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Individual and Combined Effect of Eudragit® RS 100 and Eudragit® RL 100 on Sustained Release Characteristics of Ropinirole HCl-loaded Microparticles

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ABSTRACT

Ropinirole HCl is a non-ergoline dopamine agonist which is recommended for the treatment of both Parkinson's disease and Restless Legs Syndrome (RLS). Its half-life is about 6 hours and it is metabolized in the liver primarily by CYP1A2. Its metabolites are water-soluble and rapidly excreted from the body in urine. However, its oral bioavailability is low. Therefore, this current project aimed to produce and evaluate sustained release ropinirole microparticles coated with Eudragit® RS 100 and RL 100 by varying polymer types and concentrations. Ropinirole microparticles were prepared by oil in oil emulsion solvent evaporation technique. Emulsifier concentration was constantly set at 2% with a stirring speed of 500 pm. FTIR analysis of microparticles, drugs, and polymers was carried out. Analysis of compatibility, particle size, encapsulation effciency, yield, flow properties, and release profile were also performed. The optical microscope showed the spherical microparticles with better flow properties and encapsulation. Ropinirole FTIR analysis produced sharp characteristic bands of C=O stretching at 1699 cm^{-1}, bending of CH_3 at 1457 cm^{-1}, C=C aromatic stretching at 1521 cm^{-1} and 1541 cm^{-1}, and C-H aromatic bending at 765 cm^{-1}. Eudragit® RS 100 and Eudragit® RL 100 showed a major peak with C=O stretching at 1716 cm^{-1}. Within 8 hours, the drug release was in the range of 47.48-98.78%. Increasing the polymer concentration increased particle size, entrapment efficiency, and sustained drug release. Eudragit® RS 100 alone achieved a better sustained release than in combination with Eudragit® RL 100 or Eudragit® RL 100 alone.

Keywords: *ropinirole HCl; eudragit® RS 100; eudragit® RL 100; solvent emulsion evaporation technique; microparticles; sustained release*

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INTRODUCTION

Ropinirole is a dopamine D2 and/or D3 receptor agonist (Tompson & Vearer, 2007). It is used for the management of Parkinson's disease and restless legs syndrome (RLS) as a monotherapy or in combination with levodopa for the treatment of Parkinson's disease (Azeem et al., 2012; Freeman et al., 2012; Khan et al. 2010). Ropinirole and pramipexole are approved for treating Parkinson's disease and RLS (Rewane & Nagalli, 2022). James Parkinson described that Parkinson's disease causes the death of dopaminergic neurons, called parkinsonism, defined as; voluntary movement abnormalities in the patient (Dauer & Przedborski, 2003; De Caro et al., 2012; Salawu et al., 2010). It is emphasized that 3% of the worldwide population is affected by Parkinson's disease over 66 years of age. Tremors, rigidity, and bradykinesia are well-known symptoms (Pringsheim, Jette, & Frolkis, 2014).

Microencapsulation innovation in pharmaceutical formulations provides a novel platform for sustained oral drug delivery. Modified-release formulations of microparticles have many advantages over conventional-release formulations, such as more reliable medication release and larger surface area (Costa & Sousa Lobo, 2016). Numerous investigations of microencapsulation involved depending on polymers and solubility of drugs for the optimum use as sustained release formulations. Liposomes are extensively used for sustained release formulations, but due to high production cost, relative storage instability, and untimely loss of entrapped compound limit their use. Polymeric microspheres have also been investigated for sustained drug delivery, which is more stable than liposomes physicochemically *in vivo* and *in vitro*; their safety remains questionable. Conversely, microparticle formulations are stable, permit a vast production scale with low production cost and protect the drug (Kumar et al., 2011).

