*Research Article*

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# FORMULATION AND EVALUATION OF ROPINIROLE HCL EXTENDED RELEASE MATRIX TABLETS

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**Abstract**

The present study behind this work is to find to prepare extended release matrix tablets of Ropinirole HCl by compression method. First of all to formulate Ropinirole HCl extended release matrix tablets.

**Key words:** Natural Polymers, Ropinirole HCL, Extended release tablets, UV Analysis.

## Introduction

The oral route of drug delivery is one of the most convenient means to administer drug to the human body to obtain the desired therapeutic effect. Though it is a convenient route it provides several challenges to the formulator to design a medication such that it provides the drug in an optimum concentration needed to attain a plasma level of the drug which will fall within the therapeutic window to obtain the desired effect.

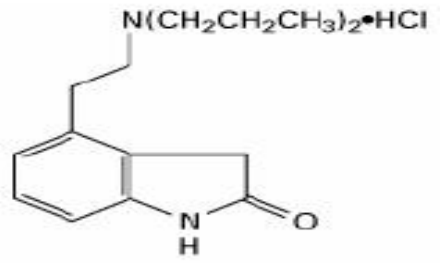
**Ropinirole hydrochloride**

**Chemical Name:** 4-[2-(dipropylamino) ethyl]-1, 3-dihydro-2H-indol-2-one mono hydrochloride

**Empirical Formula:** $C_{16}H_{24}N_2O.HCl$.

**Molecular Weight**: 296.84 (260.38 as the free base).

**Structure**




**Appearance:** White to pale greenish-yellow powder.

**Melting Range:**243° to 250°C

**Solubility**: 133 mg/ml in water, it has pH independent solubility

**Ultraviolet Spectrum**: $\lambda_{max}$ 210-250nm

**Drug Category:**Dopamine Agonists

**Dosage forms:**Tablet (0.25 mg, 0.5 mg, 1 mg, 2 mg, 4 mg or 5 mg)

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**Storage:** Protect from light and moisture. Close container tightly after each use. Stored at controlled room temperature 20°-25°C (68°-77°F).

**Pharmacokinetics**

**Absorption:** $T_{max}$ is 1 to 2 hrs. $T_{1/2}$ of the drug is 6 hrs &C $_{max}$ is 2ng/ml/mg. High-fat meal increases $T_{max}$by 2.5 hrs and reduces $C_{max}$ by 25%, but does not affect extent of absorption. Absolute bioavailability is 55%. Steady state is reached within 2 days.

Extended-release Bioavailability is 45% to 55%. Steady state is reached within 4 days. $T_{max}$ is 6 to 10 hrs.

**Distribution:** Ropinirole is widely distributed throughout the body, with an apparent volume of distribution of 7.5 L/kg (cv = 32%). It is up to 40% bound to plasma proteins and has a blood-to-plasma ratio of 1:1.

**Metabolism:** Ropinirole is extensively metabolized by the liver. The major metabolic pathways are N-despropylation and hydroxylation to form the inactive N-despropyl metabolite and hydroxy metabolites. The N-despropyl metabolite is converted to carbamylglucuronide, carboxylic acid, and N-despropyl hydroxy metabolites. The hydroxy metabolite of ropinirole is rapidly glucuronidated. Ropinirole and its metabolites will cross placental barrier and appears in the milk.

**Elimination:** The clearance of ropinirole after oral administration to patients is 47 L/hr (cv = 45%) and its elimination half-life is approximately 6 hours. Less than 10% of the administered dose is excreted as unchanged drug in urine. N-despropyl ropinirole is the predominant metabolite found in urine (40%), followed by the carboxylic acid metabolite (10%), and the glucuronide of the hydroxy metabolite (10%).

**Preparation of standard curve of Ropinirole Hcl:**

**I. Calibration curve in 0.1n HCl:**

100mg of Ropinirole HCl was accurately weighed and transferred into 100ml volumetric flask. It was dissolved and diluted to volume with 0.1N HCl to give stock solution containing 1000mcg/ml. The standard stock solution was then serially diluted with 0.1N HCl to get 2, 4, 6, 8, 12, 14 ,16, 18, 20, 25, 30 mcg/ml and the absorbance of the solution was measured against 0.1N HCl as the blank at 250 nm using with UV spectrophotometer (Analytical). The absorbance was plotted against concentration (mcg/ml) to obtain the standard calibration curve.

