Research Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

FORMULATION, OPTIMIZATION AND *INVITRO* EVALUATION OF ROPINIROLE HYDROGEL TABLETS

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ABSTRACT

Ropinirole is a non-ergoline dopamine agonist. It is used in the treatment of Parkinson's disease. In this study Ropinirole hydrogel tablets were prepared and optimized the release of Ropinirole by using HEC (Hydroxy Ethyl Cellulose), Carbopol and Sodium alginate as polymers. The tablets prepared by direct compression technique and evaluated by physical parameters and invitro dissolution parameters. A total twelve formulations were prepared with varying polymer concentrations. All tablets were acceptable with strength was observed in tablets formulated with HEC (Hydroxy Ethyl Cellulose), Carbopol and Sodium alginate. Formulation F_{11} showed maximum release 99% in 12 hrs. FT-IR studies showed no evidence of interaction between drug and polymers.

KEYWORDS

Ropinirole, Hydrogels, HEC, *In vitro* dissolution and Direct compression.

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INTRODUCTION[1]

By definition, hydrogels are polymeric networks with three-dimensional configuration capable of imbibing high amounts of water or biological fluids. Their affinity to absorb water is attributed to the presence of hydrophilic groups such as –OH, –CONH–, –CONH2–, and –SO3H in polymers forming hydrogel structures. Due to the contribution of these groups and domains in the network, the polymer is thus hydrated to different degrees

(sometimes, more than 90%wt.), depending on the nature of the aqueous environment and polymer composition. They are insoluble due to the presence of chemical and/or physical crosslinks such as entanglements.

The term hydrogels implies that the material is already swollen in water, the dried hydrogels is called a xerogels. During the drying process, water evaporate from the gel and the surface tension causes collapse of the gel body, if water is removed without disturbing the polymeric network, either by lyophilization or by extraction with organic solvents, then the remaining material is extremely light with a porosity as high as 98%, such a dehydrated hydrogel is called aero gel. Hydrogels have been widely used as a drug carrier due to its ease in manufacturing and self-application. The production of a large and constant surface area is one of the major merits for them to be widely used for clinical and fundamental applications. Various combinations of polymers are made into hydrogel formulations to investigate their potential as a drug delivery system. The combination of natural and synthetic polymers may provide mechanical stability and biological acceptability, acquiring from synergistic properties of both materials. The Hydrogels were found stable and resilient .The existence of Hydrogels dates back to 1960, when Wichterle and Lim first proposed the use of hydrophilic networks of poly(2-hydroxyethyl methacrylate) (PHEMA) in contact lenses. Since then, the use of Hydrogels has extended to various biomedical and pharmaceutical applications. Antibiotics loaded interpenetrating network hydrogel based on poly(acrylic acid) and glutaradehyde for treatment of experimental H pylori. IPN Hydrogels such as gelatin and dextran are widely used as a drug carrier due to their biodegradability and removable versatility in terms of composition and size. Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fuids.[6,7] The networks are composed of homopolymers or copolymers, and are insoluble due to the presence of chemical crosslinks (tie-points, junctions), physical crosslinks, such as entanglements or crystallites.8-15 The latter provide the network structure and physical integrity. These Hydrogels exhibit a thermodynamic compatibility with water which allows them to swell in aqueous media.

MATERIAL AND METHOD

MATERIALS

Ropinirole, Hydroxy Ethyl Cellulose, Carbopol, Sodium alginate, Mg. Stearate, Aerosil and MCC, all materials are obtained from Spectrum Pharma research lab, Hyderabad.

METHOD

The Ropinirole hydrogel tablets were prepared by using the Hydroxy Ethyl Cellulose, Carbopol, Sodium alginate as polymers in different ratios based on the give formula by direct compression method. All the ingredients mixed thoroughly and passed through sieve no. 20.

EVALUATION PARAMETERS[2,3,4]

PRE-COMPRESSION STUDIES

BULK DENSITY

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve#20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml and is given by

$$D_b = M/Vb$$

Where,

M is the mass of powder

Vb is the bulk volume of the powder.

TAPPED DENSITY

It is the ratio of the total mass powder to the tapped volume of the powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

$$D_t = M/Vt$$

Where,
M is the mass of powder
Vt is the tapped volume of the powder.
ANGLE OF REPOSE
It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula.

$$\mathbf{Tan\ \theta = h/r}$$

Therefore $\theta = Tan^{-1} h/r$
Where,
θ = Angle of repose
h = height of the cone
r = Radius of the cone base.

Compressibility Index

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

Carr's compressibility index (%)=$[(D_t-D_b)X100]/ D_t$

Where,
D_t is the tapped density
D_b is the bulk density

Hauser's Ratio

Hausner's ratio is an indirect index of the ease of powder flow. It is calculated by the following formula.

$$\mathbf{Hausner's\ ratio = D_t/D_b}$$

Where, Dt is the tapped density,
Db is the bulk density.