Eudragit® are derivatives of acrylic and methacrylic esters, which are well-tolerated, biocompatible, and used for microencapsulation of various drugs ((Nikam et al., 2023). Eudragit® RS 100 is widely used for sustained-release microcapsules due to its biocompatibility, low cost, and easy fabrication (Joshi et al., 2013; Kim & Park, 2010). While Eudragit® RL is often used for controlled-release formulations (Ferreira et al., 2015), the water permeability (swelling property) of these polymers is unaffected by pH. However, water can permeate more rapidly into Eudragit® RL 100 than Eudragit® RS 100 because of more hydrophilicity of RL 100 (Evonik, 2015).

Due to the water-soluble property of the ropinirole w/o technique is mostly used for sustained release systems. The water solubility of ropinirole HCl is 133 mg/ml (highly soluble) and is soluble in methanol, ethanol, and DCM. Its dose is 3-9 mg (t.i.d), GIT absorption is rapid, has 10-40% protein binding, and approximately 50% bioavailability is reported. It is extensively metabolized in the liver, having an elimination half-life of about 6 hours (Avachat et al., 2011). However, long-term and frequent medication use leads to non-compliance, especially for drugs with short half-lifes. These problems can be overcome by a sustained release system that provides less frequent dosing, extended duration of action, improved compliance, reduced side effects, and improved therapy management.

Furthermore, due to the solubility of the drug and permeability of polymer into water, oil in oil emulsion solvent evaporation (O/O ESE) technique is intended for this study. The present work aimed to formulate and evaluate sustained release Eudragit® RS 100 and Eudragit® RL 100 microparticles loaded with ropinirole HCl.

MATERIALS AND METHOD

Materials

The materials used in this study were Eudragit® RL 100 and Eudragit® RS 100 (Evonik Röhm GmbH demasta, Germany), ropinirole (Hilton Pharma (Pvt) Ltd Karachi Pakistan), acetone (Analer BDH Laboratory Supplies, UK), methanol (Sigma-Aldrich GmbH Stoneham, Germany), magnesium stearate (Aromatic Ltd Scotland), span 80 (Avonchem Ltd Cheshire, UK), liquid Paraffin oil (Merck Darmstad, Germany), sodium hydroxide (NaOH) (Sigma-Aldrich GmbH Stoneham, Germany), monobasic potassium phosphate (KH2PO4) (Merck KGaA Darmstadt, Germany), n-hexane analar (BDH laboratory suppliers, UK) and distilled water (Pharmaceutics Research lab, IUB Pakistan).

Microparticles Preparation

Eudragit® RS 100 and Eudragit® RL 100 microparticles containing ropinirole, O/O ESE technique was used (Basu & Adhiyaman, 2008; Joshi et al., 2013; Trapani et al., 2007). Nine formulations were produced by varying the polymer type and concentration (Table 1). All chemicals were accurately weighed using Electrical Analytical Balance (Shimadzu AUX 220 Japan). The internal phase was prepared by dissolving polymer (Eudragit® RS 100 and Eudragit® RL 100) in the solvent mixture (acetone and methanol with a ratio of 5:5) and shaking until complete dissolution. The drug and magnesium stearate were then added to the polymer solution and dissolved. The external phase was prepared with liquid paraffin oil containing span 80 as an emulsifier. The internal phase was added drop by drop into the external phase with continuous stirring, followed by evaporation for 5 hours at room temperature with a continuous stirring speed of 500 rpm using Magnetic Stirrer VELP (Scientifica, Usmate (M.B.), Italy).

Table 1. Formula and production parameters of microparticle preparation

Code	Drug (mg)	Eudragit Polymer® (mg)		Stirring speed (rpm)	Span 80 %w/v
		RS 100	RL 100		
F1	250	250	000	500	2
F2	250	000	250	500	2
F3	250	125	125	500	2
F4	250	500	000	500	2
F5	250	000	500	500	2
F6	250	250	250	500	2
F7	250	750	000	500	2
F8	250	000	750	500	2
F9	250	375	375	500	2

After 5 hours, the formulation was filtered with Whatman filter paper of size 40, followed by washing with n-hexane 30ml 5-7 times. Further washing was done with distilled water to remove the unentrapped drug. Microparticles were obtained, dried in a lyophilizer (Christ alpha 1-4 L.D., U.K.), and collected.

