this problem, methanol was used along with dichloromethane for preparation of microspheres. The microspheres prepared using dichloromethane and methanol are shown in Fig. 1c. These microspheres were spherical but lacked smooth texture. It was observed that the boiling point of internal organic solvents may affect the sphericity and surface smoothness of microspheres. The boiling point of DCM (39.75 °C) is low and leads to rapid evaporation of DCM, resulting in polymer precipitation. The use of methanol, which has a comparatively high boiling point (64.7 °C), resulted in spherical microspheres but lacked surface smoothness. Hence, instead of dichloromethane or methanol, ethanol was used. Ethanol was selected as polar organic solvent because it is a good solvent for most water-soluble drugs and water-insoluble polymers, and it is non-toxic. Ethanol also has a high boiling point (78.4 °C) compared to other organic solvents (di-
chloromethane, acetone, methanol, etc.), which prevented immediate polymer precipitation, as well as dispersion of ethanol (internal phase) as droplets in the oily phase, leading to the formation of a stable emulsion.

The emulsifier Tween 80 is a water-soluble surfactant, which is used when water is the external phase, while Span is an oil soluble surfactant used for preparation of emulsion when the external phase is oil-like mineral oil. In the present investigation, liquid paraffin was the external phase of the w/o emulsion. The required hydrophilic-lipophilic balance (HLB) for this case is 4.0. Span 20 has an HLB value of 8.9 while Span 80 has HLB 4.3 and was used as a surfactant in the present study. Span 80 also provided a protective sheath around organic polymer droplets and prevented the droplets from coalescing.

Both the shape and size distribution of the particles depended heavily on the stirring speed. Rapid rotation of the stirrer (1200–1500 rpm) resulted in smaller particle size (< 100 µm), with narrower particle size distribution. However, rapid drug release (100 % after 3 h) was observed from the microspheres prepared at higher speed. This was presumably due to the small particle size that led to a much larger surface area available for release and shorter path length for the drug to diffuse through microspheres. Encapsulation efficiency at this speed was also found to be lower, i.e., 35.0 ± 0.6 % than that obtained by stirring speed of 500–700 rpm (F3) which may be due to the increase in effective surface area that led to drug exposure to the solvent during the washing stage. However, agglomeration was observed when stirring speed was kept low (100–200 rpm). Finally, the 500–700 rpm stirring speed was selected for preparation of microspheres, at which speed encapsulation efficiency was found to be 40.5 ± 0.8 % and particle size was 300–500 µm.

Various channeling agents like HPMC, citric acid, polyvinyl pyrolidine, PEG, etc., were screened for the present study. Ethanol was used as an internal phase, so the first criterion for the channeling agent was that it must be soluble in ethanol and insoluble in

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Bulk density (g mL⁻¹)</th>
<th>Angle of repose (°)</th>
<th>Carr’s index (%)</th>
<th>Product yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>1.11 ± 0.31</td>
<td>23.7 ± 0.7</td>
<td>11.2 ± 0.9</td>
<td>75.5 ± 1.8</td>
</tr>
<tr>
<td>F2</td>
<td>1.11 ± 0.31</td>
<td>21.6 ± 0.4</td>
<td>11.2 ± 0.9</td>
<td>74.9 ± 1.9</td>
</tr>
<tr>
<td>F3</td>
<td>1.00 ± 0.22</td>
<td>24.2 ± 0.6</td>
<td>9.9 ± 0.8</td>
<td>76.1 ± 1.2</td>
</tr>
<tr>
<td>F4</td>
<td>1.11 ± 0.31</td>
<td>26.7 ± 0.8</td>
<td>11.2 ± 0.9</td>
<td>77.1 ± 1.5</td>
</tr>
<tr>
<td>F5</td>
<td>1.11 ± 0.31</td>
<td>22.6 ± 0.3</td>
<td>11.2 ± 0.9</td>
<td>78.1 ± 1.6</td>
</tr>
<tr>
<td>F6</td>
<td>1.00 ± 0.22</td>
<td>26.2 ± 0.7</td>
<td>9.9 ± 0.8</td>
<td>77.3 ± 1.5</td>
</tr>
<tr>
<td>F7</td>
<td>1.11 ± 0.31</td>
<td>22.7 ± 0.5</td>
<td>11.2 ± 0.9</td>
<td>78.7 ± 1.4</td>
</tr>
<tr>
<td>F8</td>
<td>1.11 ± 0.31</td>
<td>23.6 ± 0.9</td>
<td>11.2 ± 0.9</td>
<td>77.3 ± 2.0</td>
</tr>
<tr>
<td>F9</td>
<td>1.11 ± 0.31</td>
<td>25.2 ± 0.6</td>
<td>11.2 ± 0.9</td>
<td>77.9 ± 1.1</td>
</tr>
<tr>
<td>F3*</td>
<td>1.00 ± 0.22</td>
<td>24.7 ± 0.8</td>
<td>9.9 ± 0.8</td>
<td>68.8 ± 1.6</td>
</tr>
</tbody>
</table>

