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Formulation and Evaluation of Controlled Release Tablet of Ropinirole HCL

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ABSTRACT

The aim of the present work is to develop hydrophilic and hydrophobic polymer based control release matrix tablet of Ropinirole HCl (RPN) which can release the drug up to time period of 24 hr. Ropinirole is a non-ergoline dopamine agonist. Its biological half-life is about 5-6 hrs periods, It is given in dose of 8-10mg/day; it requires multiple dosing to maintain therapeutic drug blood levels. The most frequent side effect of RPN Immediate Release(IR) dosage form is fluctuations in plasma level concentration of drug which may lead to development of some symptoms of Parkinson Disease (PD). To avoid this, the control release formulation maintains steady plasma level concentration of drug throughout a period of 24 hrs, which avoids the symptom of PD. Differential scanning calorimetric analysis confirmed the absence of any drug polymer interaction. In present work different matrices are used to control release of Ropinirole. HPMC K100M, HPMC K15M, Gum guar, PEO etc. are used as Hydrophilic Release Rate Modifier. Hydrophobic release rate used are Ethyl cellulose, Glyceryl Monostearate, Hydrogenated Castor Oil. Tablets (F1-F12, F29-F35) were prepared by Direct Compression and other batches (F12-F25) by Melt Granulation Technique. The tablets were evaluated for thickness, diameter, weight variation test, hardness, friability, and drug content. In vitro drug release studies were carried out in citrate buffer (pH 4) using a USP II dissolution apparatus at 100 rpm, Batch F29 give 96% CDR till the period of 24 hr, it also avoids initial burst release. The best fit model for F29 formulation follows Zero order (r^2= 0.989) and n value was found to be 0.91 which signified that release pattern of optimized batch F29 follows the Fickian diffusion. SEM study of F29 was also performed. During Accelerated Stability studies formulation F29 was found to be stable. Thus the matrix tablets of Ropinirole HCl were prepared successfully.

Keywords: Ropinirole HCl, Controlled Release, Parkinson Disease

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INTRODUCTION

Oral route is the most frequently used route for administration of drugs among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms[1]. Important reasons for their popularity are their convenience of application (patient compliance); ease of preparation on industrial scale, drug given by oral administration of the drug is well absorbed.

The majority of oral tablet formulations represent the so-called immediate release (IR) dosage forms. Plasma concentration of drug administered with an IR dosage form generally rises quickly, peaks, and then declines. If the elimination of the drug is fast, this results in only short period during which the plasma concentration of the drug is within the therapeutic window[2]**.** For a successful pharmacy-therapeutic treatment, optimal control of the plasma level of administered drug is a prerequisite. For most drugs, plasma levels should ideally be constant and within the therapeutic window throughout the period of treatment as to avoid adverse side effects due to high toxic peak concentrations as well as to avoid periods of ineffectiveness due to sub therapeutic plasma levels.

Conventional IR dosage forms have to be administered several times a day as to maintain a therapeutically effective plasma level of the drug, which is a major drawback in terms of patient compliance[3]. Still oscillating plasma concentrations may result in alternating periods of toxicity and ineffectiveness, despite a proper choice of the dosing regimen. In order to improve the therapeutic efficiency of oral drug administration & to overcome many of the drawbacks of conventional IR dosage forms, pharmaceutical R&D within, academia and industry has focused on the development of oral controlled release technologies and novel release controlling excipients.

MATERIALS AND METHOD

Materials

Ropinirole HCl was a gift sample provided by Hetero Pharma, Hyderabad. Methocel- K15M (HPMC), Methocel- K100M (HPMC), Polyox WSR 301(PEO), Ethyl cellulose (EC)(Colorcon Pvt. Ltd, Goa.) were used as received. Guar Gum, Dicalcium Phosphate (DCP), Hydrogenated Castor Oil (HCO), Glyceryl Monostearate (GMS), Magnesium stearate (Loba Chemie Pvt. Ltd., Mumbai) were received. All other chemicals used were of analytical grade and were used as received.

Methods

Tablets were prepared by two methods .

Direct compression

Formulations F1-F12, were prepared by blending each polymer in three different proportions (60%, 40%, 20%) of total tablet weight. Formulation F26-F35 were prepared by using a mixture of HPMC & EC in different proportions. The total combined polymer was equal to 60% of tablet weight. The polymeric blends were thoroughly mixed with preset fixed amounts of RPN, DCP, and magnesium stearate (5%) in a polybag by a geometric dilution method. The powder mixture, thus prepared, was passed through sieve #40 and then compressed into tablets with a manually run Tablet Press, using 6-mm flat-faced tooling.

Melt granulation

Formulations F13-F25 were prepared by this method. Drug, Polymer (HCO F13-F15, GMS ,F16-F18, mixture F19-F25) were mixed homogeneously; the blend was then heated (85°C-90°C) in a water bath with continuous agitation. The molten mass was allowed to cool at room temperature. The congealed solid mass was then sieved, lubricated, and compressed.

Table1: Composition of formulations (HPMC K 15M, K 100M, Guar Gum)

Formulations	F1	F2	F3	F4	F5	F6	F7	F8	F9
RPN	9.12	9.12	9.12	9.12	9.12	9.12	.9.12	9.12	9.12
HPMCK15 M	120	80	40	-	-	-	-	-	-
HPMCK100 M	-	-	-	120	80	40	-	-	-
Guar Gum	-	-	-	-	-	-	120	80	40
DCP	60	100	140	60	100	140	60	100	140
Mg.stearate	10	10	10	10	10	10	10	10	10
Total weight	200	200	200	200	200	200	200	200	200

(All quantities are in mg)

Table2: Composition of formulations (PEO, HCO, GMS

Formulations	F10	F11	F12	F13	F14	F15	F16	F17	F18
RPN	9.12	9.12	9.12	9.12	9.12	9.12	9.12	.9.12	9.12
PEO	120	80	40	-	-	-	-	-	-
HCO	-	-	-	120	80	40	-	-	-
GMS	-	-	-	-	-	-	120	80	40
DCP	60	100	140	60	100	140	60	100	140
Mg.stearate	10	10	10	10	10	10	10	10	10
Total weight	200	200	200	200	200	200	200	200	200

