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Development and Evaluation of Sustained Release Floating Microspheres Containing Ropinirole HCl

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ABSTRACT

Current investigation was to develop gastro retentive floating microsphere for Ropinirole. These microspheres of Ropinirole were prepared by ionic gelation method with an aim of increasing the gastric residence time and for controlled release. Sodium alginate, HPMCK15, Gaur gum was used as polymers. Sodium bicarbonate was used as the gas-forming gent. Prepared microspheres were characterized for micromeretic properties, entrapment efficiency, buoyancy study, SEM analysis, FTIR, *and in vitro* dissolution studies. Among 14 formulations F12 was found to be optimized and based on the evaluation parameters. The % buoyancy, % yield, % entrapment efficiency and swelling index of F12 formulation was 94.50, 97.58, 98.10% and 96.14%, respectively. The Cumulative % drug release of F12 formulation was 98.16 ± 5.15 in 12 h when compared with marketed product 90.16 ± 5.00 in 12 h. SEM studies showed the particles were in spherical shape. Hence the formulated floating Ropinirole microspheres may establish to be potential candidate for safe and effective sustained drug delivery and improve the bioavailability in the effective management of Parkinson's disease.

Keywords: Floating microspheres, Gaur Gum, HPMC K15M, Sodium bicarbonate, SEM, *in vitro* diffusion studies.

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INTRODUCTION

To avoid the unnecessarily frequent administration, higher cost of therapy and other undesired features of release
preparations have been designed. [1] However, these systems have been of limited success in the case of drugs with a poor absorption window throughout the GIT. This has led to the development of gastro retentive dosage forms. Various approaches have been pursued over the last three decades to increase the retention of oral dosage forms in the stomach. The most common gastro retentive approaches used to increase the gastric residence time of pharmaceutical dosage forms include floating systems, swelling systems, bio/mucoadhesive

systems and high density systems. Floating dosage forms are the more reliable and commonly used gastro retentive dosage forms. [2]

FDDS have a lower density than gastric fluids and thus remain buoyant in the stomach, without affecting the gastric emptying rate for a prolonged period. While the systems are floating, the drug is released slowly from the system at a desired rate. Floating microspheres are one of the gastro retentive dosage forms that float over gastric contents due to their buoyancy and remain in the stomach for prolonged period. Suitable drugs that can be used in gastro retentive system include:

1) Drugs with narrow absorption window in the stomach.

2) Drugs locally acting in the stomach

3) Drugs which are unstable in intestinal and colonic environment

The floating system is very useful for drugs that are poorly soluble and unstable in the stomach. Floating systems are hydro dynamically balanced low-density system. Gastric retention of floating drug delivery system increases the bioavailability and therapeutic benefit of the dosage form. [3]

The Ropinirole Hydrochloride is a non-ergoline dopamine agonist with high relative specificity and full intrinsic activity at the D2 and D3 dopamine receptor subtypes. This action in humans correlates with treatment for Parkinson's disease due to stimulation of postsynaptic dopamine D2-type receptors. Ropinirole Hydrochloride after oral administration shows a lesser bioavailability up to 55% and biological half-life of 4 to 6 hours. [4] 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 hours), 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. [5]

MATERIALS AND METHODS

Materials

Ropinirole procured from Hetero Drugs Ltd, Hyderabad. Sodium alginate from Pruthvi Chemicals, Mumbai. Calcium chloride from SD Fine ltd, Mumbai. Sodium bicarbonate was purchased from Karthikeya Chemicals, Hyderabad. Gaur Gum and HPMC are from Nutriroma, Hyderabad.

Formulation of Ropinirole Floating microspheres

Floating microspheres of Ropinirole were prepared by ionic gelation technique using different proportion of polymers as shown in Table 1. A solution of sodium alginate solution is prepared weighed quantity of drug and HPMC K15 was triturated to form fine powder, and then added to above solution. Sodium bicarbonate, a gas forming agent was added to this mixture. Resultant solution was extruded drop wise with the help of syringe and needle into 100 ml 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 -2 hours in a hot air oven and stored in desiccator. [6]

Evaluation of Ropinirole Floating Microspheres

Microsphere size determination

Determination of average particle size of floating microspheres was carried out by optical microscope in which objective micrometer and ocular micrometer was employed. From each batch 100 floating microspheres were spread on a clean slide and size was compared with the ocular micrometer readings. [7]