Morphology Observation

For the morphological analysis of microparticles, a light imaging microscope (Eclipse E-200 LED, Nikon, Japan) was used. Microparticles were spread over a glass slide and placed on the microscope stage under the 10x lens. Images were obtained from a microscope using Minisee software.

Polymer-Drug Compatibility

Polymer and drug compatibility was determined by Fourier Transform Infrared (FTIR) (Spectrophotometer Bruker Tensor 27, Germany) (Jelvehgari et al., 2011). Formulations, physical mixture of drug-polymer, pure polymer, and pure drug were analyzed. Samples were placed in ATR crystal and pressed. Scanning was done within the range of 4000-600 cm^{-1} (Hou et al., 2012).

Yield Analysis

The theoretical yield was calculated by adding amounts of drug and polymer, while the actual yield was calculated by accurately weighing microparticles. The production yield was calculated using an equation (Bhardwaj et al., 2010)

$$\text{Percent yield} = \frac{\text{Actual yield}}{\text{theoretical yield}} \times 100 \quad (1)$$

Carr's Compressibility Index Determination

10 ml cylinder was taken, and with the help of this tap and bulk density was calculated. The cylinder was tapped 200 times, and the tapped density was calculated by the following expression (Sanka et al., 2014; Sahoo et al., 2005).

$$\text{Carr's compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \quad (2)$$

Particle Size Determination

An optical electron microscope was used to determine particle size. 10X lens was used for the determination of microparticle size.

$$\text{Mean particle size} = \frac{\text{Observed microparticles diameter (sum)}}{\text{No of microparticles observed}} \quad (3)$$

Encapsulation Efficiency Determination (EE)

75mg microparticles containing 25mg drug were accurately weighed and crushed in a pestle and mortar. Fine powders which were obtained were placed in 50ml phosphate buffer solution to obtain dispersion and were shaken on a shaker for 15 hours, followed by filtration. A volume of 1 ml was diluted with 50 ml of phosphate buffer solution. The standard curve was generated using the optimum absorbance obtained with UV-Spectrophotometer analysis (250 nm) using UV-Visible Spectrophotometer (IRMACO GmbH Gaeltacht, Germany). EE was calculated using the following equation.

$$\text{EE \%} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100 \quad (4)$$

***In-vitro* Drug Release**

The Paddle type USP dissolution apparatus Automatic USP Dissolution Apparatus-II and Autosampler (Pharma test Hain burg, Germany) was used to elaborate the in vitro release profile of ropinirole from Eudragit® microparticles. Microparticles containing 10 mg of ropinirole were weighed accurately and placed in a dissolution apparatus containing 900 ml phosphate buffer solution (pH 6.8). The solution was stirred at 50 rpm and at a temperature of 37±0.5^{0}C. The study was performed for up to 12 hours, and the obtained samples were analyzed using VU-Spectrophotometer. A time vs. per cent cumulative drug release graph was constructed to observe the release profile (Nath et al., 2011). A regression equation was used for release estimation.

$$\text{Percent drug release \%} = \frac{\text{Qt}}{\text{Q}load} \times 100 \quad (5)$$

Qt represents the quantity of the released drug at time't', Q_{load} = represents the number of microparticles loaded drug.

This release study also assessed the mechanism and order of drug release from the dosage form. The drug release kinetic of Higuchi, Weibull, Korsmeyer-peppas, first and zero orders were used and evaluated.

Microparticles Morphological Analysis

An imaging light optical microscope (Eclipse E-200 LED, Nikon, Japan) was employed for the morphological determination of microparticles (Van Der Pol et al., 2010). Microparticles were spread over a glass slide and placed on the microscope stage under the 10x lens. Images were obtained from a microscope by using Minisee software.