(All quantities are in mg)

Table 3: Composition of formulations (HCO+GMS

Formulations	F19	F20	F21	F22	F23	F24	F25
RPN	9.12	9.12	9.12	9.12	9.12	9.12	9.12
HCO	60	45	30	15	75	90	105
GMS	60	75	90	105	45	30	15
DCP	60	60	60	60	60	60	60

Mg.stearate	10	10	10	10	10	10	10
Total weight	200	200	200	200	200	200	200

(All quantities are in mg)

Table 4: Composition of formulations(EC, HPMC+EC)

Formulations	**F26**	**F27**	**F28**	**F29**	**F30**	**F31**	**F32**	**F33**	**F34**	**F35**
RPN	9.12	9.12	9.12	9.12	9.12	9.12	.9.12	9.12	9.12	9.12
HPMC K 100 M	-	-	-	60	45	30	15	75	90	105
Ethyl Cellulose	120	80	40	60	75	90	105	45	30	15
DCP	60	80	120	60	60	60	60	60	60	60
Mg.stearate	10	10	10	10	10	10	10	10	10	10
Total weight	200	200	200	200	200	200	200	200	200	200

Evaluation of Blend/Granules[4]

a) Loose bulk density

b) Tapped bulk density

c) Compressibility Index (Carr's index) and Hausner's ratio

d) Angle of repose

All these micromeritic characterizations for granules were done .

Determination of content uniformity:

Sample of blend was withdrawn and was analyzed for drug content uniformity. A Weighed quantity equivalent to 10 mg of RPN was dissolved in 10 mL pH 6.8 PBS. The suspension was filtered and filtrate was diluted appropriately with pH 6.8 PBS. The absorbance for drug content was measured spectrophotometrically at 249 nm and drug content was calculated.

Evaluation parameters for tablets

Hardness[4]

Although hardness test is not an official, tablet should have sufficient handling during packing and transportation. Hardness of tablet was measured using Monsanto hardness tester. It is the pressure required to fracture diametrically placed tablets by applying the force. The hardness of 6 tablets, from each batch was determined and mean hardness was taken into account, which was expressed in kg/cm^2.

Weight variation test[4]

Weigh 20 tablets individually, calculating the average weight and compare the individual tablet weight with respect to the IP weight variation test.

Friability[4]

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of

tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Pre-weighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and re-weighed.

The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100 \text{ - - - - - - - - (25)}$$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Thickness[4]

The thickness of the tablet was measured using vernier caliper. Thickness of five tablets from each batch was measured and mean was calculated.

Content uniformity[4]

For this at least 30 tablets were randomly selected. Out of 30 tablets, 10 tablets were crushed into fine powder and assayed individually.

In vitro dissolution studies [5]

The *in vitro* dissolution studies were performed using type-II dissolution apparatus at 100 rpm. The dissolution medium consisted of citrate buffer pH 4 (900 mL), maintained at 37°C ± 0.5°C. An aliquot (5 mL) was withdrawn at specific time intervals and drug content was determined by UV-visible spectrophotometer (UV-1700- Shimadzu Japan) at 249 nm for RPN. At each time of withdrawal, 5 mL of fresh corresponding dissolution medium was replaced into the dissolution flask. It was made clear that none of the ingredients used in the matrix formulations interfered with the assay. The release studies were conducted in triplicate. Table 15 shows the parameter of dissolution studies.

Table 5: Parameters for dissolution studies

Sr.No	Parameter	Value
1	USP Dissolution Apparatus	Type II(Paddle)
2	Volume of Dissolution medium	900 mL
3	Speed of paddle rotation	100 rpm
4	Temperature	37 ± 0.5°C
5	Dissolution Medium	Citrate Buffer pH 4
6	Sampling time points	2, 4, 6, 8, 10, 12, 16, 20, 24 hrs.

Scanning electron microscopy (SEM)

The surface morphology of the matrix tablets was analyzed with a scanning electron microscope (JEOL-JSM-840A, Japan).

Analysis of the prepared formulation by HPLC

20 tablets were weighed to obtain the average tablet weight and were powdered by trituration. A sample of the powdered tablets claimed to contain 50 mg of active ingredient, was mixed with 30 mL of methanol. The mixture was allowed to stand with intermittent sonication to ensure complete solubility of drug. Further the resulting solution was passed through 0.45 µm membrane filter followed by adding of methanol to obtain a stock solution of 0.5mg/mL. An aliquot of this solution (0.5 mL) was transferred to a volumetric flask and made up to a sufficient volume with mobile phase to get desired concentration of 25 µg/mL. The prepared dilution was injected five times in to the column to obtain chromatogram. From that peak area, the drug content in the tablets was quantified.

Dissolution kinetic study[6,7]

Various mathematical models like; Zero-order model, First-order model, Higuchi (Matrix) model, Hixson and Crowell cube-root equation and Korsmeyer-Peppas Model were evaluated with respect to the dissolution profiles of the optimized formulations of HPMC K100M & Ethyl Cellulose. PCP disso software was used to fit models to dissolution profiles.

Stability studies

In any rationale design and evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection. During the stability studies the product is exposed to normal conditions of temperature and humidity. However, the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature.

Stability protocol

Types of packaging material

The tablets were packed in PVC coated aluminum - aluminum strip pack of 10 tablets.

Storage condition

The tablets were subjected to stability as per following condition for 3 months.

- 40°C / 75 % RH

Test parameters and testing methods

The samples were observed periodically for any change in the following physico-chemical parameters.

Appearance

The tablets were inspected for any change in size, shape, color and surface texture.