Micromeritic Properties

Micromeritic properties were evaluated according to the standard procedure reported. [8]

Swelling index

Swelling index was determined by measuring the extent of swelling of microspheres in the given medium. Exactly weighed number of microspheres was allowed to 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° for 5 h until there was no change in the dried mass of sample. The swelling index of the microsphere was calculated by using the formula. [9]

Swelling index = (Mass of swollen microspheres – Mass of dry microspheres / Mass of dried microspheres) 100

Drug entrapment efficiency

To calculate the entrapment efficiency % (EE), 10 mg prepared microspheres were dissolved in 2 ml DCM and diluted up to 10 ml with distilled water. This solution was subjected to centrifugation at 1000 rpm. Supernatant was filtered through 0.45µm filter. The absorbances of these solutions was noted using ultraviolet (UV) spectrophotometric method at λ max 250 nm and the %EE was calculated using the following equation. [10]

Drug entrapment efficiency = Experimental drug content × 100 Theoretical drug contents

In vitro drug release studies

Release rate of drug from Floating microspheres was carried out using USP type II dissolution apparatus with 0.1N HCl (pH 1.2) of 900 ml as dissolution medium and at 37 ± 0.5°C by using USP dissolution apparatus II (Paddle type). Accurately weighed amount of microspheres from each batch were subjected to dissolution studies in triplicate manner. At appropriate intervals up to 12 h, specific volume of aliquots was withdrawn and analyzed spectrophotometrically at 250 nm. The withdrawn volume was replaced with an equivalent volume of fresh dissolution medium to maintain the volume of dissolution medium constant. The sample solutions were analyzed for the concentration of drug by UV spectrophotometer at 250 nm. The amount of drug released was calculated from the calibration curve of the same dissolution medium. [10]

Table 1: Formulation trials of Ropinirole Floating microspheres

Formulation code	Ropinirole (mg)	Sodium alginate	HPMCK15 (mg)	Sodium bi carbonate (mg)	Calcium chloride	Gaur Gum (mg)
F1	1	1%	25	25	1%	0.25
F2	1	1. 2%	50	50	1%	0.5
F3	1	1.4 %	75	75	1%	0.75
F4	1	1.6%	100	100	1%	1
F5	1	1.8 %	150	125	1%	1.25
F6	1	2.%	175	150	1%	1.75
F7	1	2.2%	200	175	1%	2
F8	1	1%	150	25	1%	0.25
F9	1	1. 2%	200	50	1%	0.5
F10	1	1.4%	250	75	1%	0.75
F11	1	1.6%	300	100	1%	1
F12	1	1.8%	400	125	1%	1.25
F13	1	2%	325	150	1%	1.75
F14	1	2.2%	350	175	1%	2

Table 2: Micromeretic properties of Ropinirole floating microspheres

Formulation code	Particle size (µm)	Bulk density g/cc³	Tapped density g/cc³	Angle of repose	Carr's index (%)	Buoyancy%
F1	72.02 ± 0.01	0.62 ± 0.02	0.70 ± 0.01	26˚.96 ± 0.05	11.60	84.20
F2	70.04 ± 0.01	0.58 ± 0.09	0.71 ± 0.88	31 ˚.45 ± 0.02	12.25	81.20
F3	77.69 ± 0.06	0.57 ± 0.08	0.69 ± 0.09	27 ˚.72 ± 0.05	14.56	75.48
F4	75.25 ± 0.04	0.61 ± 0.01	0.66 ± 0.08	25 ˚.03 ± 0.05	12.35	93.65
F5	72.56 ± 0.01	0.59 ± 0.10	0.68 ± 0.09	30 ˚.04 ± 0.01	13.99	72.54
F6	73.65 ± 0.04	0.60 ± 0.01	0.65 ± 0.08	28 ˚.54 ± 0.06	15.02	75.80
F7	75.23 ± 0.04	0.59 ± 0.09	0.71 ± 0.01	27 ˚.91 ± 0.05	12.12	76.40
F8	71.11 ± 0.01	0.58 ± 0.09	0.69 ± 0.09	30 ˚.54 ± 0.01	11.94	85.31
F9	72.68 ± 0.01	0.56 ± 0.08	0.70 ± 0.01	31 ˚.25 ± 0.01	13.56	92.21
F10	79.45 ± 0.08	0.57 ± 0.08	0.68 ± 0.09	29 ˚.67 ± 0.08	12.04	87.11
F11	77.56 ± 0.06	0.60 ± 0.01	0.67 ± 0.08	28 ˚.58 ± 0.06	14.54	89.40
F12	68.12 ± 0.07	0.54 ± 0.06	0.62 ± 0.01	21 ˚.01 ± 0.01	10.09	94.50
F13	74.66 ± 0.04	0.58 ± 0.09	0.66 ± 0.08	27 ˚.44 ± 0.05	13.25	92.22
F14	75.21 ± 0.04	0.59 ± 0.09	0.65 ± 0.08	26 ˚.06 ± 0.05	11.45	80.15