This will lead to the determination of technique efficiency and the effect of polymer type and concentration on the morphology and size of microparticles. Almost all the formulations have shown spherical microparticles. It was evident from the study that formulations (F7, F8) with higher polymer concentrations have almost spherical shapes with greater sizes of microparticles (Xie et al.,

2006). Morphological analyses demonstrated the impact of polymer concentration on microparticles. At the high level of polymer concentration, spherical microparticles were developed, but a lower concentration of polymer microparticles yielded irregularly shaped microparticles (Xie et al., 2006). The stirring speed of the present study was constant, as there is no prominent contribution to the shape of microparticles (Lee et al., 2000).

RESULTS AND DISCUSSION

A light imaging microscope (Eclipse E-200 LED, Nikon, Japan) was used for the morphological analysis of microparticles. This led to the determination of technique efficiency and the effect of polymer type and concentration of microparticles. Almost all the formulations showed spherical microparticles. Formulation F7 and F8 microparticles with higher microparticles with higher polymer concentration have spherical-like shapes, while microparticles with lower polymer concentration showed irregular shapes, i.e., F1 and F2. Formulations with a middle level of polymer concentration have shown mixed results, some spherical and some irregular in shape, i.e., F4 and F5. Figure 1 shows that as the concentration of polymer was increased, microparticles became more spherical, but with a lower concentration of polymer, microparticles have an irregular shape. The stirring speed of the present study is not high, so it also contributed to spherical shape microparticles (Guo & Chu, 2009).

Fourier transform infrared spectroscopy is very common and valuable. Before designing pharmaceutical formulations, the interaction between drugs and excipients is noted. FTIR is a technique showing the interaction between active and inactive moieties; therefore, the compatibility among components in the formulation could be analyzed (Khan et al., 2015). FTIR of pure ropinirole, Eudragit® RS 100, Eudragit® RL 100, physical mixture, and formulation were conducted to find any incompatibilities between the respective components. In the ropinirole FTIR spectrum, the characteristics bands were seen: C=O stretching at 1699 $cm^{-1,}$ bending of CH_3 at 1457 cm^{-1}, C=C aromatic stretching at 1521 cm^{-1} and 1541 $cm^{-1,}$ and C-H aromatic bending (out of plane) at 765 cm^{-1}. Eudragit® RS 100 and Eudragit® RL 100 showed a major peak with C=O stretching at 1716 cm^{-1} because both polymers have almost the same structure but only the difference between them is the number of quaternary ammonium groups (Biswal et al., 2011; Evonik, 2015; Rao & Patel, 2013; Salunkhe et al.). In the physical mixture, peaks were available at their specific wave number. At the same time, in the formulation containing the drug and both polymers, there was a little shift in peak shown by ropinirole from 765 cm^{-1} to 755 cm^{-1}. All other peaks were intact without any variation in peaks, which showed no interaction between ropinirole and other excipients.

As described in Table 2, the maximum percentage yield was found with F9, which is 95.3%, with a minimum percentage yield of F4, which is 70.5%. It is obvious that as the polymer concentration increases, the percent yield also increases as previously described (Trivedi et al., 2008). Increasing polymer concentration increases encapsulation efficiency, preventing un-entrap drug loss during washing. An increase in polymer concentration leads to the formation of a dense polymer network and the sufficiency of chains, and as a results, drug loss will be minimized with greater entrapment of the drug (Garud & Garud, 2012; Mao et al., 2008). Flow properties may be useful for the development of tablets from these microparticles.

In this study, F1 has the minimum flow, while F9 has maximum flow properties due to the microparticles' larger size and spherical shape. Compared to larger particles, smaller particles can easily stick and pack to each other, hindering flow properties (Liu et al., 2008).

