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DEVELOPMENT AND EVALUATION OF CONTROLLED RELEASE MICROSPHERES CONTAINING ROPINIROLE HCL

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Abstract:

Current investigation explains the preparation of alginate microspheres of Ropinirole by ionotropic gelation technique, we sought to develop novel Ropinirole microspheres and explore the influence of various concentrations of sodium alginate, Eudragit RS100, Gum Kondagogu and calcium chloride on particle size, entrapment efficiency, and drug release of the same. The prepared microspheres were found to be discrete, spherical with free-flowing properties and were evaluated with regarding percentage yield, entrapment efficiency followed by drug release and characterization was studied using FTIR, DSC, SEM analysis. Among the total S14 formulations, S13 formulation was selected as optimized preparation. The in vitro dissolution showed sustained release of Ropinirole up to 97.54±5.05% by diffusion mechanism over 12hrs which followed the zero order and Higuchi model (R^2 = 0.9894,0.9771) respectively, and it followed Non Fickian diffusion. The marketed product displayed the drug release of 90.16±5.00 within 12 hr. From these results it was concluded that, the drug release from the optimized formulation was in controlled manner and completely within 12h.

Key Words: *Ropinirole, Parkinson's disease, SEM, FTIR, Ionotropic gelation.*

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INTRODUCTION:

The efficiency of any drug therapy can be described by achieving desired concentration of the drug in blood or tissue, which is therapeutically effective and nontoxic for a prolonged period. This goal can be achieved based on proper design of the dosage regimen. Sustained release systems are one of such system which includes any drug delivery system that achieves slow release of drug over an extended period **[1]**.

Microspheres can be described as small particles (in 1-1000 micrometer size range) for use as carriers of drugs and other therapeutic agents. The term microspheres describe a monolithic spherical structure with the drug or therapeutic agent distributed throughout the matrix either as a molecular dispersion or as a dispersion of particles **[2]**. Microspheres have potential to deliver drug in a controlled fashion. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance. They spread out more uniformly in the GI tract, thus avoiding exposure of the mucosa to high concentration of drug and ensuring more reproducible drug absorption. The risk of dose dumping also seems to be lower than with a single unit dosage form **[3, 4 and 5]**.

Ropinirole HCl, a dopamine agonist used in the Parkinsonism in restless legs syndrome (RLS) is a highly water-soluble drug (133 mg/ml). It is generally available as a conventional solid oral dosage form which is a major problem for the patients undergoing the dopamine therapy. The Parkinsonism patients taking Ropinirole HCl conventional tablet cannot swallow the dosage form due to reduced muscular activity, unavailability of water, dryness of mouth and dysphagia. The frequency of administration of this dosage form is minimum thrice a day due to lower dose (up to 8 mg) and shorter half life (5 hrs), so the problem arises in the number of doses. To overcome both these problems the sustained release microspheres is developed to deliver the drug for the prolonged period **[6]**.

MATERIALS AND METHODS:

Materials: Ropinirole procured from Hetero Drugs Ltd**,** HYD. Sodium alginate from Pruthvi Chemicals, Mumbai. Calcium chloride from SD Fine ltd, Mumbai. Ethyl cellulose from Aay Cee Enterprises, Roorkee. Eudragit RS 100 from Rubicon Labs, Mumbai. Gum Kondagogu from Nutriroma, Hyd.

Methods:

Formulation of Ropinirole Alginate Microsphere:

Procedure: The microspheres of sodium alginate were prepared by using ion tropic gelation technique. In this method weighed quantity of Ropinirole was added to 100ml sodium alginate solution and thoroughly mixed at 500 rpm. Resultant solution was extruded drop wise with the help of syringe and needle into 100ml aqueous calcium chloride solution and stirred at 100 rpm. After stirring for 10 minutes the obtained microspheres were washed with water and dried at 60 degrees-2hours in a hot air oven and stored in desiccator it is shown in Table 1.

Table 1: Formulation trials for Ropinirole alginate microspheres

Formulation Code	Ropinirole (mg)	Sodium Alginate	Eudragit RS100 (mg)	Calcium Chloride	Gum Kondagogu
S1	1	0.5 %	0.06	6%	0.5%
S2	1	0.75%	0.0612	6%	0.5%
S3	1	1%	0.0624	6%	0.5%
S4	1	1.25%	0.0636	6%	0.5%
S5	1	1.5%	0.648	6%	0.5%
S6	1	1.75%	0.660	6%	0.5%
S7	1	2%	0.672	6%	0.5%
S8	1	0.5 %	0.06	10%	0.5%
S9	1	0.75%	0.0612	10%	0.5%
S10	1	1%	0.0624	10%	0.5%
S11	1	1.25%	0.0636	10%	0.5%
S12	1	1.5%	0.648	10%	0.5%
S13	1	1.75%	0.660	10%	0.5%
S14	1	2.2%	0.672	10%	0.5%

Evaluation of Ropinirole Alginate Microspheres:

Particle size:

The 100 microspheres were evaluated with respect to their size and shape using optical microscope fitted with an ocular micrometer and a stage micrometer. The particle diameters of more than 100 microspheres were measured randomly by optical microscope **[7]**.