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

Formulation code	Percentage Yield	Entrapment Efficiency (%)	Swelling index
F1	87.18	85.46	88.14
F2	89.46	86.32	84.29
F3	90.90	88.19	86.14
F4	78.03	90.23	87.29
F5	81.24	85.62	88.59
F6	82.36	89.18	83.27
F7	87.97	77.06	84.56
F8	80.26	81.27	81.29
F9	79.18	79.54	77.67
F10	80.12	78.19	76.32
F11	88.12	84.26	87.63
F12	97.58	98.10	96.14
F13	90.35	92.45	88.12
F14	92.14	93.67	78.25

Percentage buoyancy of Ropinirole Floating Microspheres

Buoyancy percentage: Microparticles were spread over the surface of a USP dissolution apparatus (type II) filled with 900 ml of simulated gastric fluid (0.1 N HCl) at 37°C. The medium was agitated with a paddle rotating at 100 rpm for 12 hours. The floating and the settled portion of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microspheres that remained floating and the total mass of the microspheres. [11]

$$\% \text{ Buoyancy} = \frac{\text{Microsphere remained floating} \times 100}{\text{Total mass of microspheres}}$$

Kinetic modeling of drug release

To understand the kinetics and mechanism of drug release, the result of the in vitro dissolution study of floating microspheres were fitted with various kinetic equations like Zero order as cumulative percentage released 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. [11]

Drug Excipients Compatibility Studies

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier Transform Infrared Spectrometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The IR spectrum of the samples was prepared using KBR (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons. [12]

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. [13]

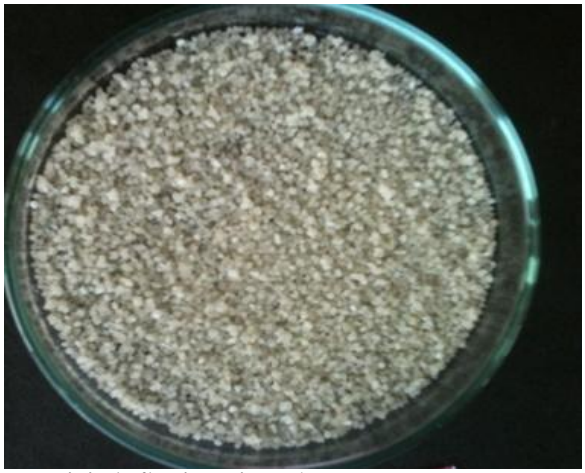

Fig. 1: Ropinirole floating microspheres

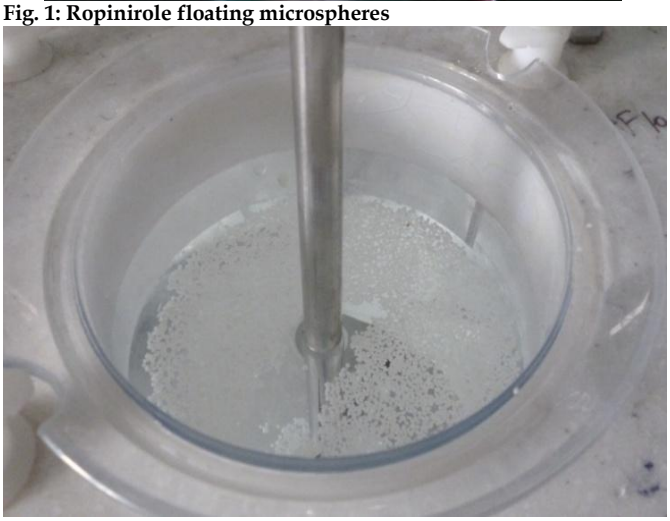

Fig. 2: *In vitro* buoyancy study of Ropinirole floating microspheres (F12)