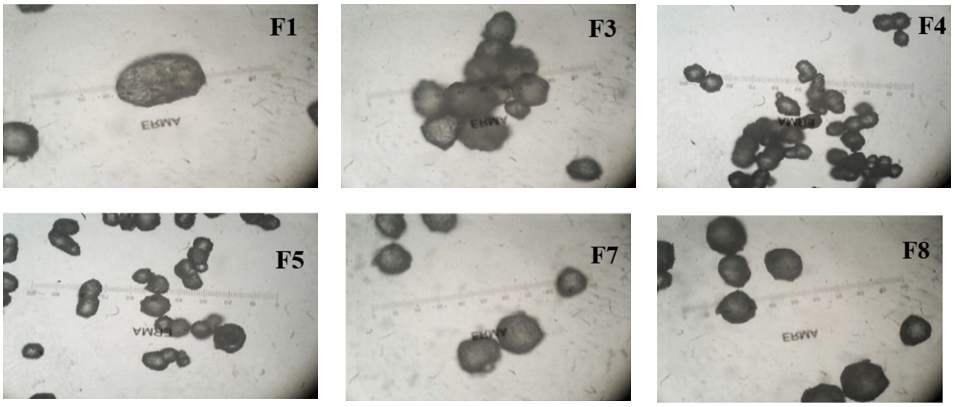

Figure 1. Microscopic image of microparticles : Microscopic image showing the impact of polymer concentration on ropinirole microparticles

F=Formulation, F1, F2, F3, F4, F5, F6, F7, F8, F9 are different formulations with varying polymer types and concentrations.

Table 2. The percentage yield of microparticles

Code	Theoretical yield (mg)	Practical yield (mg)	Percentage yield (%)
F1	500	374	74.8
F2	500	367	73.4
F3	500	389	77.8
F4	750	529	70.5
F5	750	583	77.7
F6	750	619	82.5
F7	1050	930	88.5
F8	1050	940	94.8
F9	1050	953	95.3

Table 3. Flow properties of micoparticles

Formula	Hausner's ratio	Car's index	Flow properties
F1	1.26	20.32	Passable
F2	1.20	19.53	Fair
F3	1.23	23.01	Fair
F4	1.14	15.70	Good
F5	1.15	16.21	Good
F6	1.21	19.07	Fair
F7	1.16	17.42	Good
F8	1.17	16.39	Good
F9	1.14	15.14	Good

The flow properties of all formulations were compared to the normal values, as shown in Table 3.

The mean particle size ranges from 121 µm to 238 µm with F3 showing the minimum size and F8 the maximum size, as described in Table 4. As the concentration increases, the viscosity increases, resulting in difficulty in particle dispersion and the formation of larger emulsion droplets and microparticles' diameter (Martinelli et al., 2014).

There is a greater entrapment efficiency (EE) difference among formulations. EE ranges between 48.22 -89.8, as described in Table 4. It is seen that F2 shows minimum EE and F7 gives maximum EE. Increasing the polymer concentration leads to the formation of a thick polymer network and sufficient polymeric chains. As a result, the drug loss will be minimized, and a greater entrapment of drugs (Garud & Garud, 2012).

USP dissolution apparatus type II was used to determine *in-vitro* Ropinirole release from Eudragit® RS 100 and Eudragit® RL100 microparticles. Dissolution was accomplished at 37^0C with a paddle speed of 100 rpm for 12 hours, and the dissolution apparatus baskets were filled with phosphate buffer solution pH 6.8 (900 ml). Samples were drawn after a specific period, and a U.V. spectrophotometer took absorbance. The cumulative release of all formulations is given in Table 5 and Figure 2. F2, F5, and F8 were shown to have more than 90% cumulative release within 12 hours.