**II. Calibration curve in $P^H$ 7.4 Phosphate buffer:**

100mg of Ropinirole HCl was accurately weighed and transferred into 100ml volumetric flask. It was dissolved and diluted to volume with pH 7.4 Phosphate Buffer to give stock solution containing 1000mcg/ml. The standard stock solution was then serially diluted with pH 7.4 Phosphate Buffer to get 2, 4, 6, 8, 12, 14, 16, 18, 20, 25, 30 mcg/ml and the absorbance of the solution was measured against pH7.4 Phosphate Buffer as the blank at 250nm using with UV spectrophotometer (Analytical).The absorbance was plotted against concentration (mcg/ml) to obtain the standard calibration curve.

**III. Formulation development:**

Two strategies have been adopted to extend the release of freely water soluble drug from the formulation they are:

1) Wet granulation technique.
2) Direct compression technique.

After formulating the finished dosage forms by any of the above two strategies, the finished dosage forms are charged for stability for one month, according to ICH guidelines. Finally the samples are analyzed by UV spectroscopy, whether the release of the drug from the formulation is within the specifications or not and for drug content.

The following formulations are prepared by maintaining the effective processing conditions, NMT 50% RH and NMT 30ºC temperature. The formulations are done by wet granulation method and direct compression method for matrix tablets.

**Table 01: Formulation development**

| Ingredients(mg) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Ropinirole HCl | 2 | 2 | 2 | 2 | 2 | 2 |
| Guar Gum | 2 | - | - | 5 | - | - |
| Sodium Alginate | - | 2 | - | - | 5 | - |
| Carbopol 940P | - | - | 2 | - | - | 5 |
| Magnesium Stearate | 3 | 3 | 3 | 3 | 3 | 3 |
| Talc | 3 | 3 | 3 | 3 | 3 | 3 |
| Micro Crystalline Cellulose | 290 | 290 | 290 | 287 | 287 | 287 |
| Total weight of the tablet | 300 | 300 | 300 | 300 | 300 | 300 |

**Table 02: Formulation development**

| Ingredients(mg) | F7 | F8 | F9 | F10 | F11 | F12 | F13 | F14 |
|---|---|---|---|---|---|---|---|---|
| Ropinirole HCl | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Guar gum | 2 | - | - | 5 | - | - | 1 | 1 |
| Sodium Alginate | - | 2 | - | - | 5 | - | 1 | 1 |
| Carbopol 940P | - | - | 2 | - | - | 5 | - | - |
| Magnesium Stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Talc | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Micro crystalline cellulose | 290 | 290 | 290 | 287 | 287 | 287 | 290 | 290 |
| Total weight of the Tablet | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |

IV. **Preformulation studies of drug and excipients**

Preformulation testing is the first step in the development of dosage forms of a drug substance. It can be defined as “investigation of physical and chemical propertiesof the drug substance alone and when combined with excipients”.These studies should focus on those physicochemical properties of the new compound that could affect the drug performance and development of an efficacious dosage form.The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass-produced.

**Description / Appearance**

Ropinirole hydrochloride is a white to pale greenish-yellow powder.

**Determination of Melting Point:**

Melting point of Ropinirole Hcl was determined by capillary method found to be in the range 243° to 250°C, which complied with USP standards, indicating purity of the drug sample.

**V. Standard curve of Ropinirole HCl**

Standard curve of Ropinirole HCl was determined in $P^H$ 7.4 Phosphate buffer and 0.1N HCl, by plotting Absorbance against Concentration at 250 nm, and it follows the Beer's law. Results were tabulated below.