Drug content

Twenty tablets were accurately weighed and crushed. Powder equivalent to 10 mg of RPN was placed in a 100 mL volumetric flask containing 50 mL of PBS pH 6.8. The suspension was sonicated in ultrasonicator water bath for 30 min. These were allowed to stand and volume was made with PBS pH 6.8. The suspension was filtered through whatman filter paper (45µm) and 1 mL of the filtrate was transferred to a 10 mL volumetric flask. Volume was made with PBS pH 6.8. This solution was transferred to a analyzed by UV spectrophotometer at 249 nm by to determine contents of RPN.

***In vitro* dissolution studies**

The *in vitro* dissolution studies were performed using USP type-II dissolution apparatus .

RESULTS AND DISSCUSION

Evaluation of Blend/Granules

For formulations F1 to F12 and F26 to F35 dry blends were prepared by mixing all the excipients. For formulations F12 to F25 blends were prepared by mixing all the excipients by melt granulation technique. The blends were evaluated for different parameters and it was observed that Carr's Index (%) was in the range of 13.44±0.02 to 16.20±0.03, Hausner's ratio in the range of 1.190 to 1.282 and Angle of Repose was found to be in the range of 28^{o} 24' to 34^{o} 34'. From these observations it was concluded that blend formulations have desired physical and flow properties for tablets to be prepared by direct compression method.

Evaluation of tablets

Table 6: Tablet evaluation parameters

Formulations	Tablet Hardness Kg/cm^2)	Tablet thickness(mm)	Uniformity of content	Friability (%)	Weight variation(mg)
F1-F3	6-7	3.5 ± 0.02	100.1 ± 0.74	0.7 ±0.24	200±1.1
F4-F6	6-7	3.5 ± 0.02	99.87 ± 1.02	0.72 ±0.34	200±1
F7-F9	6-7	3.6 ± 0.01	101.45 ± 0.50	0.71 ±0.44	200±2
F10-F12	6-7	3.5 ± 0.02	100.23 ± 1.13	0.76 ±0.12	200±1
F13-F15	3-4	3.7 ± 0.02	99.23 ± 1.07	0.78 ±0.01	200±2
F16-F18	3-4	3.7±0.01	99.13 ± 0.50	0.69 ±0.14	200±3
F18-F25	3-4	3.7±0.02	98.27 ± 0.63	0.64 ±0.24	200±1
F26-F28	5-6	3.6±0.03	101.58 ± 0.42	0.8 ±0.21	200±1
F29-F35	6-7	3.7±0.01	98.22±0.45	0.79 ±0.22	200±2

(*Average of three determinants)*

Formulations containing HPMC K15M & HPMC K100M

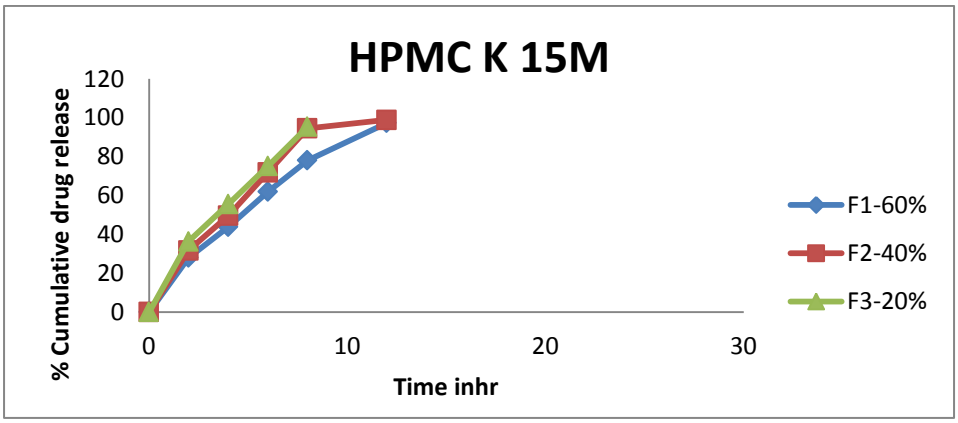


Figure 1: Dissolution profile of RPN using HPMC K15M

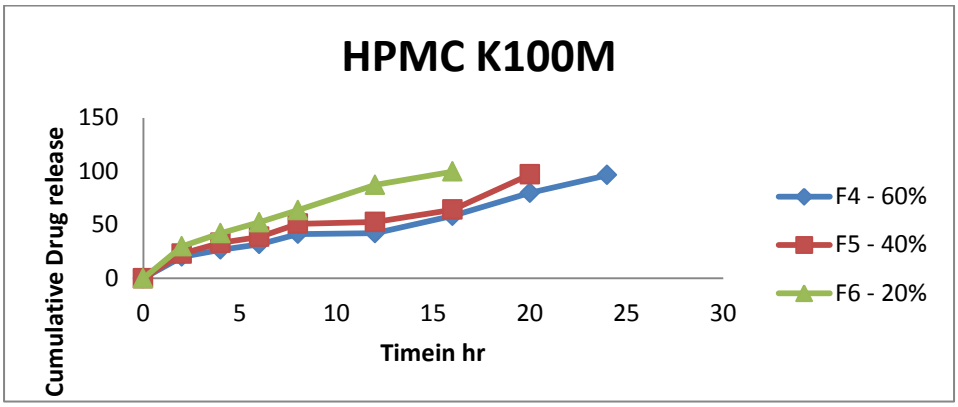


Figure 2: Dissolution profile of RPN using HPMC K100M

From comparative dissolution profile of the formulations containing different percentages of HPMC K15M it was observed that, as the percentage of the HPMC K15M increased, there is a decrease in the percentage cumulative release of the drug from the formulation. HPMC K15M was used in conc. of 60%, 40%, 20%. Formulation containing HPMC K15M could not withstand for period of 24hrs. Also it was observed that, as the percentage of HPMC K100 increased above 40%, there was a substantial decrease in the RPN release, as compared with the formulation containing HPMC K15M. From the above different formulations, F4 containing 60% HPMC K100M showed the desired release profile for RPN but it showed initial burst release (% CDR upto 30 % within 2 hrs).