Angle of repose:

Angle of repose (Θ) of microspheres measures the resistance to particles flow and is calculated according to fixed funnel standing cone method. Where (Θ) is angle of repose, H/D is surface area of the free-standing height of the microspheres heap that is formed on a graph paper after making the microspheres flow from glass funnel [8].

$$\theta = \tan^{-1}(h/r)$$

Bulk density:

Volume of the microspheres in the measuring cylinder was noted as bulk density **[9]**.

$$\text{Bulk density} = \frac{\text{Wt of powder}}{\text{Bulk volume of powder}}$$

Tapped density:

Change in the microspheres volume was observed in mechanical tapping apparatus **[10]**.

$$\text{Tapped density} = \frac{\text{Wt of microspheres}}{\text{Tapped volume of microspheres}}$$

Compressibility index:

Also called as Carr's index and is computed according to the following equation **[11].**

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

Hausner's ratio:

Hausner's ratio of microspheres is determined by comparing the tapped density to the fluff density using the equation **[12]**.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Swelling index:

Swelling index was determined by measuring the extent of swelling of microspheres in the given medium. Exactly weighed number of microspheres could swell in given medium. The excess surface adhered liquid drops were removed by blotting and the swollen microspheres were weighed by using microbalance. The hydro gel microspheres then dried in an oven at 60 degrees for 5h until there was no change in the dried mass of sample. The swelling index of the microsphere was calculated by using the formula **[13]**.

(Swelling index= (Mass of swollen microspheres - Mass of dry microspheres/mass of dried microspheres) 100.

Drug entrapment efficiency and %yield:

To determine the incorporation efficiency, 10 mg of formulated microspheres were thoroughly crushed by triturating and suspended in required quantity of methanol followed by agitation to dissolve the polymer and extract the drug. After filtration, suitable dilutions were made and drug content assayed spectro-photometrically at 254nm wavelength using calibration curve. Each batch should be examined for drug content in a triplicate manner **[14]**.

% Drug entrapment = Calculated drug concentration /Theoretical drug concentration x 100

% yield = [Total weight of microspheres / Total weight of drug and polymer] x 100

***In vitro* drug release studies:**

In vitro drug release studies were conducted by using USP dissolution apparatus II (Paddle type) for ropinirole microspheres. Accurately weighed quantity of floating microspheres were equivalent to 1mg of drug transferred into 900 ml of 0.1 N HCl (pH 1.2) medium maintained at 37±0.5°C and stirring at 100rpm. Aliquots of samples were withdrawn at specified time intervals, filtered and diluted with similar medium finally assayed at 254nm using UV-Visible spectrophotometer. The samples withdrawn were replaced with same dissolution medium at predetermined time intervals. All the samples were analyzed in triplicate [15].

Kinetic modeling of drug release:

To understand the kinetics and mechanism of drug release, the result of the in vitro dissolution study of microspheres were fitted with various kinetic equations like Zero order as cumulative percentage drug release Vs. time, first order as log percentage of drug remaining to be released Vs. time, Higuchi's model cumulative percentage drug released Vs. square root of time. r^2 and K values were calculated for the linear curves obtained by regression analysis of the above plots.

To analyze the mechanism of drug release from the tablets the in vitro dissolution data was fitted to zero order, first order, Higuchi's release model and Korsmeyer – Peppas model.

Zero order equation:
This equation describes the systems where the release rate is independent of the concentration of the dissolved species. The dissolution data are fitted into the Zero order equation

$$Q=Q_0K_0 t$$

Where Q= Amount of drug released at time t, Q_0= Amount of drug released initially K_0 t = Zero order rate constant. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and the intercept at the origin of the axes. The zero order plots are derived from plotting the cumulative the cumulative percent drug dissolved vs. time **[16]**.

First order Equation:
The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species.
Release behavior generally follows the following first order release equation:

$$\ln M=\ln M_0- K1t$$

Where M is the amount of drug dissolved at time, M_0 is the amount of drug dissolved at t=0 and K1 is the first order rate constant. A graph of log concentration of drug release vs time yields a straight line **[17].**

Higuchi Square Root Law:
A form of the Higuchi Square Root Law is given by equation:

$$Q=Ks \sqrt{t}$$

Where Q = Amount of drug dissolved at time t Ks = Higuchi rate constant
The Higuchi square root equation describes the release is related to the rate of drug diffusion **[18]**.