The maximum time for % drug release was in the range of 6.89 hours to 19.26 hours. The microparticle formulation F7 shows the maximum sustained release of ropinirole formulated at Eudragit® RS 100 (750mg), stirring speed (500rpm), and span 80 (2%), as described in Table 5. All formulations showed a fast release of the drug initially and then prolonged slow release (biphasic behaviour) (Nath et al., 2011). The initial fast release of the drug is due to the presence of the drug on the surface of microparticles. It is possible in the solvent evaporation technique due to spinning and shearing processes (Qi et al., 2014).

Formulations F2, F5, and F8 showed more than 93% drug release within 10 hours, as previously studied (Basu

Table 4. Particle size and entrapment efficiency of microparticles

Formulation	Particle size (mm)	% Encapsulation efficiency
F1	127±8.23	81.37
F2	133±10.15	48.22
F3	121±6.13	69.37
F4	147±7.41	58.22
F5	135±9.05	86.8
F6	152±5.89	75.08
F7	234±4.44	89.8
F8	238±3.45	84.8
F9	207±5.05	80.51

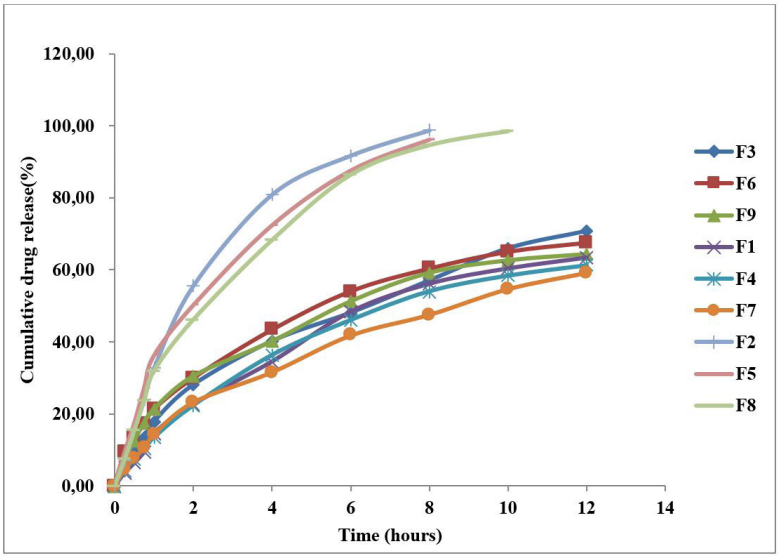

Figure 2. Drug release profile of ropinirole microparticles

& Adhiyaman, 2008). It is because Eudragit® RL 100 has a higher number of quaternary ammonium groups, which swell upon contact with water. As a result, quick release of the drug into the medium by diffusion was found (Nath et al., 2011). Formulations F1, F4, and F7 contain Eudragit® RS 100 alone and showed a better-sustained release of ropinirole. The release of these formulations was not more than 65% after 12 hours because they contained Eudragit® RS 100 less number of quaternary ammonium groups, so the permeability is lesser than Eudragit® RL 100 (Biswal et al., 2011). Eudragit® RS 100 is a potent drug-release retardant. Formulations F3, F6, and F9 are formed by combining both Eudragit® RS 100 and Eudragit® RL 100. These formulations showed better-sustained drug release than F2, F5, and F8 but lesser than F1, F4, and F7. It is because Eudragit® RL 100 causes the quick release of the drug, but Eudragit® RS 100 is a potent drug release retardant and drug releases with a slow rate as compared to F2, F5, and F8 in which Eudragit® RL 100 is used alone (Biswal et al., 2011; Nath et al., 2011). In all formulations, as the concentration of the polymer was increased resulted in the lesser release of the drug. The increased viscosity leads to less permeability and porosity, so it captures the drug more firmly. It is also due to increased particle size, which results in lower surface area, causing a reduced drug dissolution and release rate. An increase in polymer concentration leads to the formation of a dense network of the polymer as well as the sufficiency of polymeric chains; as a result, drug loss will be minimized with greater entrapment of the drug (Garud & Garud, 2012; Mao et al., 2008). From the above discussion it is clear that drug release from microparticles mainly depends upon the polymer type and concentration.