**Table 03: Standard curve of Ropinirole HCl in 0.1N HCl at 250nm**

| Concentration (in mcg/ml) | Absorbance |
|---|---|
| 2 | 0.064 |
| 4 | 0.124 |
| 6 | 0.187 |
| 8 | 0.248 |
| 10 | 0.305 |
| 12 | 0.371 |
| 16 | 0.496 |
| 20 | 0.605 |

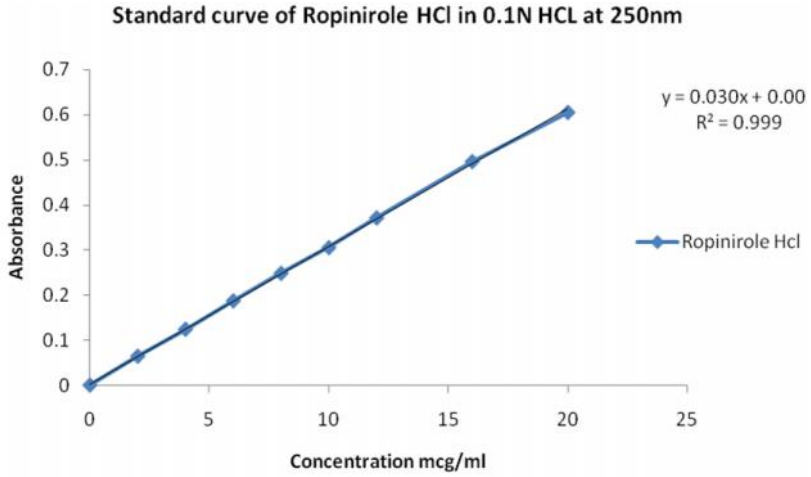


**Figure 01: Standard curve of Ropinirole HCl in 0.1N HCl at 250nm**

**Table 04: Standard curve of Ropinirole HCl in pH 7.4 Phosphate buffer at 250nm**

| Concentration (in mcg/ml) | Absorbance |
|---|---|
| 2 | 0.055 |
| 4 | 0.110 |
| 6 | 0.185 |
| 8 | 0.225 |
| 12 | 0.334 |
| 14 | 0.400 |
| 16 | 0.450 |
| 18 | 0.524 |
| 20 | 0.580 |
| 25 | 0.705 |
| 30 | 0.850 |

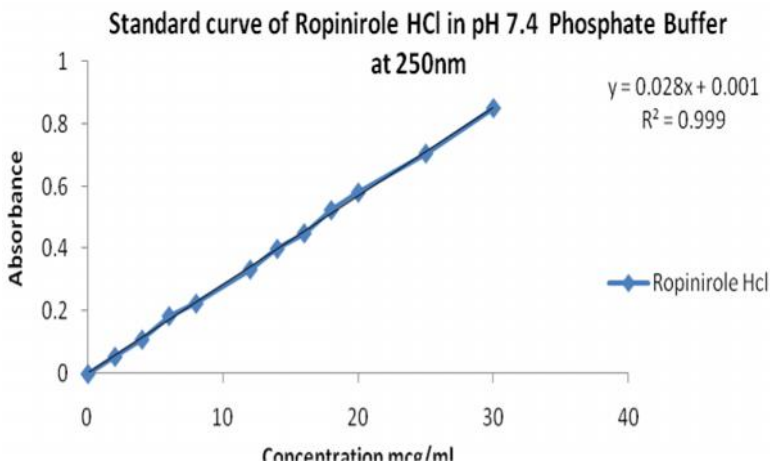


**Figure 02: Standard curve of Ropinirole HCl in pH 7.4 Phosphate buffer at 250nm**

**VI. Formulation development**

Extended Release tablets of Ropinirole hydrochloride were prepared. In the present study 14 formulations with variable concentration of polymer were prepared and evaluated for physico-chemical parameters, in vitro release studies and stability studies.

**Evaluation of tablet formulations:**

**Pre-Compression Parameters:**

a. **Angle of Repose:**The angle of repose for the formulated blend was carried out and it was found to be in the range $20^0$.88' to 29..
b. **Bulk density:** The bulk density for the formulated blend was carried out.