*Microspheres prepared without n-heptane in dispersion medium.
external phase, i.e., liquid paraffin. Polyethylene glycol is chemically stable, soluble in ethanol (95 %) and methanol, but insoluble in fats, fixed oils, and mineral oil. Besides, PEG has good plasticity and binding properties. Thus due to these favourable properties, PEG appeared to be an ideal channeling agent and was selected for these microspheres.

Microspheres were washed to remove residual traces of liquid paraffin and the drug, which could have been adhering on the surface of microspheres. The solvent has to be selected based on the fact in which polymer is insoluble, but the drug and liquid paraffin are soluble. Various washing solvents such as water, ether, hexane and petroleum ether were used for washing the formed microspheres. Petroleum ether is the solvent in which liquid paraffin and the drug are soluble, while EC is insoluble; so petroleum ether was employed for washing formed microspheres.

Characterization of microspheres

The yield of formed microspheres was found in the range of 74 to 78 %, as shown in Table IV.

Encapsulation of the drug increased from F3 to F9 due to increase in polymer concentration in a fixed volume of organic solvent. Highest encapsulation (79.4 ± 0.8 %) was observed for formulation F9. Encapsulation efficiency of the microspheres prepared with ethylcellulose alone was higher (F3, F6, F9) than for the microspheres prepared with the ethylcellulose/PEG combination. This can be attributed to the hydrophilic nature of PEG, which might have facilitated the diffusion of some of the entrapped drug to the surrounding medium during formation of the microspheres (Table II).

Surface morphology characteristics were studied using SEM (Figs. 1a–c). SEM indicated that the microspheres prepared with ethanol were perfectly spherical with a smooth surface (Fig. 1a). The photomicrographs also showed the presence of loose crystals on the surface of a few microspheres prepared with the combination of dichloromethane and methanol (Fig. 1c), while the particles made using only DCM were irregular in shape and were not able to retard drug release even at higher concentration of ethylcellulose (Fig. 1b).

Drug-polymer interactions were studied by DSC. Fig. 2 depicts the DSC thermograms of ropinirole hydrochloride, physical mixture (ropinirole hydrochloride + ethylcellulose + PEG 400) and ropinirole microspheres. The DSC of ropinirole hydrochloride exhibited a single sharp endothermic peak at 250 °C corresponding to its melting transi-

Table IV. Dissolution models and kinetics

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Zero-order</th>
<th>First-order</th>
<th>Higuchi/matrix</th>
<th>Korsmeyer-Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R_k$ (mg h$^{-1}$)</td>
<td>$k_0$ (h$^{-1}$)</td>
<td>$R_k$ (mg h$^{-1/2}$)</td>
<td>$k_p$ (mg h$^{-n}$)</td>
</tr>
<tr>
<td>F9</td>
<td>0.626</td>
<td>0.0075</td>
<td>0.627</td>
<td>0.963</td>
</tr>
<tr>
<td>F8</td>
<td>0.712</td>
<td>0.0102</td>
<td>0.712</td>
<td>0.984</td>
</tr>
<tr>
<td>F7</td>
<td>0.700</td>
<td>0.0118</td>
<td>0.700</td>
<td>0.980</td>
</tr>
</tbody>
</table>