We also calculated the time needed for 50% and 100% drug release from microparticles, as depicted in Table 6. From the table, the cumulative ropinirole release can be

Table 5. *In vitro* drug release profile of ropinirole microparticles

Time (hr)	Cumulative drug release (%)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00	0 ± 0.00
0.25	3.46 ± 0.01	6.98 ± 0.01	6.98 ± 0.01	4.15 ± 0.04	9.29 ± 0.03	9.23 ± 0.02	4.53 ± 0.05	7.29 ± 0.02	7.30 ±0.12
0.50	6.32 ± 0.05	15.33 ±0.02	15.33 ±0.02	7.44 ± 0.01	17.43 ±0.01	13.46 ±0.02	7.67 ± 0.04	15.43± 0.08	12.50± 0.45
0.75	9.44 ± 0.02	23.80 ±0.01	23.80 ±0.01	10.25 ±0.07	27.26 ±0.07	17.26 ±0.01	10.49 ±0.17	23.60± 0.16	17.57± 0.56
1	14.59 ±0.08	32.61 ±0.91	32.61 ±0.91	13.43 ±0.07	36.17 ±0.23	21.29 ±0.07	14.24 ±0.22	31.90 ±0.35	21.34± 1.78
2	22.66 ±0.01	55.51 ±1.86	55.51 ±1.86	22.34 ±0.57	50.15 ±0.75	29.93 ±0.15	23.15 ±0.43	46.19 ±2.03	30.45± 1.45
4	34.49 ± .04	80.87 ±0.54	80.87 ±0.54	36.33 ±1.16	72.34 ±0.89	43.34 ±0.09	31.51 ±1.12	68.29 ±1.22	40.11± 0.99
6	48.33 ±0.95	91.72 ±0.66	91.72 ±0.66	46.06 ±0.27	87.55 ±0.05	54.02 ±1.17	41.72 ±0.20	86.45 ±0.24	51.19± 1.33
8	56.09 ±2.19	98.73 ±1.01	98.73 ±1.01	54.03 ±0.98	96.13 ±0.03	60.33 ±1.11	47.48 ±0.78	94.67 ±0.19	59.10± 0.57
10	60.33 ±0.83			58.36 ±1.14	99.98 ±0.01	65.01 ±0.09	54.63 ±0.65	99.54 ±0.12	62.55 ±0.23
12	63.34 ±1.14			61.23 ±1.03		67.51 ±0.16	59.14 ±0.77		64.29 ±0.34

Table 6. Time for 50% and 100% drug release from ropinirole microparticles

Formulation	**$t_{50\%\ (hour)}$**	**$t_{100\%\ (hour)}$**
F1	7.86	16.98
F2	2.89	6.89
F3	7.10	15.89
F4	8.14	17.68
F5	3.29	8.39
F6	6.89	16.17
F7	8.87	19.26
F8	3.51	8.53
F9	7.29	16.97

put into the following descending order: F2> F5 > F8 > F3 > F6 > F9 > F1 > F4 > F7.

In this study, hydrophilic polymers can be combined, which may result in better results. Different variables' effects can be investigated and evaluated on these formulations. *In-vivo* studies can be undertaken to estimate more fruitful results. Furthermore, stability studies can be done for better dosage form stability. Good flow properties may be useful for the development of tablets from these microparticles.

CONCLUSION

This study successfully prepared sustained-release microparticles of ropinirole HCl to reduce dose frequency for better patient compliance in Parkinson's disease. Increasing the polymer concentration increased particle size, entrapment efficiency, and sustained drug release. Eudragit® RS 100 alone achieved a better sustained release than in combination with Eudragit® RL 100 or Eudragit® RL 100 alone. It is clear from the conducted research that drug release from microparticles mainly depends upon the polymer type and concentration.

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