Formulations containing Guar Gum & PEO

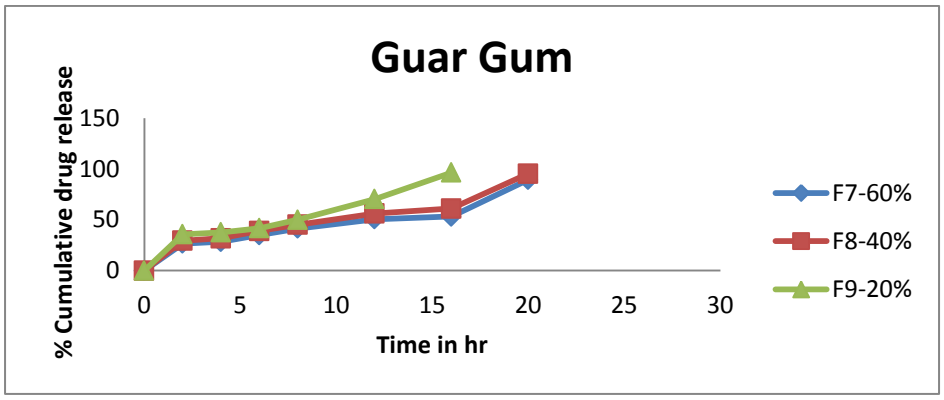


Figure 3: Dissolution profile of RPN using Guar Gum

From dissolution profile of the formulations containing different percentages of Guar Gum it was observed that, as the percentage of the Guar Gum increased, there is a decrease in the percentage cumulative release of the drug from the formulation. Guar Gum was used in conc. of 60%, 40%, 20%. Formulation containing Guar gum could not withstand for period of 24 hrs.It gives initial burst release due to its hydrophilic nature.

Trial batches of tablets (F10-F12) were prepared using different percentages of PEO i.e. 60%, 40%, 20%, of tablet weight respectively and dissolution profiles of the trial batches were studied.

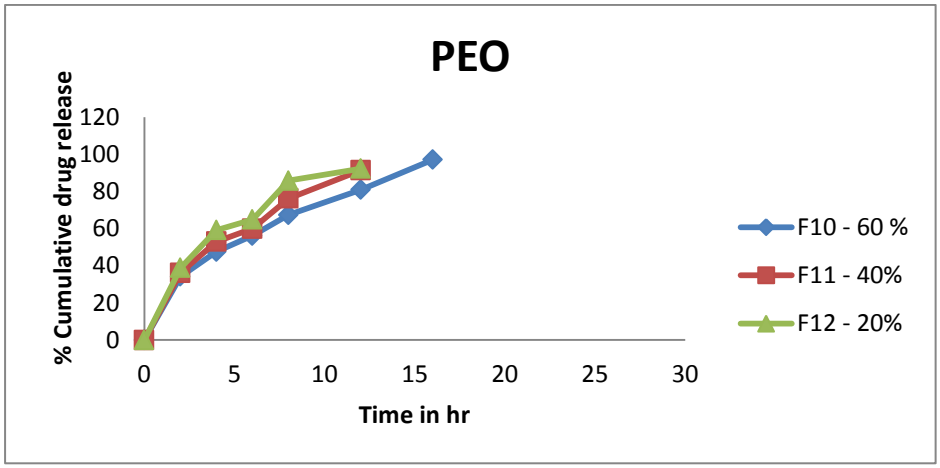


Figure 4: Dissolution profile of RPN using PEO

From dissolution profile of the formulations containing different percentages of it was observed that, the formulations containing PEO swells rapidly as it come in contact with dissolution medium. Also it was observed that as the percentage of the PEO increased, it doesn't affect on the initial burst release of ropinirole. The PEO fails to control initial burst release of ropinirole & couldn't withstand till the period of 24 hrs. All formulations containing PEO bursts till period of 16 hrs

Formulations containing HCO & GMS & HCO+GMS

Trial batches of tablets (F13-F15, F16-F18, and F19-F25) were prepared using different percentages each of HCO, GMS i.e.60%, 40%, 20%, of tablet weight respectively and a mixture of HCO & GMS. Dissolution profiles of the trial batches were studied