Korsmeyer - Peppas release model:
The release rate data were fitted to the following equation,

$$Mt/M\alpha=K.t^n$$

Where Mt/Mα is the fraction of drug released,
'K' is the release constant't' is the release time.
'n' is the diffusion exponent, if n is equal to 0.89, the release is Zero order. If n is equal to 0.45 the release is best explained by Fukien diffusion, and if 0.45<n<0.89 then the release is through anomalous diffusion or non fickian diffusion (Swell able & Cylindrical Matrix).
In this Model, a plot of log (Mt/Mα) verses log time was plotted and slope was noted tp explain release pattern.

Drug Excipient Drug Compatability Studies
The drug excipient compatibility studies were carried out by Fourier Transmission Infrared Spectroscopy (FTIR) method, SEM and Differential Scanning Colorimetry

Fourier Transform Infrared Spectroscopy (FTIR)
FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The samples were dispersed in KBr and compressed into disc/pellet by application of pressure. The pellets were placed in the light path for recording the IR spectra. The scanning range was 400-4000 cm^{-1} and the resolution was 1 cm^{-1}.

SEM studies
The surface and shape characteristics of pellets were determined by scanning electron microscopy (SEM) (HITACHI, S-3700N). Photographs were taken and recorded at suitable magnification.

Stability studies
The stability study of the optimized formulation was carried out under different conditions according to ICH guidelines. The optimized microspheres were stored in a stability chamber for stability studies (REMI make). Accelerated Stability studies were carried out at 40 ^{0}C / 75 % RH for the best formulations for 6 months. The microspheres were characterized for the percentage yield, entrapment efficiency & cumulative % drug released during the stability study period.

RESULTS AND DISCUSSION:

Alginate Microspheres of Ropinirole:

Fig. 1: **Ropinirole alginate microspheres**

Alginate microspheres of Ropinirole were formulated by ionic gelation method, using different polymers like sodium alginate, calcium chloride in different concentration and the formulation codes S1, S2, S3, S4, S5, S6, S7, S8, S9, S10, S11, S12, S13 and S14

were prepared. All the formulations were evaluated for their various physical parameters.
Particle size was measured by using optical microscopy. All the formulations S1 to S14 varied from 62.14±0.03µm to 70.02±0.08µm are shown in Table 2.

The bulk densities of all the formulations S1 to S14 were measured and they are ranged from 0.48±0.05g/cc³ to 0.55±0.04g/cc³ are shown in Table 2.

The tapped densities of all the formulations S1 to S14 were measured and they are ranged from 0.58±0.05g/cc³ to 0.66±0.06g/cc³ are shown in Table 2.

The compressibility index values were found to be in the range of 9.18 to 16.89 %. These findings indicated that the all the batches of formulations exhibited good flow properties are shown in Table 2.

Angle of repose of all the formulations was found satisfactory result. The angle of repose of formulation S13 was found to be 23^0. 55±0.02, it is having good flow property are shown in Table 2.

Table 2: Formulated Ropinirole sodium alginate microspheres micromeritic properties:

Formulation code	Particle size (µm)	Bulk density(g/cc³)	Tapped density (g/cc³)	Angle of repose	Carr's index	Swelling index
S1	69.43±0.10	0.50±0.04	0.60±0.03	30˚.48±0.10	12.89%	81%
S2	65.28±0.06	0.54±0.03	0.61±0.03	29 ˚.15±0.07	14.90%	85%
S3	64.21±0.05	0.53±0.03	0.64±0.04	28 ˚.25±0.07	16.89%	91%
S4	70.02±0.08	0.55±0.04	0.66±0.06	29 ˚.55±0.07	11.90%	82%
S5	69.40±0.10	0.53±0.03	0.65±0.06	30 ˚.19±0.10	15.28%	90%
S6	68.15±0.10	0.52±0.01	0.62±0.04	29 ˚.35±0.07	11.21%	83%
S7	66.23±0.07	0.51±0.01	0.65±0.06	27 ˚.75±0.05	13.94%	58%
S8	65.54±0.06	0.55±0.04	0.63±0.04	30 ˚.90±0.10	11.35%	72%
S9	64.30±0.05	0.54±0.03	0.62±0.04	28 ˚.65±0.07	14.65%	75%
S10	69.13±0.10	0.53±0.03	0.60±0.03	29 ˚.93±0.07	15.87%	81%
S11	66.17±0.07	0.52±0.01	0.62±0.04	27 ˚.53±0.05	12.89%	82%
S12	65.23±0.06	0.51±0.01	0.61±0.03	28 ˚.12±0.07	11.87%	60%
S13	62.14±0.03	0.48±0.05	0.58±0.05	23˚.55±0.02	9.18%	97%
S14	68.16±0.10	0.52±0.01	0.60±0.03	26 ˚.85±0.04	12.06%	70%

The percentage swelling obtained from the water uptake studies of the formulations is shown in table. All the formulations S1 to S14 showed the swelling of microspheres. The swelling index of the formulation S13 was found to be 97% are shown in Table 3.

The other formulation S8 to S14 showed better swelling index, and entrapment efficiency. The drug release was very less due to more concentration of sodium alginate and calcium chloride.