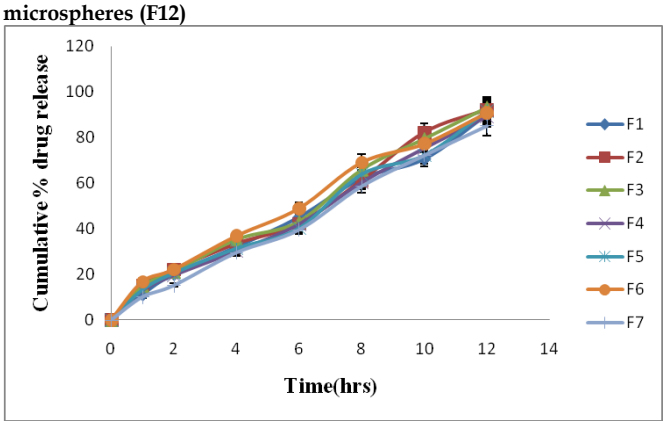

Fig. 3: *In vitro* cumulative % drug release of Ropinirole floting microspheres

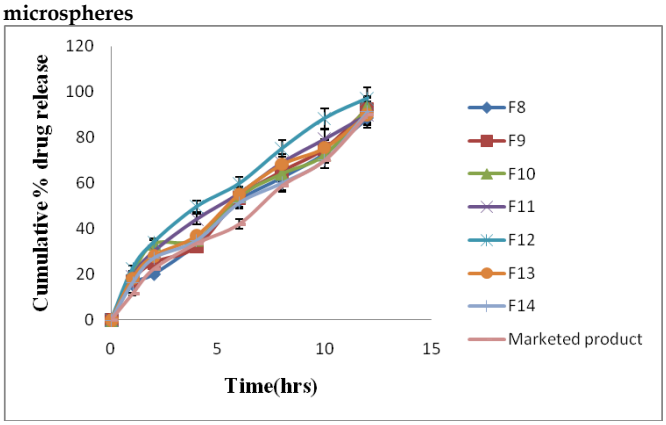

Fig. 4: *In vitro* cumulative % drug release of Ropinirole floating microspheres

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°C / 75% RH for the best formulations for 6 months. The microspheres were characterized for the percentage yield, entrapment efficiency and cumulative % drug released during the stability study period.

RESULTS AND DISCUSSION

Formulation of Ropinirole Floating microspheres

Floating microspheres of Ropinirole were formulated by ionic gelation method, using different polymers like sodium alginate, HPMC K15M, sodium bicarbonate, Gaur gum, calcium chloride in different concentration and the formulation codes F1 - F14 were prepared and shown in Table 1 and Figure 1. All the formulations were evaluated for their various micromeritic properties, physical parameters are shown in Table 2.

Particle size was measured by using optical microscopy. All the formulations F1 to F14 varied from 68.12 ± 0.07µm to 79.45 ± 0.08µm.

The bulk densities of all the formulations F1 to F14 were measured and they are ranged from 0.54 ± 0.06g/cc³ to 0.62 ± 0.02g/cc³.

The tapped densities of all the formulations F1 to F14 were measured and they are ranged from 0.62 ± 0.01g/cc³ to 0.71 ± 0.88g/cc³.

The compressibility index values were found to be in the range of 10.09 to 14.54%. These findings indicated that the all the batches of formulations exhibited good flow properties.

Angle of repose of all the formulations was found satisfactory result. And the formulation F12 was found to be 21 ˚.01.

In vitro buoyancy studies of floating microspheres

Buoyancy was determined by the weight ratio of the floating microspheres to the sum of floating and sinking microspheres after 12 hours in 0.1N HCl is shown in Figure 2.

All the 14 formulations of floating microspheres were exposed to buoyancy test. The formulation F12 shows the buoyancy of 94.50% and shown in Table 2.

The entrapment efficiency values of all the 14 formulations were ranged from 77 to 98.10%. The formulation F12 shown highest entrapment efficiency of 98.10 when compare with other formulations.