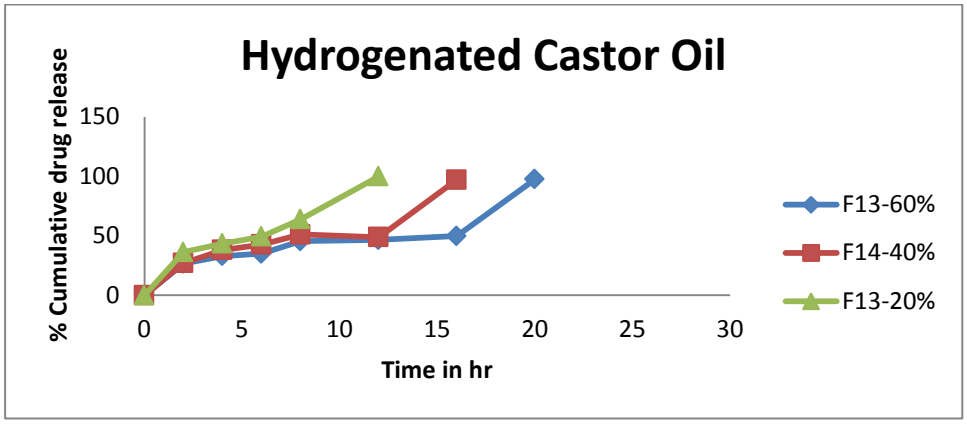


Figure 5: Dissolution profile of RPN using HCO

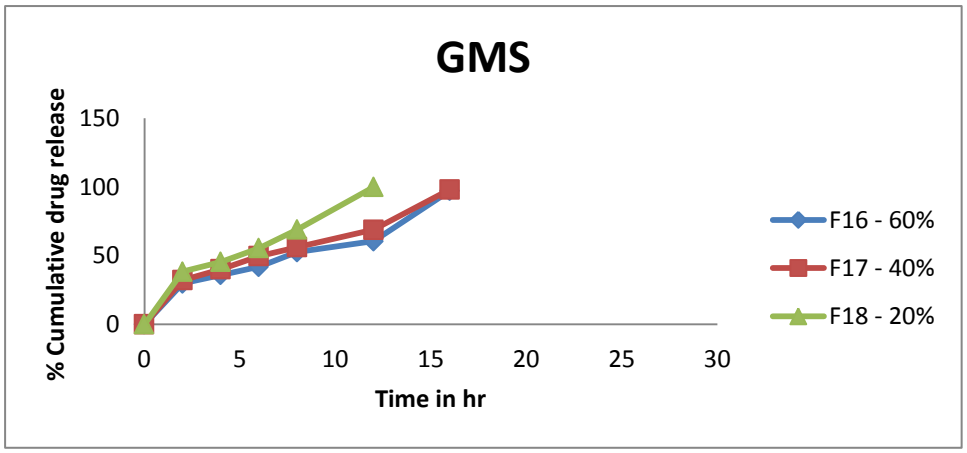


Figure 6: Dissolution profile of RPN using GMS

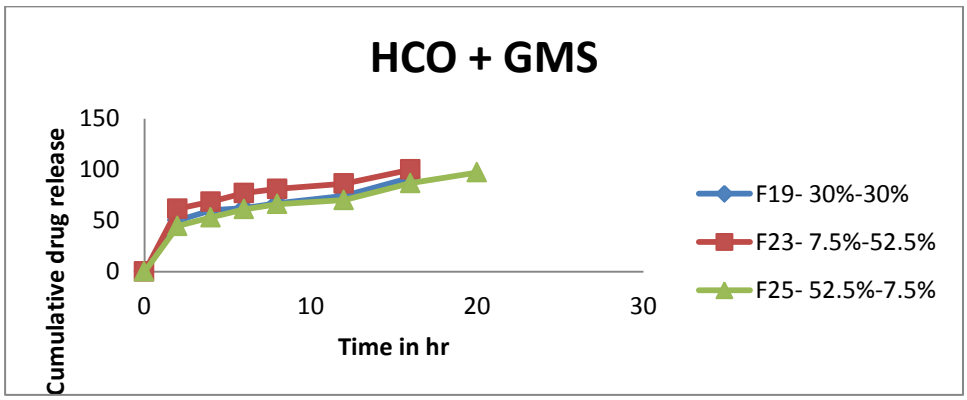


Figure 7: Dissolution profile of RPN using HCO+GMS

From dissolution profile of the formulations containing different percentages of HCO, GMS & mixture of HCO & GMS it was observed that, the formulations containing HCO & GMS releases

drug rapidly due to soft nature of matrix, mixture of HCO & GMS can withstand drug release till the period of 20 hrs and then it gets bursted.

Formulations containing EC, HPMC: EC combination

Trial batches of tablets (F26-F28, F29-F35,) were prepared using different percentages of EC i.e.60%, 40%, 20%,of tablet weight respectively and mixture of HPMC & EC. dissolution profiles of the trial batches were studied.

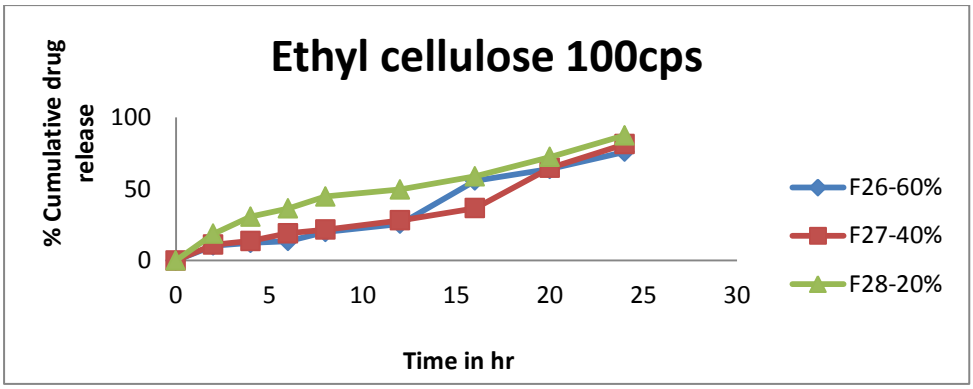


Figure 8: Dissolution profile of RPN using EC

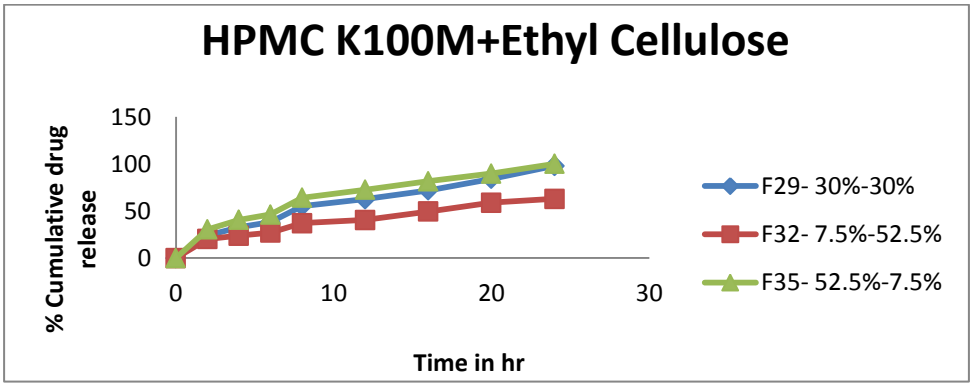


Figure 9: Dissolution profile of RPN using HPMC+EC

From dissolution profile of the formulations containing different percentages of EC it was observed that, the formulations containing EC releases drug very slowly as it come in contact with dissolution medium. Also it was observed that as the percentage of the EC increased, % CDR of RPN is reduced. The mixture of HPMC K100M & EC was tried in different proportion of **1:1, 0.75:1.25 , 0.5:1 , 0.25:1.75 , 1.25:0.75 , 1.5:0.5, 1.75:0.25** . The formulation batch F29 (1:1) ratio gives convenient release till the period of 24 hrs with reduced initial burst and steady release of drug upto 24 hrs. So the formulation F29 gives good results and it's considered as the best formulation among all trial batches of formulation.