Post Compression Studies[4]

TABLET THICKNESS**TEST**

Randomly 10 tablets were taken from each formulation trial batch and their thickness was measured using a Venire caliperse.

Weight Variation Test

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Measurement of Tablet Hardness

The hardness of tablet is an indication of its strength. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Friability test

It is measured of mechanical strength of tablets. Roche Friabilator is used to determine the friability by following procedure. Twenty tablets were weighed and placed in Roche Friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions, tablets are removed, dedusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Friability = (loss in weight / Initial weight) X 100

In-Vitro Release Studies

The drug release rate from Gastro retentive tablets was studied using the USP (II) dissolution test apparatus (Lab India dissolution test apparatus Disso 2000). The assembly is kept in a jacketed vessel of water maintained at 37±5C. The beaker is filled with 900ml of buffer pH 1.2. The vessel maintained at 50rpm under stirring conditions by means of paddle fabricated for purpose in dissolution apparatus. At various intervals of time, samples were withdrawn and filtered through whatmann filter paper no.42. It is replaced immediately with equal amount of fresh buffer. The samples are then analyzed U.V. spectrophotometrically at 246 nm up to 12hours.

Drug Release Kinetic Studies

To describe the kinetics of the drug release from the matrix base Gastro retentive tablets of optimized batch F11, mathematical models such as zero-order, first order, Higuchi, Korsmeyer-Peppas models are where use. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-or fit test.

Drug Excipient Compatibility Study

FTIR Spectroscopic studies were conducted for Loratidine pure drug, excipients and optimized formulation.

Physical Evaluation

The weights of all tablets were within ±5% of the average weight, thickness between 3.54 and 3.6mm, and hardness between 5.2 and 6.0 kg/cm^2. Friability ranged between 0.75 and 0.85 thus all the physical parameters of the compressed tablets prepared were practically within the acceptable limits.

***In-Vitro* Release Studies**

In vitro dissolution test was carried out by using USP type II (paddle) apparatus. 900 mL of buffer pH 1.2 was used as dissolution medium and the paddle was rotated at 50 rpm at temperature (37^0C ± 0.5^0C). Sampling was done at regular intervals and was replaced by media after each sampling interval. The samples are then analysed spectrophotometrically at λmax of the drug. (FDA method).

Medium**:**	buffer pH 1.2
Volume:	900mL
Temperature:	37^0C±0.5^0C
Apparatus:	USO type-II (paddle)
RPM:	50 RPM
Time interval:	1 hr up to 12 hrs

Table No.1: Composition of different additives with Ropinirole

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
API	12	12	12	12	12	12	12	12	12	12	12	12
Hydroxy Ethyl Cellulose	40	__	__	20	__	__	10	__	__	5	5	__
Carbopol	__	40	__	__	20	__	__	10	__	5	__	5
Sodium alginate	__	__	40	__	__	20	__	__	10	__	5	5
Mg. Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Aerosil	1	1	1	1	1	1	1	1	1	1	1	1
MCC	144	144	144	144	144	144	144	144	144	144	144	144
Total weight	200	200	200	200	200	200	200	200	200	200	200	200

Table No.2: Results of flow properties

FORMULATIONS	Tapped density	Bulk density	Carr's compressibility	Hausner's ratio	Angle of repose
F1	0.4312	0.511367	13.52	1.22	29.25
F2	0.509967	0.658833	21.78667	1.193333	28.93
F3	0.512133	0.658833	17.28	1.246667	31.26
F4	0.470767	0.5414	12.80333	1.213333	33.73
F5	0.481667	0.6131	16.74667	1.316667	29.13
F6	0.513233	0.523367	13.22	1.246667	31.48333
F7	0.509967	0.611167	21.78667	1.193333	29.25
F8	0.509967	0.6131	12.80333	1.316667	28.93
F9	0.513233	0.511367	13.52	1.22	29.13
F10	0.509967	0.658833	21.78667	1.193333	28.93
F11	0.512133	0.611167	17.28	1.246667	31.26
F12	0.470767	0.5414	12.80333	1.213333	33.73

Table No.3: Results of Post compression Studies

Formulation	thickness	hardness	Friability	Weight Variation	Drug content
	2.466667	5.566667	0.166667	201	98.44667
F1	2.5	6.6	0.33	197.3	95.57
F2	2.366667	6.433333	0.153333	201.3	92.95333
F3	2.533333	5.533333	0.26	199.3	100.3433
F4	2.433333	6.366667	0.32	199	97.77333
F5	2.433333	6.066667	0.34	199.6	99.64667
F6	2.5	6.433333	0.153333	197.3	95.57
F7	2.466667	5.533333	0.26	201.3	92.95333
F8	2.433333	6.366667	0.32	199.3	100.3433
F9	2.5	6.6	0.33	197.3	95.57
F10	2.366667	6.433333	0.153333	201.3	92.95333
F11	2.533333	5.533333	0.26	199.3	100.3433
F12	2.433333	6.366667	0.32	199	97.77333