**Compressibility Index:** Compressibility index was carried out, it found between 28.34% and 32.30% and results were shown in table.

**Post-compression Parameters:**

The tablets of different formulations were physically characterized by parameters like thickness, average weight, hardness, and friability, uniformity of weight and In vitro dissolution studies.

**1. Average weight***:* Weigh 20 tablets and average weight was calculated.

**2. Thickness:** The thickness of the formulations was found in the range of 5.6± 0.3mm. The tablets exhibited uniform thickness among the different formulations.

**3. Hardness:** The hardness of the tablets of all batches was ranged from 7-8 kg/cm$^2$ which were sufficient to maintain the mechanical strength.

**4. Friability:** The percentage friability was less than 0.1%. In the present study, the percentage friability for all the formulations was found below 0.1% indicating that friability (%) is within the acceptable limits.

**5. Uniformity of Weight:** As per USP limit, the percentage deviation for tablets of weight greater than 324 mg is ± 5%. The percentage deviation of all tablet formulations was found within ±5% and hence all formulations pass the test for uniformity of weight.

**6. Assay:** Good uniformity in drug content was found among different batches of the tablets

and the percentage content was with in90%-110%.

**7. Dissolution profile:** The dissolution profile of the tablets has been tabulated (according to strategies I, II respectively).

**Table 05: Pre-compression Parameters for strategy I**

| Powder blend | Angle of Repose ($^0$) | Loose Bulk Density (g/ml) | Tapped Bulk Density (g/ml) | Compressibility Index (%) | Hausner ratio |
|---|---|---|---|---|---|
| **F1** | 24 | 0.59 | 0.77 | 23.41 | 1.33 |
| **F2** | 23.5 | 0.6 | 0.765 | 19.91 | 1.27 |
| **F3** | 22.0 | 0.562 | 0.692 | 18.78 | 1.23 |
| **F4** | 20.8 | 0.551 | 0.656 | 16.26 | 1.19 |
| **F5** | 21.9 | 0.556 | 0.684 | 18.71 | 1.22 |
| **F6** | 22.5 | 0.557 | 0.679 | 17.96 | 1.21 |

**Table 06: Pre-compression Parameters for strategy II**

| Powder blend | Angle of Repose ($^0$) | Loose Bulk Density (g/ml) | Tapped Bulk Density (g/ml) | Compressibility Index (%) | Hausner ratio |
|---|---|---|---|---|---|
| **F7** | 24°.30' | 0.422 | 0.600 | 29.57 | 1.42 |
| **F8** | 26°.77' | 0.461 | 0.666 | 29.41 | 1.5 |
| **F9** | 25°.28' | 0.410 | 0.652 | 34.24 | 1.52 |
| **F10** | 28°.56' | 0.447 | 0.638 | 29.85 | 1.42 |
| **F11** | 29°.88' | 0.434 | 0.652 | 33.33 | 1.41 |
| **F12** | 25°.30' | 0.416 | 0.638 | 34.72 | 1.53 |
| **F13** | 26°.47' | 0.404 | 0.603 | 32.432 | 1.48 |
| **F14** | 24°.28' | 0.428 | 0.612 | 30.00 | 1.42 |

**Table 07: Post -Compression parameters for strategy I**

| Formulations | Average Weight (mg) (n = 20) | Friability (%) (n = 10) | Hardness (kg/cm$^2$) (n = 3) | Thickness (mm) (n = 3) | Assay (%) (n = 6) |
|---|---|---|---|---|---|
| **F1** | 298 | 0.01 | 7-8 | 5.6 | 98.02 |
| **F2** | 289 | 0.02 | 7-8 | 5.7 | 103.9 |
| **F3** | 305 | 0.01 | 7-8 | 5.6 | 99.53 |
| **F4** | 305 | 0.02 | 6-8 | 5.5 | 98.01 |
| **F5** | 298 | 0.04 | 6-8 | 5.6 | 101.1 |
| **F6** | 295 | 0.01 | 6-8 | 5.6 | 99.3 |
| **MP** | 300 | 0.02 | 6-8 | 5.2 | 99.8 |