The formulation S13 shows the good percentage yield and entrapment efficiency the values were 96.42% and 94.18% with better release profile are shown in Table 3.

Table 3: Percentage drug yield, entrapment efficiency, in vitro cumulative % drug release of alginate Ropinirole microspheres.

Formulation code	Percentage yield (%)	Entrapment efficiency (%)
S1	72.14	85.12
S2	81.98	81.10
S3	72.15	88.47
S4	66.19	76.20
S5	80.16	82.09
S6	79.54	79.18
S7	72.30	74.51
S8	71.59	79.55
S9	82.18	90.15
S10	72.15	74.67
S11	65.34	89.97
S12	70.25	55.18
S13	96.42	94.18
S14	78.16	52.19

***In vitro* drug release studies**: The in vitro drug release study was performed in US Type 2 dissolution apparatus using following conditions. The samples are drawn at the specified time intervals and the absorbance was noted using UV- visible spectrophotometer at 254 nm. The cumulative percentage drug release was calculated. An attempt is being made in designing controlled release dosage form of Ropinirole alginate microspheres. The study began by designing a alginate microsphere using different excipients like sodium alginate and calcium chloride in different concentration. Initially seven formulations were developed S1 to S7 having Ropinirole sodium alginate concentration 0.5 %, to 2%, and calcium chloride concentration 6%. These formulations were evaluated for in vitro release studies in 0.1N HCL. The next seven formulations were developed S8 to S14 having Ropinirole sodium alginate concentration 0.5 % to 2% and calcium chloride concentration 10%. These formulations were evaluated for in vitro drug release studies in 0.1N HCL. The formulations S13 was developed using Ropinirole, sodium alginate in concentration of 1.75% and calcium chloride 10%. Results revealed that the % drug Release of 97.54±5.05% in 12 hours is shown in Table 4 and 5.

Table 4: In vitro cumulative % drug release of Ropinirole sodium alginate microspheres formulations:

Time	S1	S2	S3	S4	S5	S6	S7
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	18.19±0.98	15.26±0.95	16.23±0.96	17.25±0.97	19.12±0.99	12.16±0.93	14.98±0.93
2	28.14±1.39	22.45±1.32	23.67±1.33	26.19±1.36	25.89±1.35	20.18±1.29	29.67±1.40
4	32.15±2.01	38.96±2.40	35.29±2.05	33.67±2.02	30.16±2.08	38.45±2.40	42.03±2.46
6	55.21±2.87	54.67±2.88	48.98±2.65	52.19±2.84	56.89±2.90	49.67±2.68	59.45±2.96
8	65.45±3.15	75.67±3.81	70.12±3.80	69.89±3.21	65.15±3.15	68.98±3.20	71.65±3.83
10	78.67±3.94	80.12±4.55	82.16±4.58	79.67±3.95	75.19±3.81	71.12±3.83	82.13±4.58
12	88.45±4.92	90.22±5.00	92.12±5.02	91.60±5.01	89.14±4.99	93.67±5.03	90.12±5.01

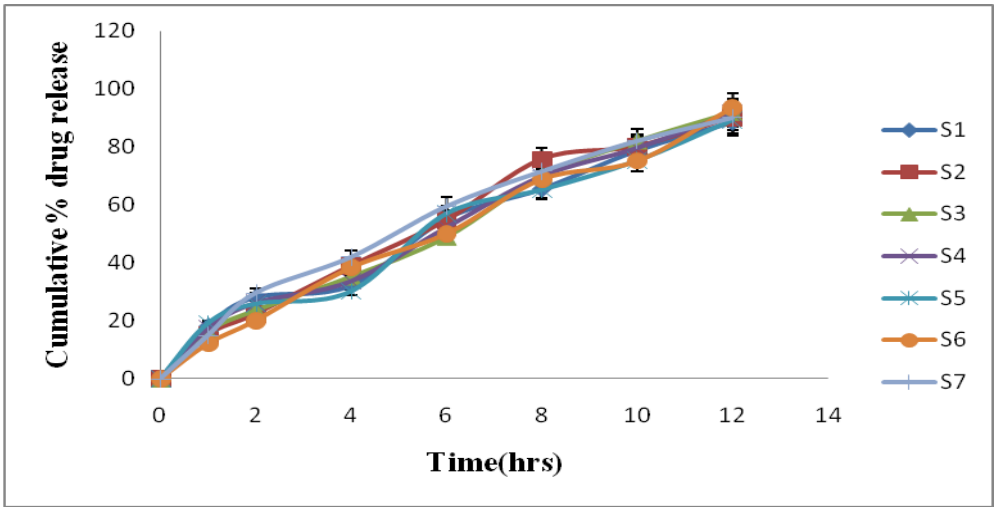

Fig. 2: In vitro cumulative % drug release of Ropinirole sodium alginate microspheres formulation

Table 5: In vitro cumulative % drug Ropinirole sodium alginate release of microspheres formulation:

Time	S8	S9	S10	S11	S12	S13	S14	Marketed Product
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	16.32±0.96	17.65±0.97	13.67±0.92	15.23±0.95	18.15±0.98	20.15±1.28	19.62±0.99	11.45±0.89
2	20.18±1.28	33.18±2.02	22.18±1.32	23.24±1.33	35.18±2.15	32.16±2.10	25.98±1.35	22.45±1.32
4	35.67±2.26	44.67±2.50	35.67±2.15	34.22±2.24	48.16±2.74	49.99±2.75	33.67±2.02	33.65±2.19
6	63.89±3.15	61.29±3.11	55.63±2.38	51.93±2.35	58.19±2.95	65.69±3.15	59.45±2.96	42.16±2.48
8	70.97±3.28	75.89±3.83	72.18±3.82	76.31±3.82	69.45±3.25	78.36±3.94	75.66±3.81	58.92±2.95
10	80.12±4.55	86.33±4.69	85.67±4.68	83.16±4.59	81.26±4.90	89.12±4.99	82.14±4.58	70.15±3.79
12	89.99±4.99	90.12±5.00	93.64±5.03	91.89±5.01	94.67±5.04	97.54±5.05	92.15±5.01	90.16±5.00

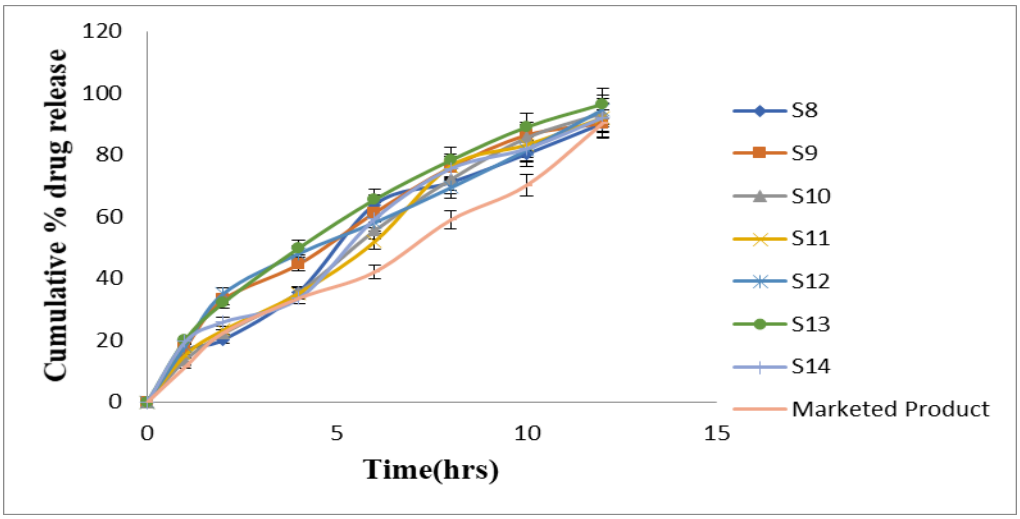

Fig. 3: In vitro cumulative % drug Ropinirole sodium alginate release of microspheres formulations

Mathematical modeling of ropinirole optimized alginate microspheres and marketed product:

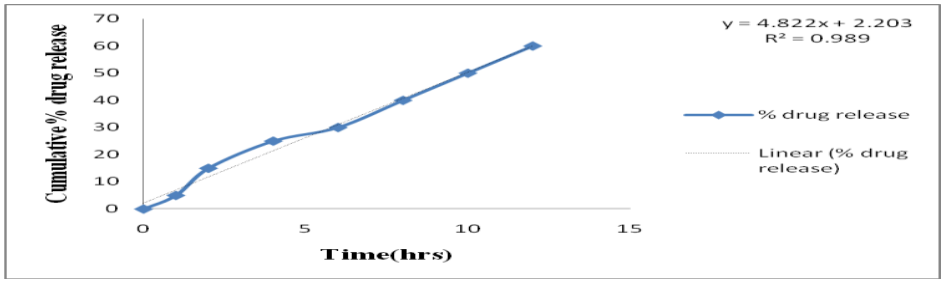

Fig. 4: Zero order plot for the optimized formulation of Ropinirole alginate micropsheres S13

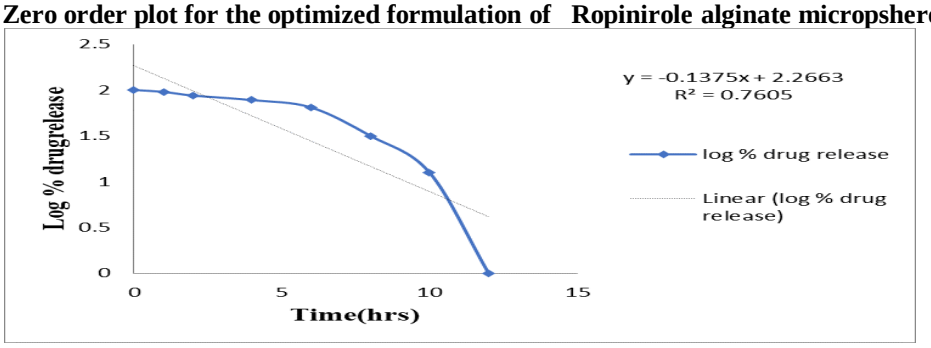

Fig. 5: First order plot for the optimized formulation of Ropinirole alginate microspheres S13