Table No.4: *In vitro* dissolution results of formulations (F1 to F6)

Time(hrs)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	22.24792	28.28125	26.96146	32.80625	33.9375	35.44583
2	26.96146	36.57708	28.65833	41.10208	36.57708	35.82292
3	30.73229	40.34792	33.9375	42.79896	42.79896	44.11875
4	34.31458	45.62708	45.25	45.81563	45.62708	51.84896
5	40.34792	53.92292	47.88958	50.71771	50.71771	54.67708
6	42.9875	58.825	58.825	58.44792	53.92292	58.825
7	47.32396	63.16146	62.21875	61.27604	58.825	62.21875
8	54.48854	66.36667	77.30208	65.80104	62.97292	65.98958
9	63.16146	71.45729	80.88438	72.96563	66.93229	69.76042
10	70.70313	79.75313	83.90104	82.01563	72.58854	77.30208
11	82.20417	83.90104	88.61458	88.61458	85.78646	92.38542
12	89.18021	91.44271	89.18021	94.27083	96.15625	97.66458

Table No.5: *In vitro* dissolution results of formulations (F7 to F12)

Time(hrs)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
1	32.05208	39.59375	36.76563	39.59375	40.15938	41.47917
2	37.33125	45.06146	39.59375	43.36458	44.49583	50.90625
3	41.47917	48.26667	43.74167	50.15208	45.25	54.86563
4	45.62708	52.60313	47.5125	54.48854	51.28333	58.44792
5	49.96354	56.5625	52.60313	55.05417	55.24271	64.10417
6	58.44792	59.39063	56.37396	58.44792	62.21875	70.70313
7	64.85833	63.72708	60.52188	64.85833	69.76042	75.41667
8	70.32604	69.19479	69.76042	71.26875	77.30208	83.52396
9	73.53125	73.53125	75.22813	77.30208	81.07292	92.7625
10	79.94167	77.67917	81.63854	83.7125	89.55729	94.27083
11	86.72917	91.44271	92.38542	94.08229	96.15625	96.72188
12	95.77917	98.04167	98.04167	96.15625	99.73854	99.55

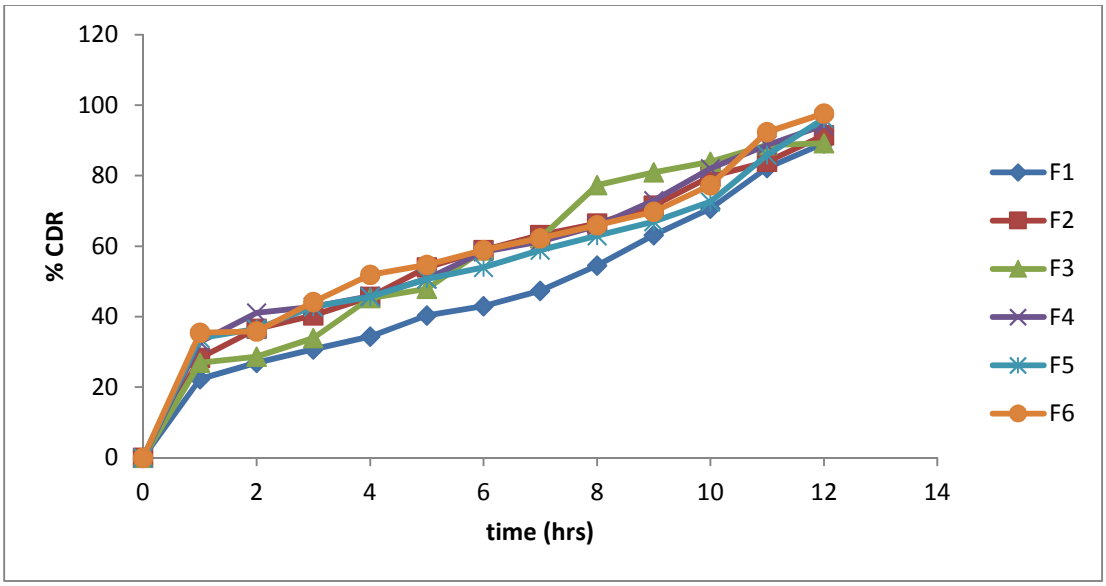

Figure No.1: *In-vitro* drug release profiles of formulations (F1 to F6)