In vitro drug release studies

The *in vitro* drug release from the prepared microspheres was studied (F1- F14) and showed in the Table 4 & 5 and Figure 3 & 4. The drug release from the microspheres was found to decrease with increase in the polymer concentration. Among all the formulations F12 showed maximum drug release of 98.16 ± 5.15% within 12 h.

Table 4: *In vitro* cumulative % drug release of Ropinirole floting microspheres

Time	F1	F2	F3	F4	F5	F6	F7
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
1	11.26 ± 0.92	15.18 ± 0.94	14.96 ± 0.93	12.90 ± 0.93	13.22 ± 0.94	16.84 ± 0.96	10.16 ± 0.89
2	20.15 ± 1.29	22.15 ± 1.32	21.16 ± 1.31	19.56 ± 0.99	20.55 ± 1.29	22.18 ± 1.32	15.18 ± 0.94
4	32.15 ± 2.01	33.45 ± 2.02	35.28 ± 2.05	30.18 ± 2.08	31.40 ± 2.09	36.89 ± 2.06	29.60 ± 1.40
6	45.16 ± 2.48	42.18 ± 2.46	43.18 ± 2.47	41.96 ± 2.45	40.29 ± 2.44	48.99 ± 2.65	39.60 ± 2.47
8	62.18 ± 3.10	61.15 ± 3.09	65.90 ± 3.15	60.19 ± 2.97	63.90 ± 3.10	69.12 ± 3.21	58.67 ± 2.95
10	70.69 ± 3.82	82.15 ± 4.58	79.45 ± 3.95	75.22 ± 3.81	72.19 ± 3.82	77.25 ± 3.93	72.19 ± 3.82
12	90.15 ± 5.01	92.16 ± 5.02	93.16 ± 5.03	89.16 ± 4.99	91.60 ± 5.01	90.88 ± 5.00	85.14 ± 4.98

Table 5: *In vitro* cumulative % drug release of Ropinirole floating microspheres formulation

Time	F8	F9	F10	F11	F12	F13	F14	Marketed
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
1	15.60 ± 0.95	17.20 ± 0.97	20.15 ± 1.01	19.12 ± 0.99	22.56 ± 1.32	18.24 ± 0.98	16.22 ± 0.96	11.45 ± 0.89
2	20.18 ± 1.29	25.19 ± 1.35	33.45 ± 2.02	30.15 ± 2.08	34.18 ± 2.04	28.16 ± 1.39	27.19 ± 1.37	22.45 ± 1.32
4	33.45 ± 2.02	32.15 ± 2.01	35.18 ± 2.05	44.25 ± 2.48	49.67 ± 2.68	36.98 ± 2.06	34.90 ± 2.03	33.65 ± 2.19
6	52.30 ± 2.84	53.64 ± 2.87	54.16 ± 2.88	55.61 ± 2.87	59.84 ± 2.96	55.18 ± 2.89	51.40 ± 2.85	42.16 ± 2.48
8	62.55 ± 3.09	65.12 ± 3.15	64.12 ± 3.12	69.12 ± 3.21	75.18 ± 3.81	68.16 ± 3.20	60.11 ± 2.97	58.92 ± 2.95
10	73.18 ± 3.85	75.18 ± 3.81	72.44 ± 3.82	79.45 ± 3.95	88.45 ± 4.98	75.45 ± 3.81	70.21 ± 3.82	70.15 ± 3.79
12	88.61 ± 4.98	92.55 ± 5.02	93.45 ± 5.03	90.12 ± 5.01	98.16 ± 5.15	89.99 ± 4.99	91.24 ± 5.01	90.16 ± 5.00

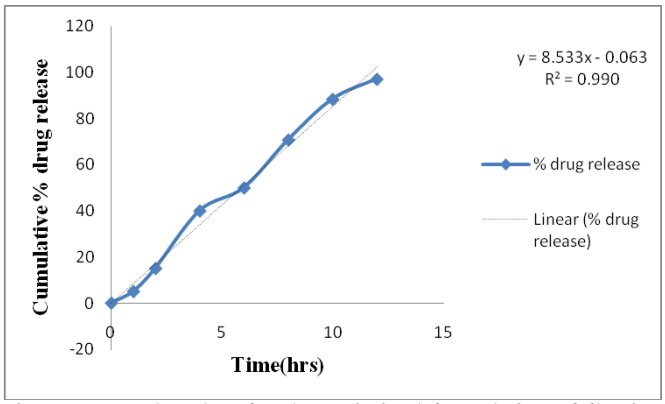

Fig. 5: Zero order plots for the optimized formulation of floating microspheres F12