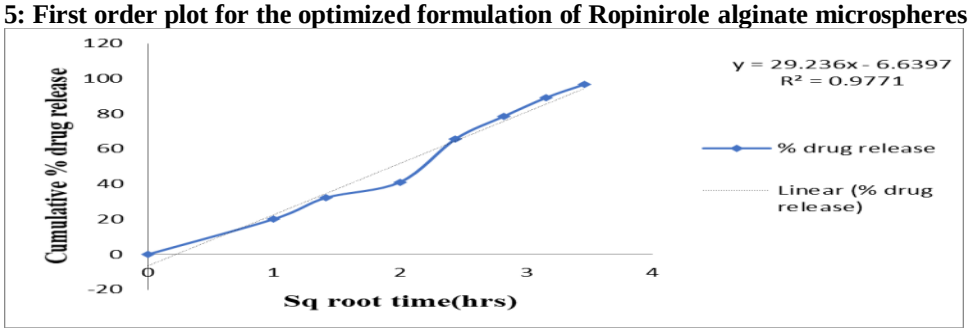

Fig. 6: Higuchi plot for the optimized formulation of Ropinirole alginate microspheres S13

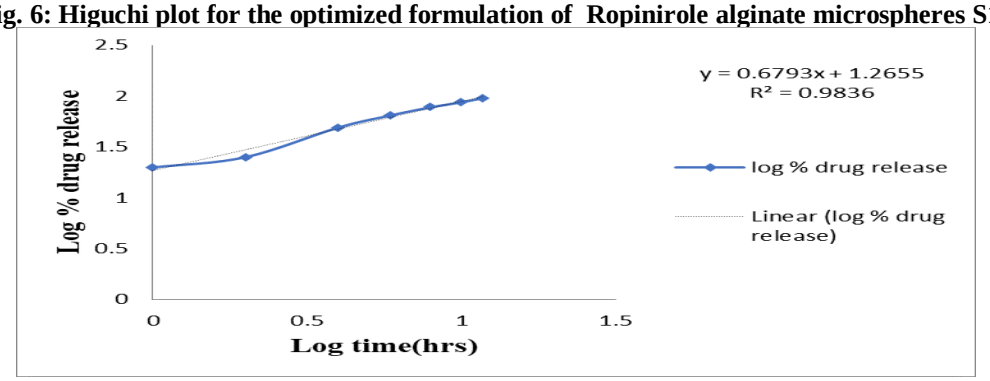

Fig. 7: Korsmeyer-peppas plot for the optimimized Ropinirole alginate microspheres S13
Marketed Product