**Table 08: Post -Compression parameters for strategy II**

| Formulations | Average Weight (mg) (n = 20) | Friability (%) (n = 10) | Hardness (kg/cm2) (n = 3) | Thickness (mm) (n =3) | Assay (%) (n = 6) |
|---|---|---|---|---|---|
| **F7** | 298 | 0.01 | 7-8 | 5.7 | 102.3 |
| **F8** | 300 | 0.02 | 7-8 | 5.6 | 101.2 |
| **F9** | 305 | 0.01 | 6-8 | 5.6 | 99.3 |
| **F10** | 289 | 0.01 | 6-8 | 5.7 | 103.9 |
| **F11** | 303.5 | 0.02 | 7-8 | 5.6 | 99.53 |
| **F12** | 310 | 0.02 | 6-7 | 5.5 | 98.01 |
| **FT13** | 300 | 0.0 | 7-8 | 5.6 | 101.1 |
| **FT14** | 305 | 0.0 | 7-8 | 5.6 | 99.3 |
| **MP** | 300 | 0.01 | 6-8 | 5.2 | 99.8 |

**Dissolution studies for strategy (Wet granulation)**

Dissolution studies were conducted by taking 0.1N HCl as dissolution media for the first two hours period and replacing the medium with $p^H$ 7.4 Phosphate buffer for the next six hours.

**Table 09: Dissolution data of Ropinirole Hcl extended release tablets**

| Time (in hrs) | Cumulative % Drug Release | | | | | | |
|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
| 0.5 | 35.28±0.11 | 41.51±1.25 | 49.61±1.26 | 49.26±1.07 | 43.25±1.27 | 35.24±0.08 | 36±0.21 |
| 1 | 53.11± 0.09 | 63.46±0.08 | 74.45±1.06 | 60.14±1.42 | 68.36±1.65 | 48.96±0.7 | 40.7±0.9 |
| 2 | 76.94± 1.26 | 78.98±1.19 | 87.71±1.11 | 69.25±1.44 | 71.48±1.05 | 67.28±1.09 | 45.5±1.01 |
| 3 | 87.31± 0.7 | 86.61±1.05 | 98.45±1.16 | 78.24±1.29 | 79.26±0.15 | 79.31±0.12 | 54.5±1.06 |
| 4 | 97.68± 0.59 | 99.86±1.01 | 99.45±1.26 | 88.26±0.12 | 89.24±0.35 | 92.36±1.16 | 68.5±1.07 |

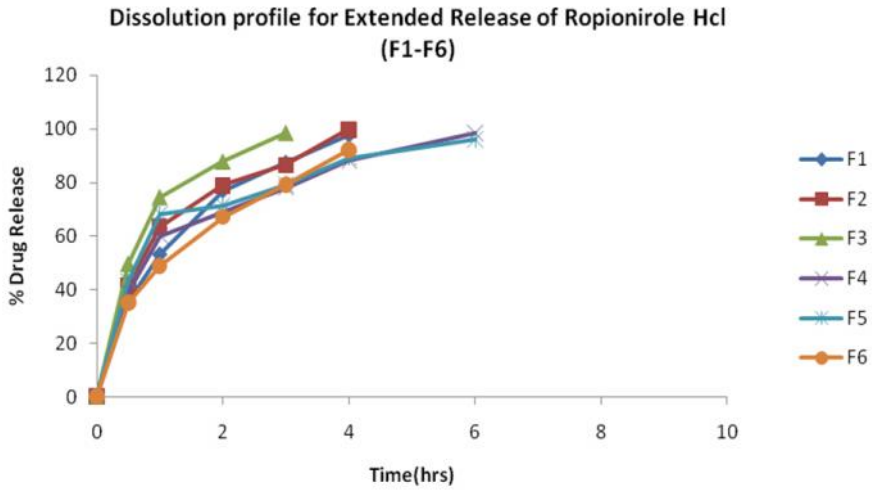


**Figure 03: Dissolution Data of Ropinirole Hcl Extended Release Tablets of F1-F7.**

**Dissolution studies for strategy ii (direct compression)**

Dissolution studies were conducted by taking 0.1N HCl as dissolution media for the first two hours period and replacing the medium with pH 7.4 Phosphate buffer for the next six hours.