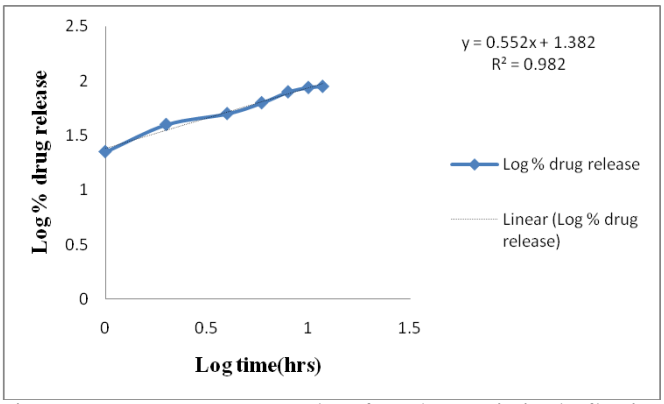

Fig. 8: Korsmeyer-Peppas plot for the optimized floating microspheres formulation F12

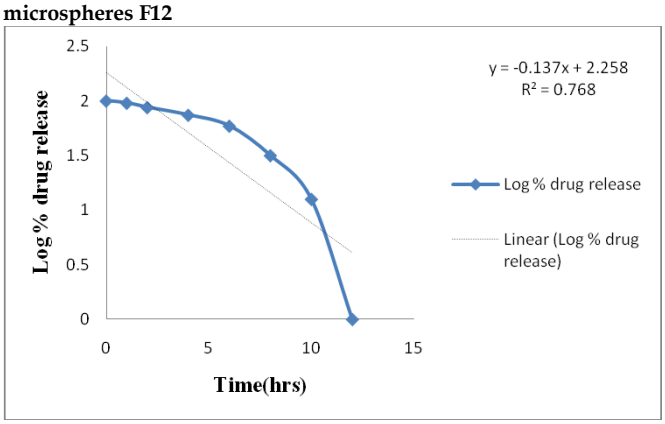

Fig. 6: First order plot for the optimized formulation of floating microspheres F12