Scanning Electron Microscopy (SEM)

The SEM images of the tablet batch F29 were taken before and after dissolution as shown in figure 35.

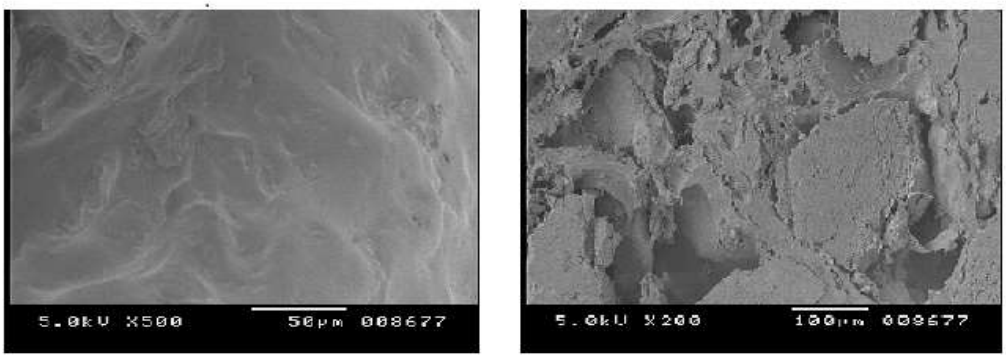


Figure 10: SEM images of sample tablets of F29

The SEM images of the tablet before dissolution shows intact surface without any perforations, channels, troughs. After dissolution revealed many pores with increasing diameter. The solvent front enters the matrix and moves slowly towards center of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium, which clearly indicated the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of ropinirole from formulated matrix tablet.

Analysis of the tablet formulation

The chromatograms of the drug from tablet formulation F29, exhibited peak at retention time of 4.867 min. Figure 36 shows typical chromatogram of F29 formulation. The results of the analysis of tablet formulation and its statistical validation are given in Table 25.

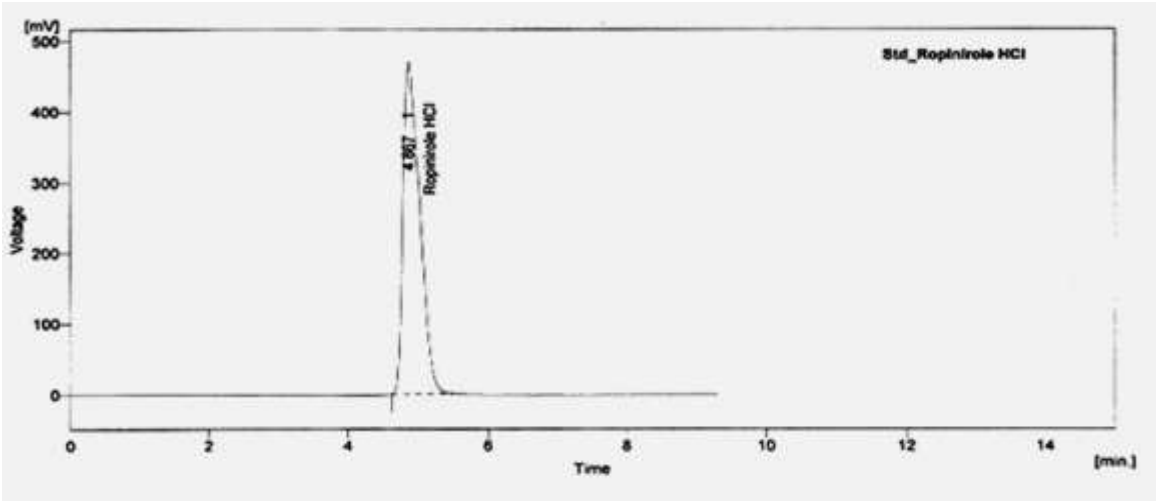


Figure 11: Typical chromatogram of F29 tablet formulation

Table 7: Analysis of tablet formulation by HPLC

Name of drug	Drug content (%)*	Rt
RPN	98.991	4.867

**Average of three determinants*

Dissolution kinetic study

Kinetics treatment

To analyze the mechanism of drug release from the matrix tablets, data obtained from the drug release studies was subjected to different mathematical models (Zero order, First order, Matrix (Higuchi) and Korsmeyer's Peppas)

The correlation coefficient (R^2) was used as an indicator for the best fitting for each of the models. Table 26 shows the Kinetics treatment for the optimized formulations.

Table 7: Kinetic treatment

Formulation	r^2			
	Zero order	First order	Higuchi's Model	Korsmeyer Peppas
F29	0.989	0.933	0.929	0.980
F30	0.955	0.878	0.93	0.93
F31	0.956	0.917	0.956	0.959
F32	0.974	0.951	0.970	0.945
F33	0.940	0.944	0.930	0.955
F34	0.992	0.943	0.972	0.942
F35	0.981	0.909	0.970	0.970

Table 8: Dissolution kinetics

Formulation	% Total Cumulative Release*	Time for Release (hours)	Best Fit model	Regression Coefficient (r^2)	N	K
F29	97.9± 0.15	24	Zero order	0.989	0.91	15.9
F30	71.1± 0.20	24	Zero order	0.955	0.890	16.1
F31	65.9± 0.43	24	Korsmeyer Peppas	0.959	0.206	26.42
F32	62.8± 0.50	24	Zero order	0.974	0.892	16.2
F33	52.2± 0.28	24	Korsmeyer Peppas	0.955	0.189	25.52
F34	99.9± 1.01	24	Zero order	0.972	0.895	16.5
F35	100.4± 0.96	*24*	Zero order	0.981	0.897	16.8