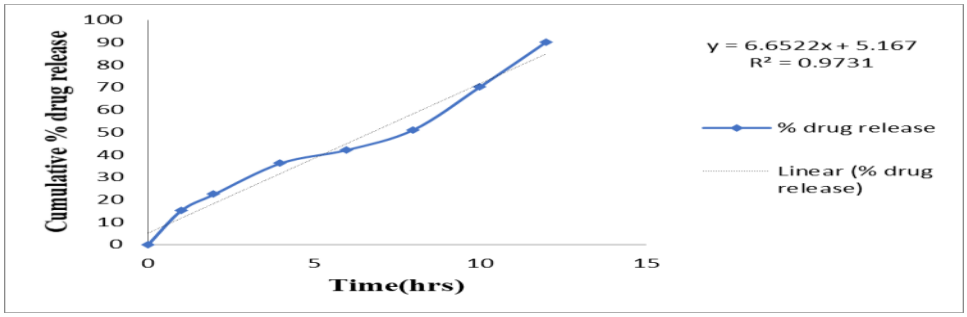

Fig. 8 : Zero order plot for the Marketed Product

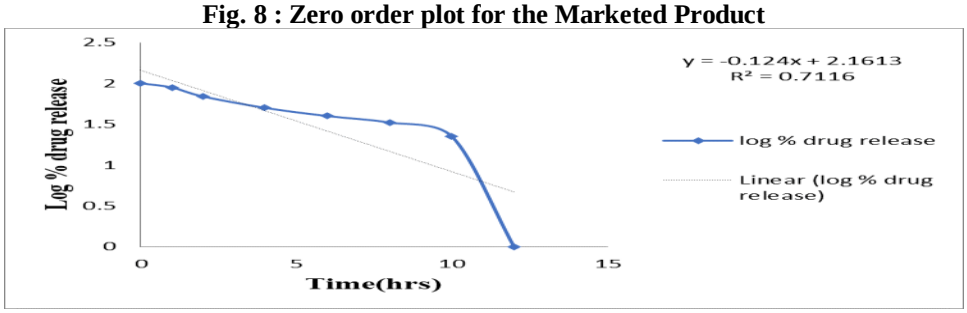

Fig. 9 : First order plot for the Marketed Product

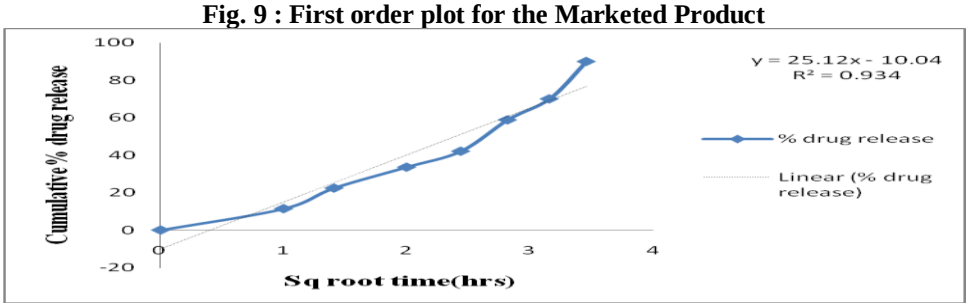

Fig. 10 : Higuchi plot for the Marketed Product

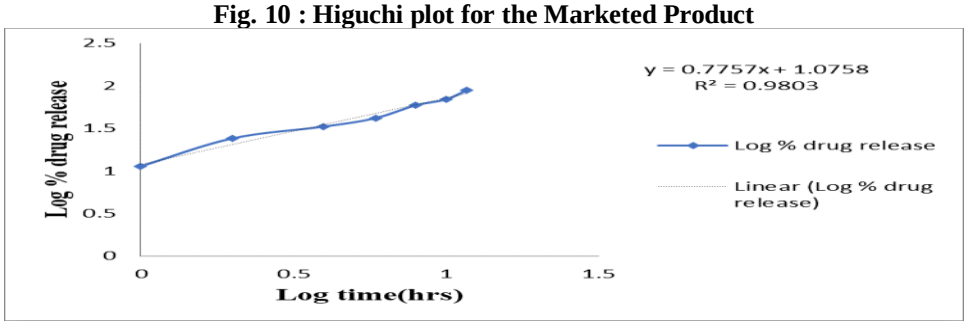

Fig. 11 : Korsmeyer-peppas plot for the Marketed Product

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.989 indicates that the drug release follows a zero-order mechanism. This data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics.

Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsmeyer plots.

The mass transfer with respect to square root of the time has been plotted, revealed a linear graph with regression value close to one i.e. 0.9771 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer plots i.e. 0.679 suggest that the drug release from microspheres was anomalous Non Fickian diffusion are shown in Table 6. The plots of optimized formulation and marketed product are shown in Figure 4-7 and 8-11 respectively.

Table 6: Release order kinetics of optimized alginate microspheres (S13) and marketed product

Formulation Code	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	R^2	K	R^2	K	R^2	K	R^2	N
S13	0.9894	4.8226	0.7605	0.1375	0.9771	29.236	0.9836	0.6793
Marketed Product	0.9731	6.6522	0.7116	0.124	0.9344	25.127	0.9803	0.7757

Drug Excipient Compatibility Studies

Fourier Transform Infrared Spectroscopy (FTIR)