$k$ – rate constant, $n$ – diffusion exponent.
tion temperature. A slightly broadened peak was observed in the thermogram of the physical mixture at the same temperature. This may be due to the fact that the presence of ethylcellulose in the physical mixture depresses the melting point of ropinirole hydrochloride and broadens its melting point endotherm. The peak of the drug did not appear in the thermogram of drug microspheres. This may indicate that the drug was uniformly dispersed at the molecular level in the microspheres (20).

Angle of repose, bulk density and Carr’s index were determined to predict flow properties. The prepared microspheres exhibited good flow properties (Table III).

The mean diameter of microspheres was found to be 400 µm. Particle size mainly depends on the stirring speed, which was kept constant throughout the process. Particle size distribution of the optimized batch is shown in Fig. 3.

In vitro drug release profiles and kinetics

Drug release decreased as the portion of polymer. Formulations F1 to F3 (drug/EC 1:1) show higher drug release as compared to other formulations, F4 to F6 (drug/EC 1:2), as well as to F7 to F9 (drug/EC 1:3). Formulations containing PEG (F7 and F8) showed more rapid drug release than those containing only ethylcellulose (F3, F6, F9). Formulation F7 (10 % of PEG) showed more rapid release than F9 (no PEG). As the concentration of PEG increases, the pores on surfaces also increase, which leads to faster drug release (21). Formulation F7 with high levels of both 1:3 drug/ethylcellulose and 10 % of PEG was able to control drug release for 12 h (Fig. 4).

When fitted into various mathematical models, the best linearity was found in the Korsmeyer-Peppas plot ($R = 0.995$), indicating that the release of the drug from microspheres follows the Korsmeyer-Peppas model (17) (Table IV).
The \( n \) value in the Korsmeyer-Peppas model describes the drug release mechanism. It is known that when \( n < 0.5 \), Fickian diffusion is observed and the release rate is independent of \( t \), while \( 0.5 < n < 1.0 \) indicates anomalous (non-Fickian) transport and when \( n = 1 \) the release is zero-order (17). Here \( n \) was found to be less than 0.5, which may indicate that the release of ropinirole from ethylcellulose matrix follows Fickian diffusion.

Regression analysis

The surface quadratic model generated for encapsulation efficiency was found to be significant, with an \( F \)-value of 197.56 (\( p < 0.0006 \)) and \( R^2 \) value of 0.9970. The polynomial equation for the response variable encapsulation efficiency was:

\[
EE\% = 59.67 + 19.64X_1 - 1.06X_2 - 0.41X_1X_2 + 0.074X_1^2 - 1.54X_2^2
\]
The model indicated that both factors, i.e., drug/EC ratio and % of PEG exerted independently a significant influence on the encapsulation efficiency. The 3-D plot (Fig. 5a) shows that the encapsulation efficiency increased from 37.5 ± 0.8 % (F1) to 79.4 ± 0.8 % (F9) at lower and higher levels of ethylcellulose, respectively. In contrast, encapsulation efficiency declined from 79.4 ± 0.8 % in F9 to 77.0 ± 0.7 % in F7 at high ethylcellulose load as PEG level increased from low to high, which could be due to the hydrophilic nature of PEG. Similar results were obtained with intermediate and low levels of ethylcellulose with respect to PEG amounts. A linear relationship was observed between the two variables of encapsulation efficiency, i.e., drug/EC ratio and % of PEG, which is clearly visible from the corresponding contour plots, which suggest that encapsulation efficiency could be enhanced using low PEG levels at high ethylcellulose levels. From the equation, it is clearly visible that the positive value is obtained for factor X1, which shows a positive effect on encapsulation. Negative values were obtained for X2 and X1X2, which show a negative effect on encapsulation leading to a decrease in encapsulation efficiency (Fig. 5a). A similar kind of relationship was observed for loading efficiency (DL). Namely, for a constant drug/EC ratio, there was a corresponding increase in loading efficiency, with the decrease in PEG concentration. The change was significant when the drug/EC ratio was low, but as the drug/EC ratio increased, the change was minimal (Table II).