To elucidate the mechanism of drug release from Ropinirole controlled-release matrix tablets, dissolution data for the 100% of drug release was subjected to different kinetic treatments (Zero order, First order, Higuchi, and Korsmeyer's Peppas, (Table 26). The correlation coefficient (r^2) was used as an indicator of the best fitting for each of the models considered. The release exponent n was calculated through the slope of the straight line upon fitting data into the Korsemeyer–Peppas model The best fit model for prepared formulation follows Zero order (r^2= 0.989) and n

value was found to be 0.91 which signified that release pattern of optimized batch F29 follows the Fickian diffusion. The best fit model, values of release exponent (n) and release rate constant (K) are shown in Table 27. In the case of cylinders (i.e., tablets), the value of n ≤0.45 shows Fickian release; values of n between 0.45-0.89 show anomalous transport, while the value of n ≥0.89 shows a zero-order release .Fickian diffusion proposes the diffusion of drug through pores of the matrix and zero-order express release of drug with erosion of the polymeric chains, while anomalous transport reveals release of drug by a combined process of Diffusion and erosion. The decisive factor for selecting the most appropriate model (among the mathematical models) was based on the n value and/or goodness-of-fit test (i.e., linearity of the curves, where the coefficient of determination R^2 approaches 1) values.

Stability study

Formulation F29 was kept for stability study, tablets were packed in PVC –PVDC coated aluminum - aluminum strip pack of 10 tablets and were kept at 45ºC and 75% RH for 3 months. These formulations were evaluated for following parameters after stability study.

Appearance

Tablets kept for stability studies were examined. The colour of all the formulation, i.e. F29, was similar before and after stability studies.

Drug content

Drug content was determined by HPLC on 0 day and after period of 90 days, the drug content for F1 and F11 formulation is shown in Table 28.

Table 9: Drug content-stability study (A) on 0 day, (B) on 90th day

(A)

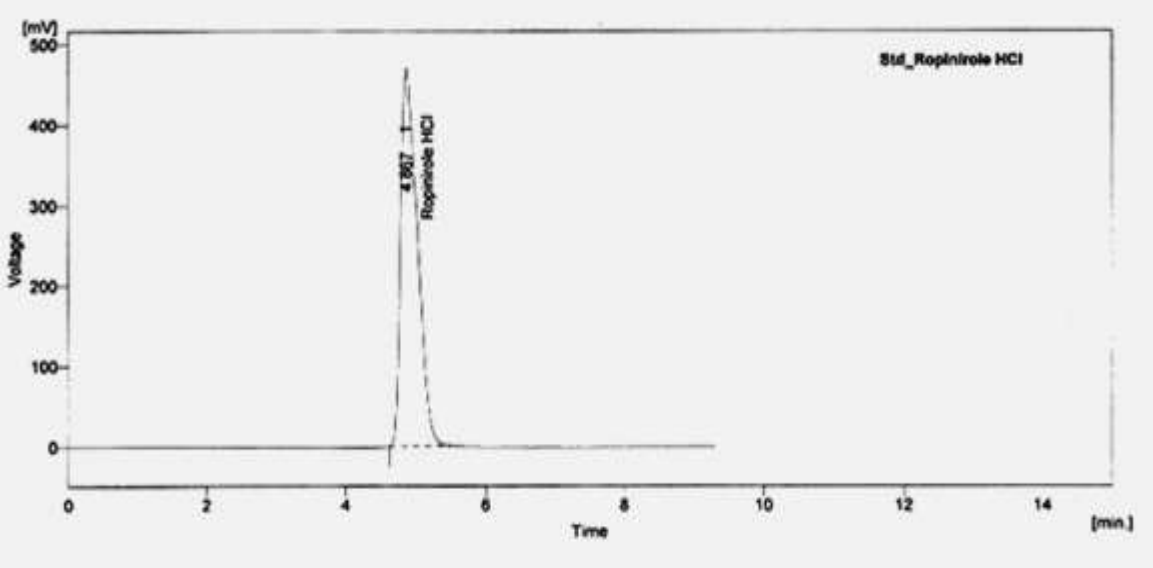
Sr.No	Drug	AUC	% Drug content
1	RPN	1428	95%

(B)

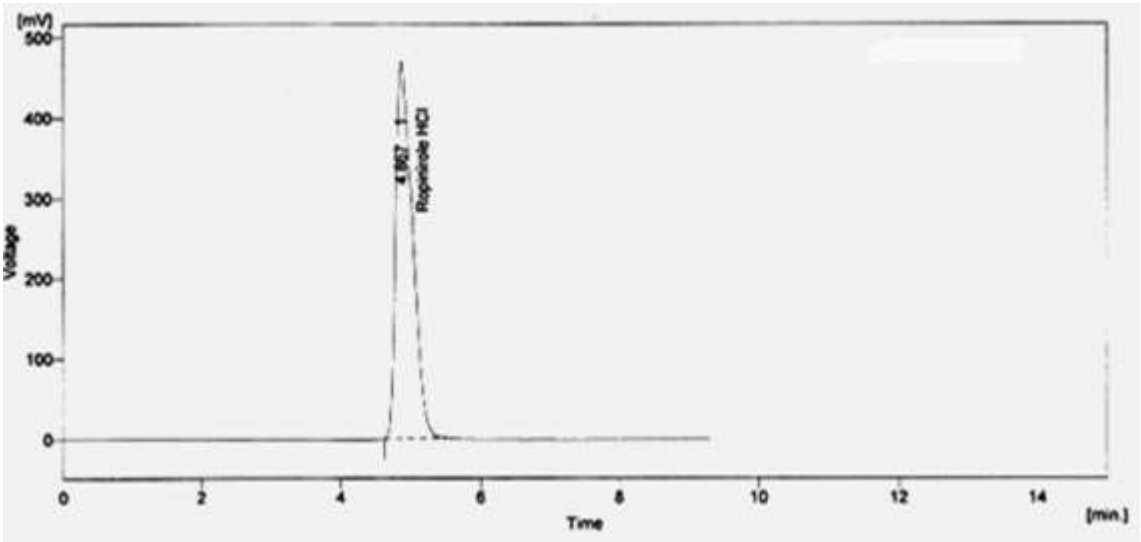
Sr.No	Drug	AUC	% Drug content
1	RPN	1421	94.1%

Drug content was found to be within acceptable limits as per I. P. This indicates that RPN was stable in presence of the excipients used at accelerated stability conditions of temperature and humidity.