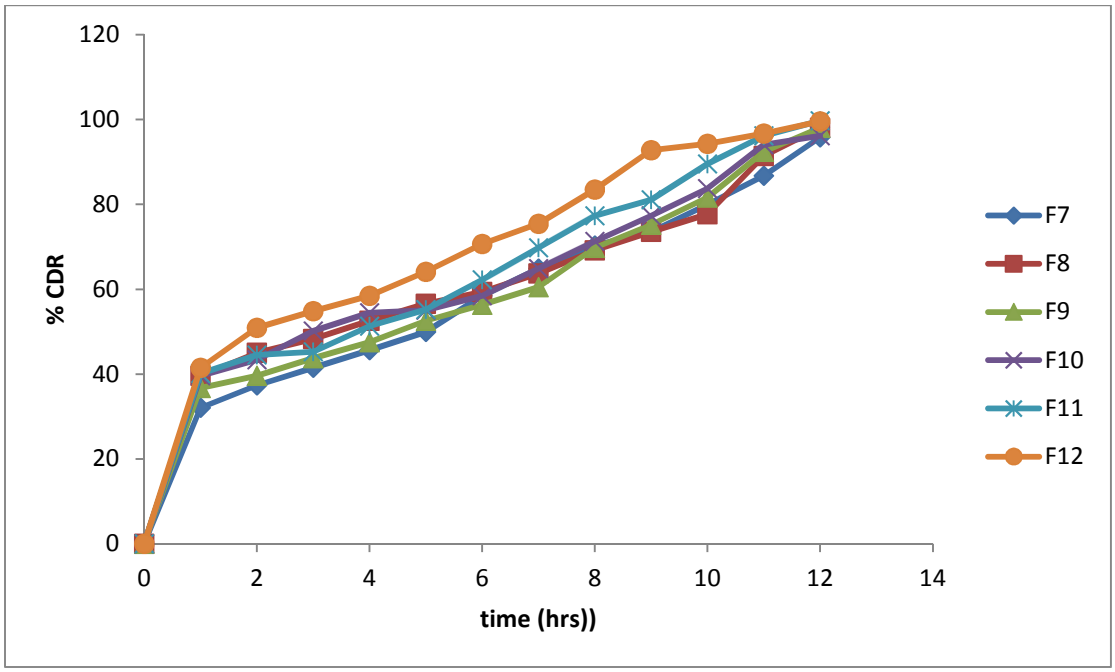

Figure No.2: *In-vitro* drug release profiles of formulations (F7 to F12)

Release kinetics and mechanism of optimized formulation

The optimized formulation F11 follows **Zero order** and follows **Higuchi mechanism.**