The mathematical model generated for time taken for 100 % drug release (T100) was found to be significant with F-value of 19.87 (p < 0.0166) and R2 value of 0.9707. The polynomial equation for the response variable time for 100 % drug release was:

\[ T100 = 6.72 + 8.02X_1 - 3.90X_2 - 4.18X_1X_2 + 4.08X_1^2 + 1.33X_2^2 \]

The mathematical models generated indicated that both the ethylcellulose loads and PEG levels exerted independently a significant influence on T100. The positive influence of the levels of both these factors on T100 is clearly demonstrated by the response surface plots (Fig. 5b). Slower drug release with increased ethylcellulose loads was due to better encapsulation of the drug in the polymer matrix, which resulted in high T100 values. The 3-D plots also show that the T100 reduces from 32.5 ± 0.5 to 12.1 ± 0.3 h at higher ethylcellulose loads as PEG content increased from lower to higher levels. Similarly for
lower ethylcellulose loads, T100 reduced from 4.0 ± 0.6 to 2.0 ± 0.3 h when the PEG concentration increased from lower to higher levels. This can be attributed to the hydrophilic and leaching property of PEG, which increased the magnitude of the voids and consequently the channels from the microsphere surface, resulting in the formation of a heavily structured, microporous matrix. The equation suggests that factor $X_1$ has a positive effect on T100. As the level of $X_1$ increases, T100 also increases. $X_2$ and $X_1X_2$ have a negative effect on the T100 leading to decrement in T100 as the level of $X_2$ increases.

The results of ANOVA, as shown in Table V, indicate that the quadratic model was significant for all response parameters investigated. The multiple linear regression analysis revealed that both the formulation variables analyzed had a significant influence on all response parameters. The results obtained indicate that optimum amounts of ethylcellulose and PEG are essential to produce microspheres with desirable encapsulation and release characteristics.

### CONCLUSIONS

Microspheres containing ropinirole hydrochloride were successfully prepared by the emulsion solvent evaporation method. The factorial data suggests that a high ratio of drug to ethylcellulose and high level of PEG (F7) play a significant role in controlling the release of ropinirole hydrochloride with the desired release profile from its microspheres. Process parameters like the viscosity of the external phase, properties of the internal phase, surfactant, washing solvent and stirring speed had a major influence on the characteristics of microspheres and can be optimized to obtain the desirable properties built in the microcapsules. This also suggests that microspheres can be a good alternative to matrix-based tablets in Parkinsonism therapy, which offers dose flexibility, prolongs GI residence and can prevent dose dumping.
REFERENCES


**SAŽETAK**

**Mikrosfere ropinirol hidroklorida za polagano oslobađanje: Utjecaj procesnih parametara**

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Mikrosfere ropinirol hidroklorida, ljekovite tvari vrlo dobro topljive u vodi, pripravljene su metodom isparavanja otapala, koristeći etilcelulozu i PEG te $3^2$ potpuno faktorijalno dizajniranje. Mikrosfere su pripravljene na sljedeći način: otopina ljekovite tvari u polarnom organskom otapalu emulgirana je s tekućim parafinom kao vanjskom uljnom fazom. Ispitivan je utjecaj različitih procesnih parametara poput viskoznosti vanjske faze, vrste interne faze i površinski aktivne tvari te brzine miješanja. Za pripravljene mikrosfere određeno je iskorištenje, učinkovitost inkapsuliranja i veličina čestica. Ispitavanje je različiti odnosi ljekovite tvari i etilceluloze te koncentracija PEG-a. *In vitro* pokusi su pokazali da je oslobađanje ljekovite tvari kontrolirano tijekom 12 h.

**Ključne riječi:** ropinirol hidroklorid, mikrosfere, etilceluloza, isparavanje otapala, faktorijalno dizajniranje

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