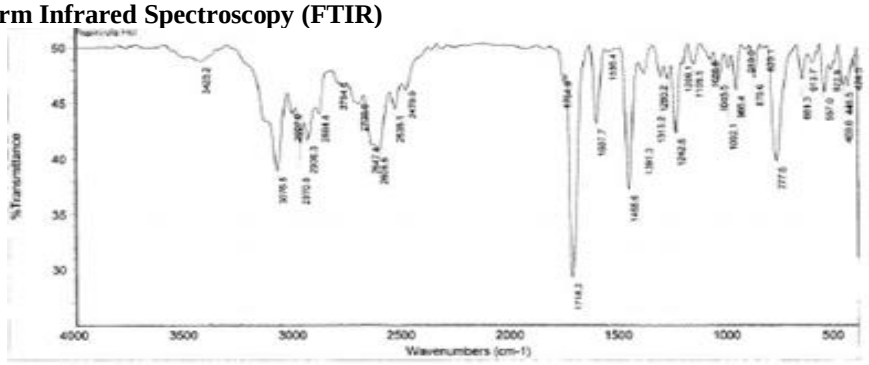

Fig. 12: FT-IR spectra of Ropinirole hydrochloride pure drug

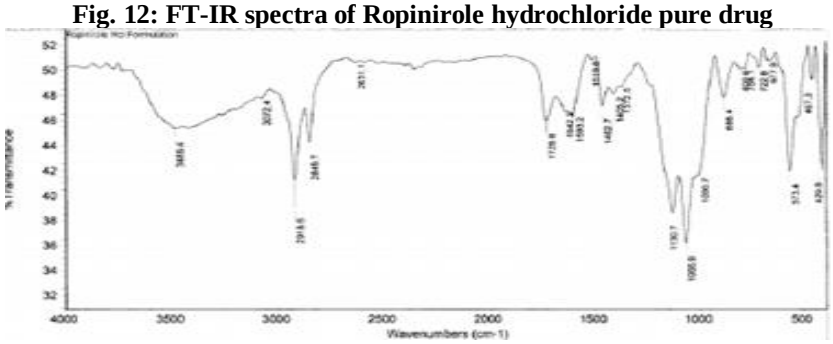

Fig. 13: FT-IR spectra Ropinirole optimized formulation (S13)

The major peaks obtained in the FT-IR studies of pure drug Ropinirole hydrochloride like –NH, -C=O, -C=C stretching's were remained unchanged when mixed with the polymers and in the formulation.

Overall there was no alteration in peaks of Ropinirole pure drug **(Figure 12)** and optimized formulation **(Figure 13)**, suggesting that there was no interaction between drug and excipients. There is additional peaks appeared or disappeared hence no significant changes in peaks of optimized formulation was observed when compared to pure drug indicating absence of any interaction

SEM of Ropinirole microspheres

The external and internal morphology of controlled release microspheres were studied by Scanning Electron Microscopy.

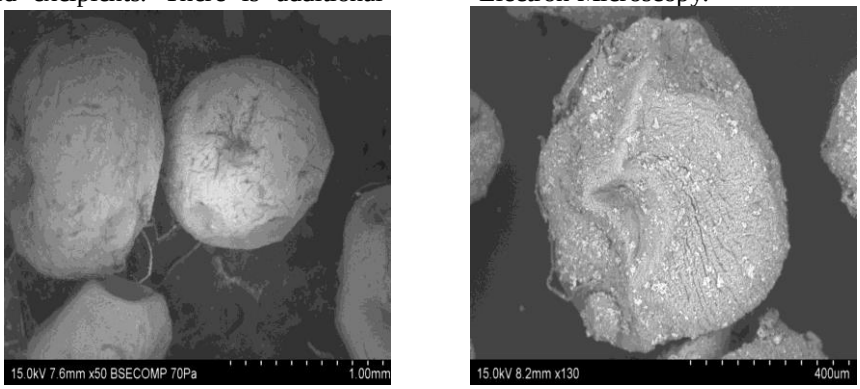

Fig. 14: Scanning electron micrographs of Ropinirole microspheres

Table 7 : Stability studies of optimized alginate microspheres

Retest Time for Optimized formulation	Percentage yield (%)	Entrapment efficiency (%)	*In-vitro* drug release profile (%)
0 days	96.42	94.18	97.54
30 days	95.18	92.15	94.18
60 days	94.70	91.58	93.02
120 days	92.15	90.60	92.18
180 days	91.32	90.02	91.40

Morphology of the various formulations of Ropinirole microspheres prepared was found to be discrete and spherical in shape (Figure 14). The surface of the Ropinirole microspheres was rough due to higher concentration of drug uniformly dispersed at the molecular level in the sodium alginate matrices. There are no crystals on surface which states that is drug is uniformly distributed.

Stability studies:

Optimized formulation was selected for stability studies based on high cumulative % drug release. Stability studies were conducted for 6 months according to ICH guidelines. From these results it was concluded that, optimized formulation is stable and retained their original properties with minor differences which depicted in Table 7.

CONCLUSION:

The prepared microspheres were found to be discrete, spherical with free-flowing properties. These microspheres were prepared by ionotropic gelation technique for oral delivery in the treatment of Parkinson's disease. The flow properties of all the formulations were found out by measuring the Angle of repose, Compressibility index and Hausner's ratio. The microspheres were prepared by ionotropic gelation method using different polymers like sodium alginate, calcium chloride, and Eudragit RS100etc. All formulations were evaluated for their various physical parameters. Particle size was measured by using optical microscopy. All the formulations S1 to S14 varied from 62.14±0.03µm to 70.02±0.10µm. The bulk density of all the formulations S1 to S14 was measured and they are ranged from 0.48±0.05g/cc³ to 0.55±0.04g/cc³. The compressibility index values were found to be in the range of 9.18 % to16.89 %. These findings indicated that the all batches of formulation exhibited good flow properties. Angle of repose of all the formulations was found satisfactory result. The percentage swelling obtained from the water uptake studies of the formulations. All the formulations S1 to S14 showed the swelling of microspheres. The swelling index of the formulation S13 was found to be 97%. The formulation S13 shows the good percentage yield and entrapment efficiency the values were 94.18% and 96.42% with better release profile.

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