**Table 10: Dissolution profile for innovator**

| Time(hrs) | INOVATOR | F7 |
|---|---|---|
| 0 | 35±0.21 | 36±0.21 |
| 1 | 42.7±0.9 | 40.7±0.9 |
| 2 | 49.5±1.01 | 45.5±1.01 |
| 3 | 56.5±1.06 | 54.5±1.06 |
| 4 | 63.5±1.07 | 68.5±1.07 |
| 6 | 85.6±0.12 | 82.6±0.12 |
| 8 | 98.1±0.09 | 98.4±0.09 |

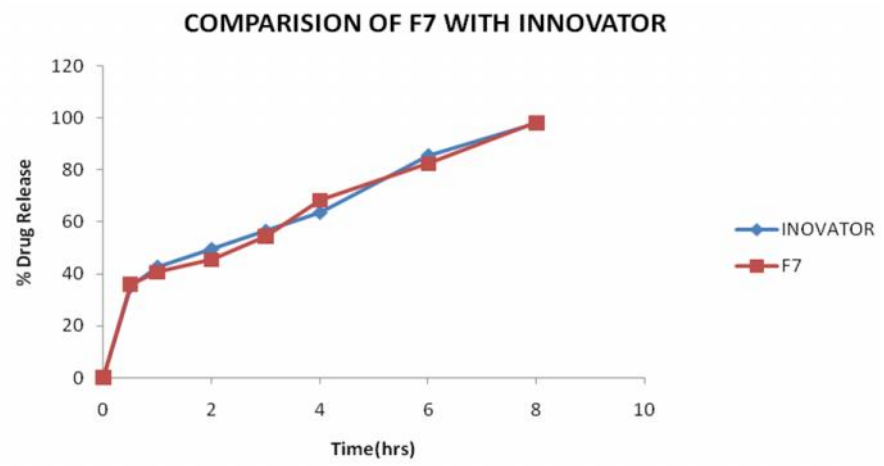


**Figure 04: Dissolution Profile for Innovator Vs F7**

## Results and discussion

Extended release tablets have come into light due to the development of several new chemical entities which have high solubility. The primary applications for rate controlling polymers is for decreasing dissolution rate and extend the release of water soluble drug. Successful drug design with polymers depends largely on understanding the physical, chemical and physiological factors that promote bioavailability. It requires a grasp of not only the drug candidates but also the role of the delivery system or the potential of the drug- excipient interplay in vitro as well as in vivo.

The development of an extended release tablets for a drug having high solubility is an approach to obtain a controlled release.

In one strategy, matrix formers are Guar gum, Sodium alginate, Carbopol 940P, were used in different quantities by using Wet Granulation method.

In other strategy same matrix formers are Guar gum, Sodium alginate, Carbopol 940P were employed in different quantities and formulated by using Direct compression technique.

## Conclusion

The conclusion of the study is as follows:

- In the Preformulation studies, it was found that Ropinirole HCl has solubility with independent of $P^H$, i.e it is freely soluble in all $P^H$ values.
- The tablets prepared were found to be within the official limits with respect to hardness, weight variation, drug content, friability, thickness etc.
- In Strategy I, an Optimized formulation was obtained by using “Wet granulation technique”.
- In Strategy II, an Optimized formulation was obtained by using “Direct compression technique”.
- Among all the Fourteen formulations of strategy I and strategy II, the release profile of trial F7 was found to be showing better controlled release for an extended period of time.
- The Stability data reveals that the F7 of strategy II showed a negligible change in drug content after storage in various

conditions for one month according to ICH guidelines.

- The optimised extended release formulation (F7) was found similar and comparable to the innovator product.
- From the study, it may be concluded that F7 of strategy II is a successful formulation.

In Conclusion, The results demonstrated that the finished product formulations F7 fulfilled all the specifications of the physical properties and In vitro release in accordance with the extended release formulation.

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