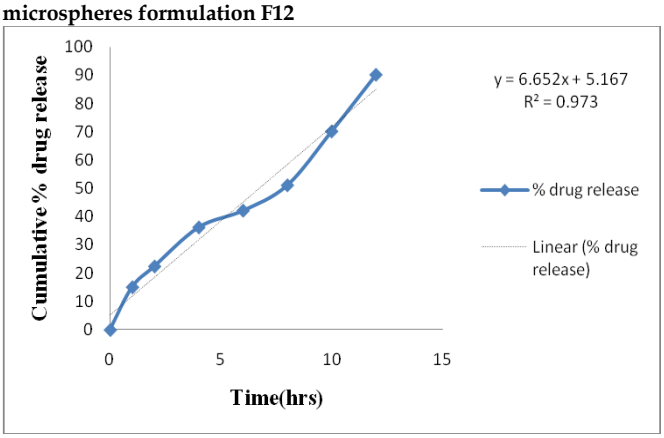

Fig. 9 : Zero order plot for the Marketed Product

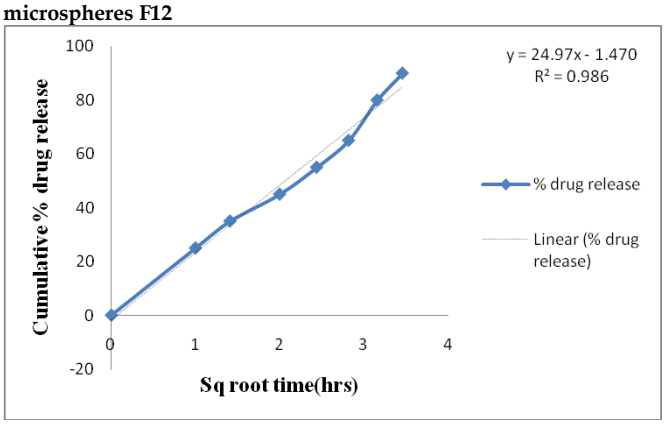

Fig. 7: Higuchi plot for the optimized floating microspheres formulation F12

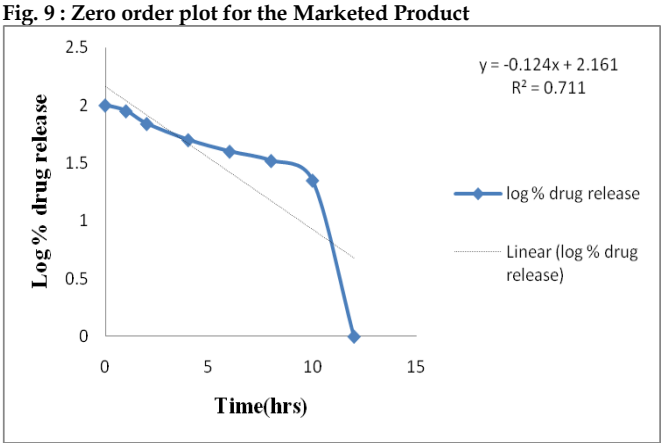

Fig. 10: First order plot for the Marketed Product

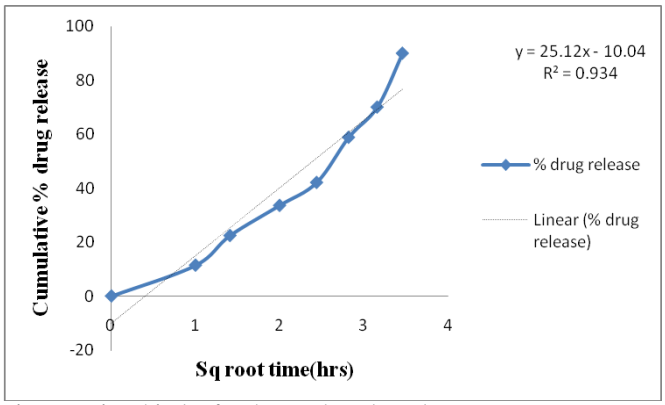

Fig. 11 : Higuchi plot for the Marketed Product

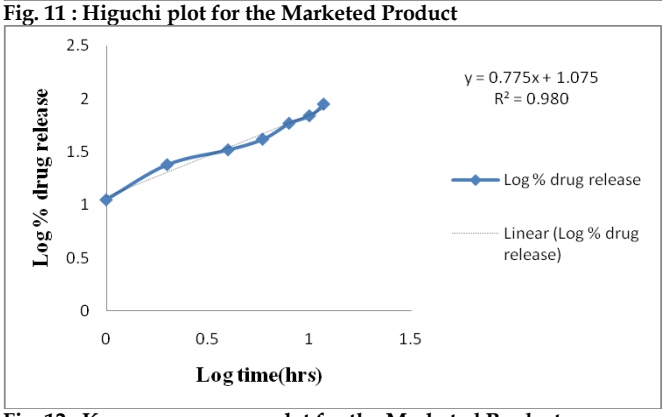

Fig. 12 : Korsmeyer-peppas plot for the Marketed Product

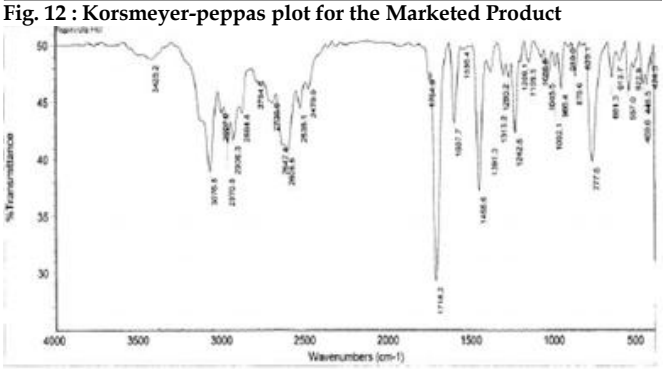

Fig. 13. FT-IR spectra of Ropinirole hydrochloride pure drug

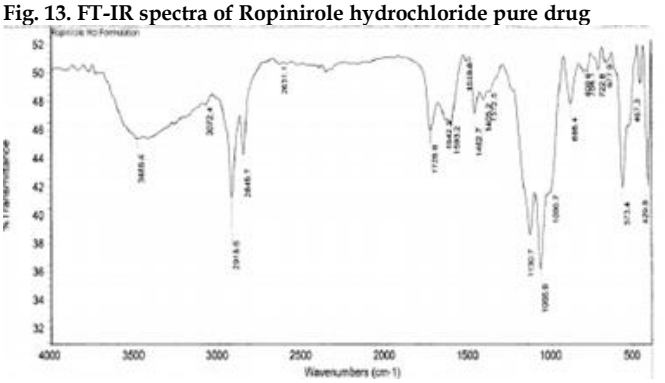

Fig. 14. FT-IR spectra Ropinirole optimized formulation (F12)

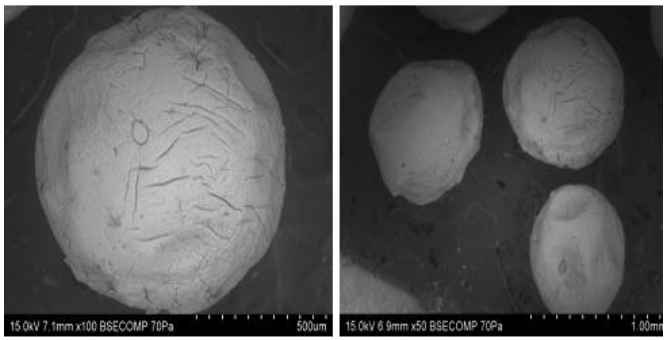

Fig. 15: Scanning electron micrographs of Ropinirole microspheres

Kinetic modeling of drug release

From the above results it is apparent that the regression coefficient value of optimized formulation F12 was closer to unity in case of zero order plot i.e.0.9902 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.

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. 0.986 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer plots i.e. 0.552 suggest that the drug release from floating tablet was anomalous Non fickian diffusion and shown in Table 6 and Figures 5, 6, 7, 8.

Drug Excipient Compatibility Studies

FT-IR

Overall there was no alteration in peaks of Ropinirole pure drug and optimized formulation, suggesting that there was no interaction between drug & excipients and shown in Figures13 and 14.

Scanning Electron Microscopy

The external and internal morphology of controlled release microspheres were studied by Scanning Electron Microscopy are shown in Figure 15.

Stability studies