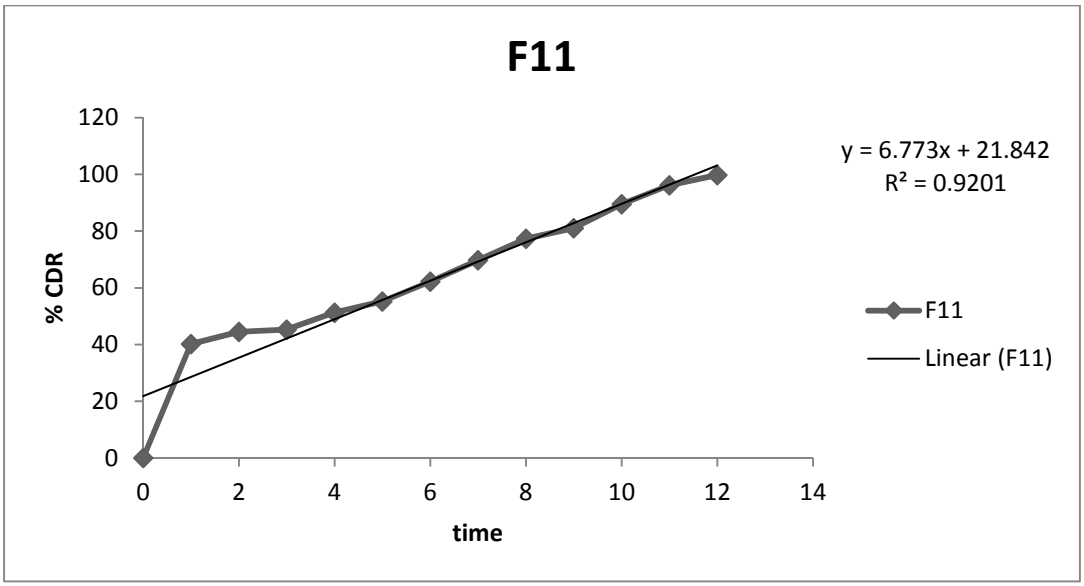

Figure No.3: Zero order

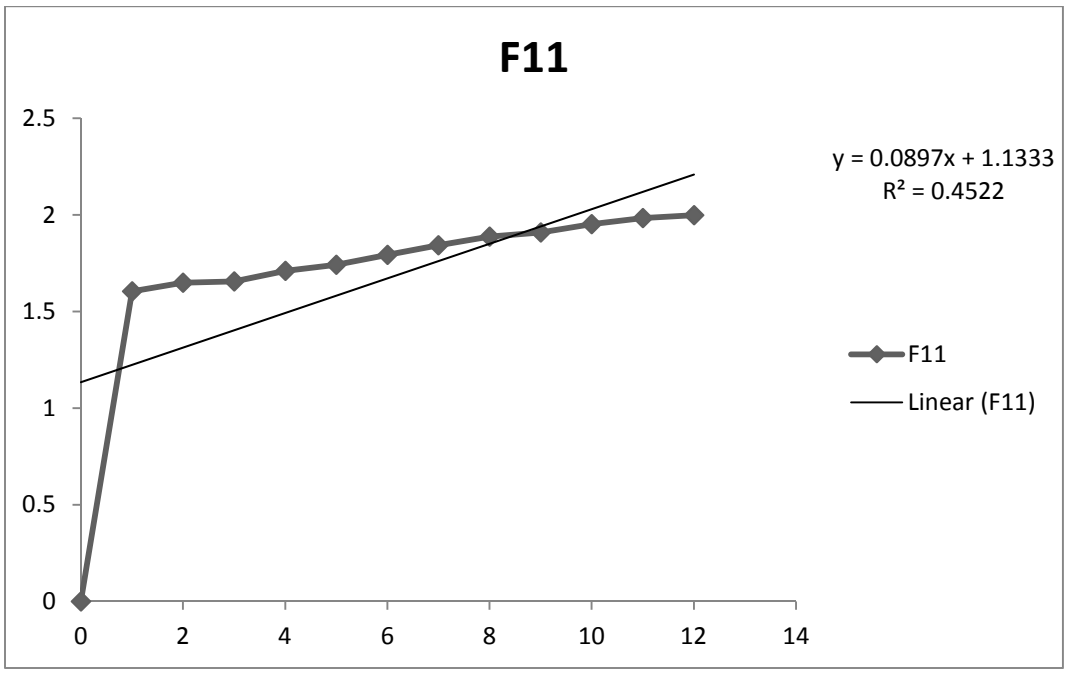

Figure No 4: 1st order

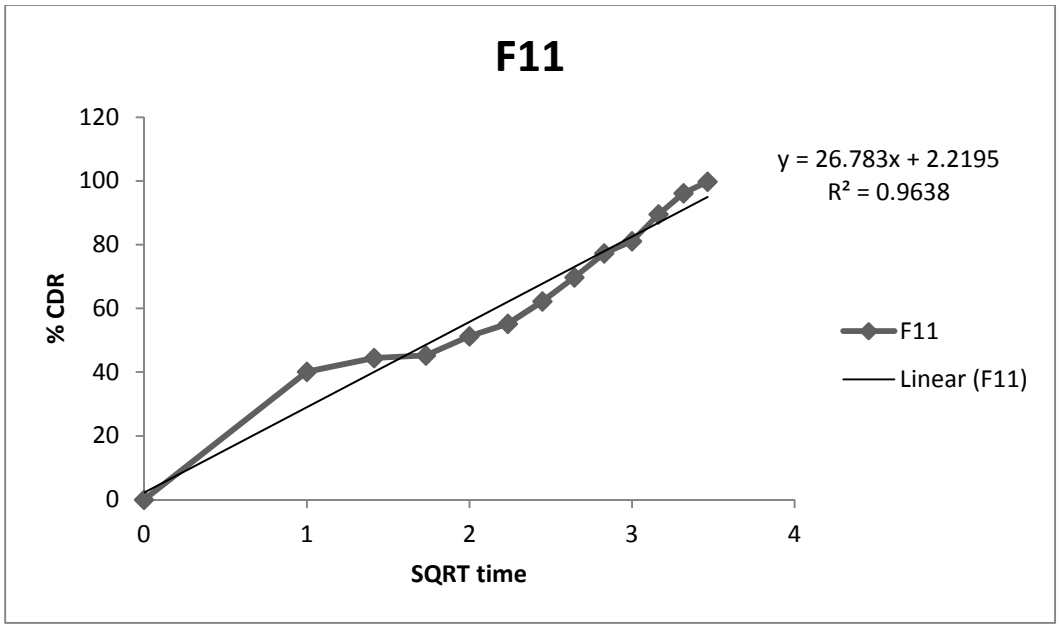

Figure No.5: Higuchi

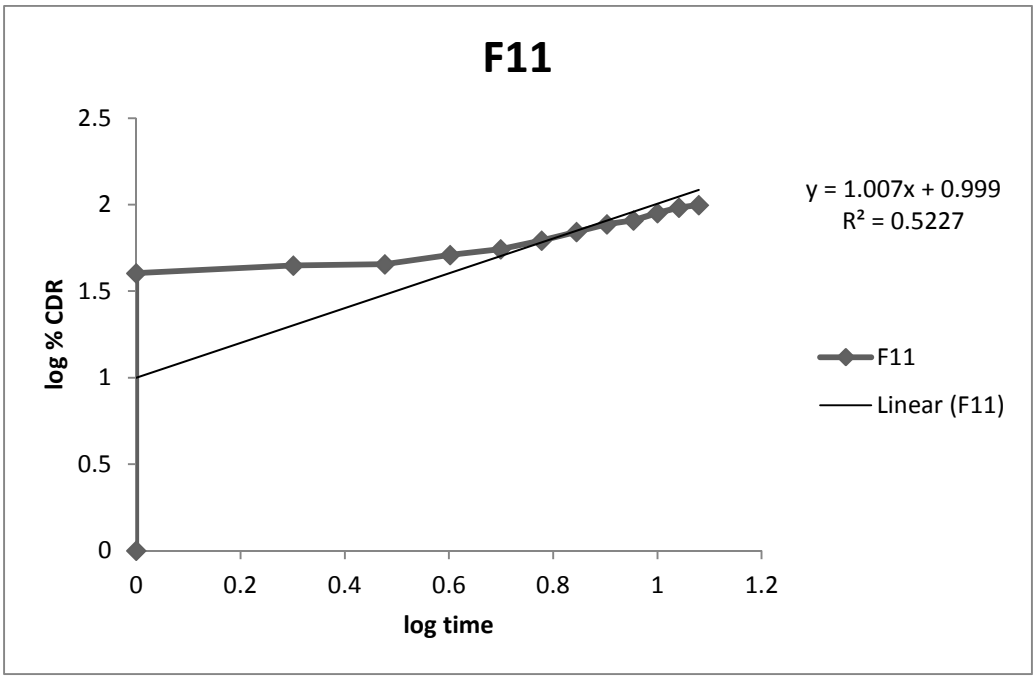

Figure No.6: Pepas

FT- IR Studies

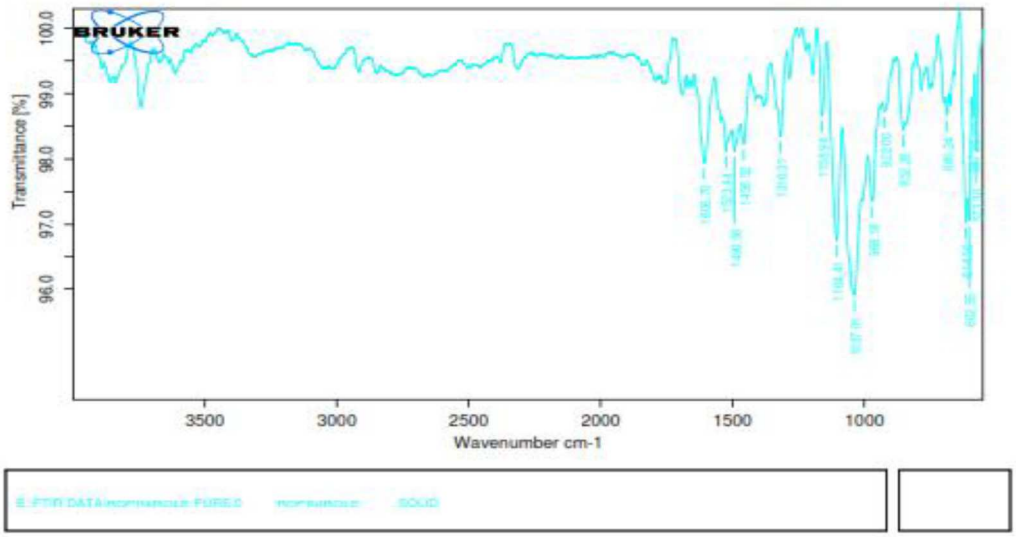

Figure No.7: Pure Ropinirole