Figure 12 shows the chromatograms of F29 formulation respectively on 0 day on 90th day.



(A)



(B)

Figure 13: Chromatograms of F29 formulation (A) on 0 day (B) on 90th day

From the above chromatograms it can be concluded that there is no significant change in the retention time and area under the curve (AUC) for the formulation F29. So the formulations were found to be stable.

In vitro dissolution study

Dissolution profiles of formulation F29 on before and after stability study is shown in Figures respectively. After stability study it was observed that there was no significant change in release profiles of both the formulations. The dissolution profile of the formulation considered at time zero and after 3 months of storage at 45°C/75% RH are completely super imposable.

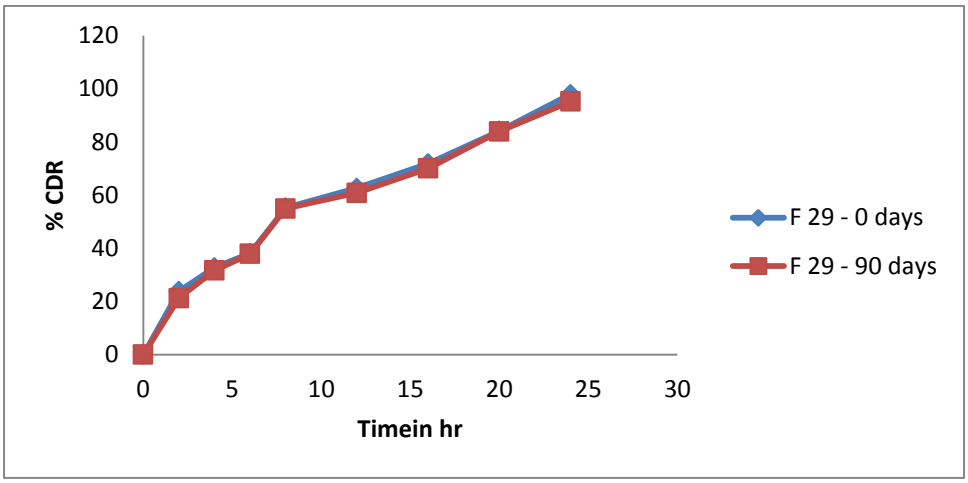


Figure 14: Dissolution profile of RPN for F29 formulation on 0 day & on 90th day

From the above dissolution profile it was concluded that formulations were stable and gave the similar dissolution profile for RPN w.r.t. the initial profile.

CONCLUSION

With only a few market Immediate release formulations for therapy for Parkinson Disease treatment, it calls for efforts to be made to prepare single controlled release formulation for delivery of drugs with low dose, with negligible side effects for PD. This study was thus a step towards the goal of rendering Ropinirole HCl in a single dosage form. Therefore, a controlled-release tablet of ropinirole was developed to optimize its blood level, minimize its side effects, to reduce its initial burst release, and ultimately improve its treatment adherence. Ropinirole HCl is a non ergoline dopamine agonist used for the treatment of Parkinson's disease. It act by stimulating post-synaptic dopamine D2-type receptors within the caudate-putamen in the brain.

The aim of present investigation was to formulate & evaluate controlled release tablets of RPN. Tablets were prepared by Direct Compression & melt granulation method. During pilot studies, the widely used release-retarding hydrophilic polymer HPMC K100 M, HPMC K 15 M was tried alone starting from 20% up to 60% of tablet weight (with 20% increments), HPMC K 100 M could hardly extend the drug release upto 20 hr & HPMC K 15 M up to period of 16-20 hrs. A highly water-soluble compound, Ropinirole in a HPMC matrix generates an additional osmotic gradient, thereby resulting in a faster rate of polymer swelling and drug diffuses out fast out of matrix so these formulations suffered from the problem of initial burst release. Among hydrophilic polymers other polymers like Guar gum and PEO were also used but these polymer formulation could not withstand up to period of 24 hrs. Among hydrophobic polymers Ethyl cellulose and waxy substances like HCO & GMS were used alone and in mixture, these were prepared by melt granulation method, these polymers due to soft nature of its matrix were unable to withstand for

period of 24 hrs. Ethyl cellulose was used starting from 20% up to 60% of tablet weight (with 20% increments), tablet remains intact for period of 24 hrs, but releases drug very slowly which couldn't release all drug till end of 24 hr period. So the mixture of HPMC K100M & EC was tried to counteract the problem of initial burst release as well as slow release from matrix of EC alone. A major difficulty experienced after the inclusion of 30% EC in formulation F4 when wet granulation was tried was the poor flowability and compressibility of the powder mixture, which led us to use the direct compression method for manufacturing the tablets. During the formulation development process, formulation F4 was modified by the addition of EC in varying concentrations to yield F29-F35 and F29 released 97.9% of RPN, within 24 hours. Tablet formulations were also evaluated for various parameters such as hardness, friability, weight variation test etc.

From dissolution profile It was found that formulations containing HPMC K100M and EC in the ratio of 1:1 (F29) were able to deliver RPN in desired fashion for about 24 hrs More than 95% of the drug was released in 24 hrs from optimized formulations, SEM study indicated that the drug release occurred via diffusion and erosion mechanism. Sustained release matrix systems developed were able to deliver the drug by zero order drug release model.

Further formulation (F29) was subjected to accelerated stability studies, it was found that at the end of 3 months, batch F29 didn't show any additional peak during its chromatographic (HPLC) studies, which indicated that the product is stable.

Thus, it was concluded that batch F29 is the final batch which satisfies all requirements with respect to

- Release characteristic of the drug for 24 hrs
- Stability

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