Optimized formulation was selected for stability studies based on percentage yield, entrapment efficiency and 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.

Table 6: Release order kinetics of optimized formulation of floating microspheres F12

Formul. Code	Zero Order		First Order		Higuchi		Korsmeyer Peppas	
	R^2	K	R^2	K	R^2	K	R^2	N
F12	0.9902	8.533	0.768	0.137	0.98	24.97	0.98	0.55
Marketed	0.9731	6.6522	0.7116	0.124	0.9344	25.1027	0.9803	0.5757

Table 7: Stability studies of optimized Floating Microspheres

Retest Time for Optimized formulation	Percentage yield	Entrapment efficiency	*In-vitro* drug release profile (%)
0 days	96.10	96.30	98.16
30 days	95.40	95.4	95.20
60 days	94.22	94.53	94.33
120 days	93.13	93.55	93.68
180 days	92.34	92.22	92.45

Ropinirole loaded floating microspheres were prepared by ionotropic gelation method. From the results it concluded that formulation F14 was found to be satisfactory results in terms of excellent Micromeretic properties, particle size (68.12 ± 0.07µm), yield of

microsphere (97.58%), Entrapment efficiency (98.10%), % buoyancy (94.50%), swelling index (96.14%) and highest *in vitro* drug release of 98.16 ± 5.15% in a sustained manner with constant fashion over extended period for 12 h compared with marketed product 90.16 ± 5.00 in 12 h. The drug and excipients were compatible studied by using FTIR. Drug release from Ropinirole microspheres followed Zero order and Higuchi model. It was suggested that mechanism of drug release from microspheres was diffusion controlled. The prepared microspheres were spherical in shape studied by SEM studies. The optimized formulation F12 was stable. Hence the formulated and prepared floating Ropinirole microspheres may establish to be potential candidate for safe and effective sustained drug delivery and improve the bioavailability.

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