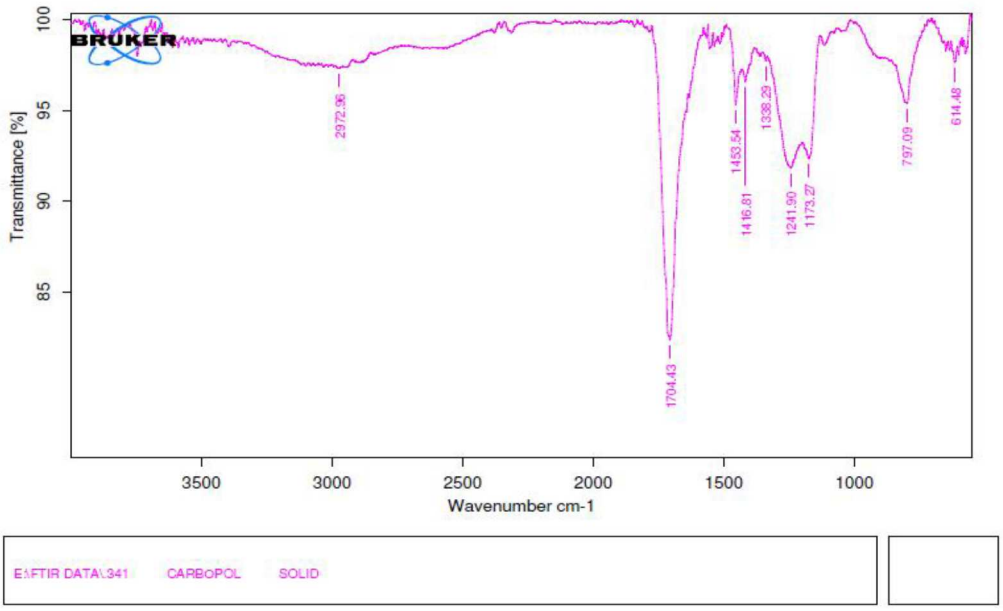

Figure No.8: Carbopol

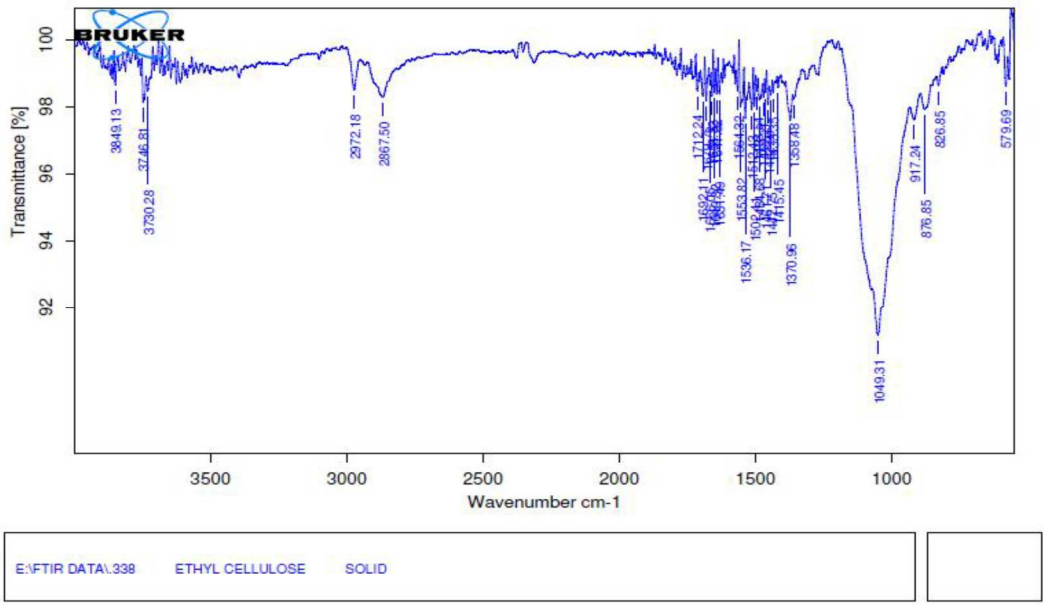

Figure No.9: Ethyl Cellulose

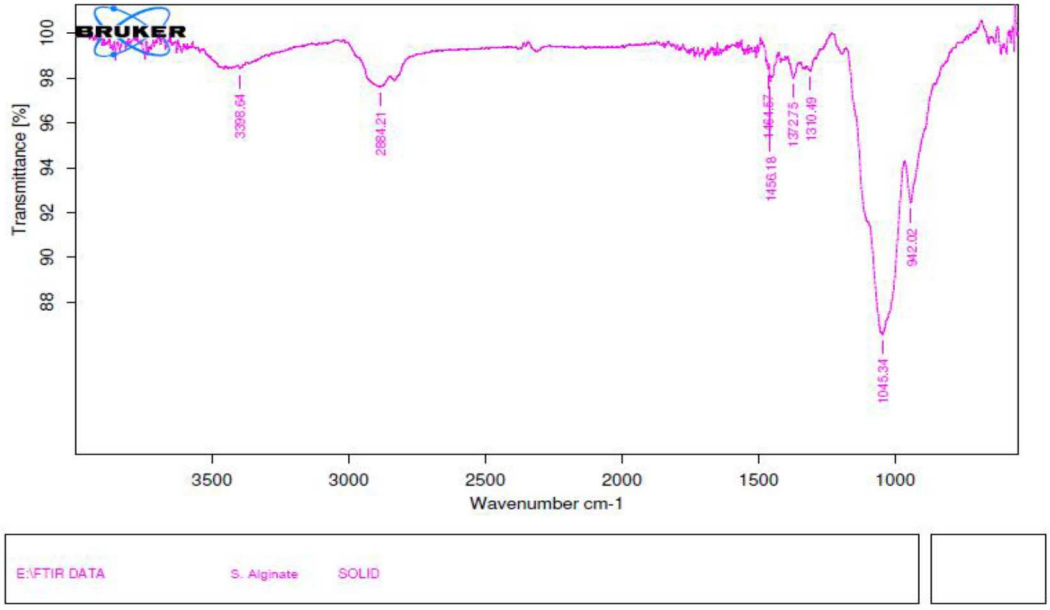

Figure No.10: FTIR spectra of Sodium alginate

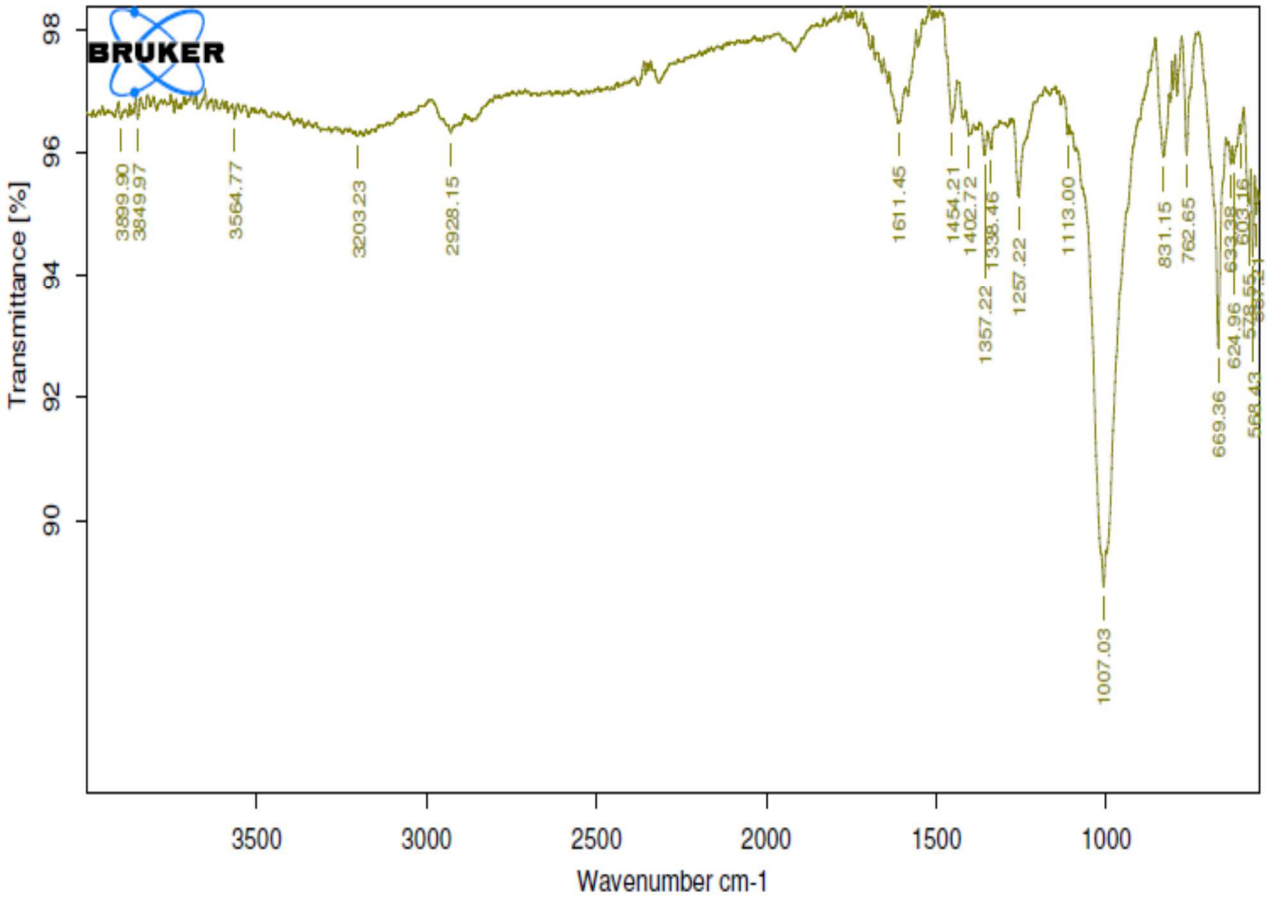

Figure No.11: Best formulation (F11)

CONCLUSION

This study suggests that formulation 11 (F_{11}) shows the optimized release in all aspects. The optimized formulation shows required physical and formulation parameters. By using the formulation we can deliver the Ropinirole drug in optimized manner.

ACKNOWLEDGEMENT

The Spectrum Pharmaceutical lab provides all the facilities and our college A.M. Reddy Memorial college of Pharmacy supports for doing this project.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Raghuram Reddy D. *et al.* Formulation, optimization and *in vitro* evaluation of ropinirole Hydrogel tablets, *International Journal of Research in Pharmaceutical and Nano Sciences,* 2(5), 2013, 559-571.