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Preparation and Evaluation of Floating Microspheres of Pramipexole HCL

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ABSTRACT

The present study was to formulate and characterize oral floating microspheres of Pramipexole to sustain the gastric residence time and to target gastritis. The floating microspheres were prepared by ionotropic gelation technique. Sodium alginate was used as polymer, sodium bicarbonate as gas generating agent, calcium chloride as cross-linking agent, HPMC K4, as rate retarding agent. Microspheres were characterized for the Micromeretic properties, incorporation efficiency, buoyancy test, SEM analysis, FTIR, *and in vitro* diffusion studies. The diffusion studies were carried out in 0.1N HCl and the results were applied to various kinetic models. Among the total 14 formulations F12 was found to be optimized on the basis of different evaluation parameters. The % yield of F12 formulation was found to be 98.58%. On the basis of optical microscopy, the particle size was 65.12±0.04µm. The % buoyancy, % entrapment efficiency and swelling index of F12 formulation was 98.12%, 96.56% and 97.10, respectively. The Cumulative % drug release of F12 formulation was 98.3±5.10% in 12h. SEM studies showed the particles were in spherical shape. On the basis of obtained results, Floating microspheres were of good candidate for targeting to GIT.

Keywords: Pramipexole, floating microspheres, SEM, Ionotropic gelation technique, Parkinson's disease.

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INTRODUCTION

Among the different routes of drug administration, the oral route has achieved the most attention, partly due to the ease of administration and to the important flexibility in dosage form design. Most drugs are well absorbed throughout the entire intestinal tract, but some compounds, usually those that are polar in nature, are poorly absorbed from the large intestine. For such drugs, the main area from which absorption occurs is the small intestine. Gastric emptying of dosage forms is an extremely variable process and the ability to prolong and control emptying time is a valuable asset for dosage forms that reside in the stomach for a longer period of time than conventional dosage forms [1].

The high level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of these forms. There are lot of advancements have been seen in oral controlled drug delivery system in the last few decades, this system has been of limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). To modify the GIT time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms. Several difficulties are faced in designing controlled released systems for better absorption and enhanced the bioavailability [2].Principally, controlled drug delivery systems (CDDS) consist of a reservoir of drug from which released the drug in GIT, in a programmed rate to sustain the drug absorption[3].

Pramipexole is a non-ergot dopamine agonist recently approved for the treatment of early and advanced Parkinson's disease (PD). It has preferential affinity for the D (3) dopamine receptors, compared to previous dopamine agonists that have higher affinity for D (2) dopamine receptors[4]. Along with the enhanced patient compliance seen with once a day dosing, there are other potential advantages of extended release preparations of dopamine agonists. Patients initiated on Pramipexole have a lower incidence of developing motor fluctuations including dyskinesia than those initiated on L-DOPA. Pramipexole requires a prolonged dose titration compared to L-DOPA, and generally does not have the efficacy of L-DOPA[5].

MATERIALS AND METHOD

Materials:

Pramipexole procured from Sun Pharmaceutical Industries Ltd. Sodium alginate from Pruthvi

Chemicals, Mumbai. Calcium chloride from SD Fine ltd, Mumbai. Sodium bicarbonate and HPMCK4 from Karthikeya Chemicals,Hyd. Olibanum Gum and Gum Kondagogu Nutriroma,Hyd.

Methods:

Formulation of Pramipexole Floating microspheres

Floating microspheres of Pramipexole 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 K4 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 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 -2 hours in a hot air oven and stored in desiccator[6].

Evaluation of Pramipexole Floating Microspheres:

Micromeritic Studies:

The prepared microspheres are characterized by their micromeritic properties, such as microsphere size, tapped density, Carr's compressibility index, Hausner's ratio and angle of repose[7,8].

Swelling index:

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of microspheres was determined by placing the microspheres in the basket of dissolution apparatus using dissolution medium 0.1N HCl at 37 ± 0.5°C. After 0.5, 1, 2, 3, 4, 5, and 6 h, each dissolution basket containing microspheres was withdrawn, blotted with tissue paper to remove the excess water and weighed on the analytical balance. Swelling index was calculated by using the following formula [9,10].

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

Drug entrapment efficiency and% yield:

In order 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 particular wavelength using calibration curve. Each batch should be examined for drug content in a triplicate manner[11].

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

% yield = [Total weight of floating Microspheres/Total weight of drug and polymer] X 100

In vitro drug release studies:

Release rate of drug from Floating microspheres was carried out using USP dissolution apparatus Accurately weighed amount of microspheres from each batch were subjected to dissolution studies in triplicate manner. At appropriate intervals up to 12h, specific volume of aliquots were withdrawn and analyzed spectrophotometrically at 263nm.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. The amount of drug released was calculated from the calibration curve of the same dissolution medium[12].

Conditions for Sodium alginate microspheres:

- Performed using USP dissolution apparatus II
- Dissolution medium – 0.1N HCL.
- Temperature – 37 ±0.5°C
- Stirring speed – 100 rpm
- Bath volume – 900 ml
- Time intervals – 0, 1, 2, 3, 4, 6, 8, 10& 12 hours.

Percentage buoyancy Pramipexole Floating Microspheres:

The in vitro buoyancy was determined by floating lag time, and total floating time. The microspheres were placed in a 100ml beaker containing 0.1N HCl. The time required for the microspheres to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the microspheres constantly float on the dissolution medium was noted as the total floating time respectively[13,14], and it is determined by the formula:

$$\% \text{ Floating Microspheres} = \frac{\text{Weight of floating microspheres}}{\text{Initial weight of floating microspheres}} \times 100$$

Kinetic modeling of drug release:

In order 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.[15],

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

DRUG EXCIPIENT COMPATABILITY STUDIES [16]

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.,

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 [17]

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 and cumulative % drug released during the stability study period.

RESULTS AND DISCUSSION

Floating microspheres:

Floating microspheres of Pramipexole were formulated by ionic gelation method, using different polymers like sodium alginate, calcium carbonate, calcium chloride in different concentration and the formulation codes F1, F2, F3, F4, F5, F6, F7, F8, F9, F10, F11, F12, F13 and F14 were prepared. All the formulations were evaluated for their various physical parameters.it is shown in **Table 1** and **Figure 1**

Table 1: Formulation trials of Pramipexole Floating microspheres:

Formulation code	Pramipexole (mg)	Sodium alginate	HPMCK4 (mg)	Sodium-bi carbonate(mg)	Calcium chloride	Olibanum Gum	Gum Kondagogu
F1	0.5	1%	50	25	1%	0.5	0.5%
F2	0.5	1. 2%	75	50	1%	0.75	0.5%
F3	0.5	1.4 %	100	75	1%	1	0.5%
F4	0.5	1.6%	150	100	1%	1.5	0.5%
F5	0.5	1.8 %	175	125	1%	1.75	0.5%
F6	0.5	2.%	200	150	1%	2	0.5%
F7	0.5	2.2%	250	175	1%	2.5	0.5%
F8	0.5	1%	150	25	1%	0.5	0.5%
F9	0.5	1. 2%	200	50	1%	0.75	0.5%

F10	0.5	1.4%	250	75	1%	1	0.5%
F11	0.5	1.6%	300	100	1%	1.5	0.5%
F12	0.5	1.8%	400	125	1%	1.75	0.5%
F13	0.5	2%	350	150	1%	2	0.5%
F14	0.5	2.2%	375	175	1%	2.5	0.5%

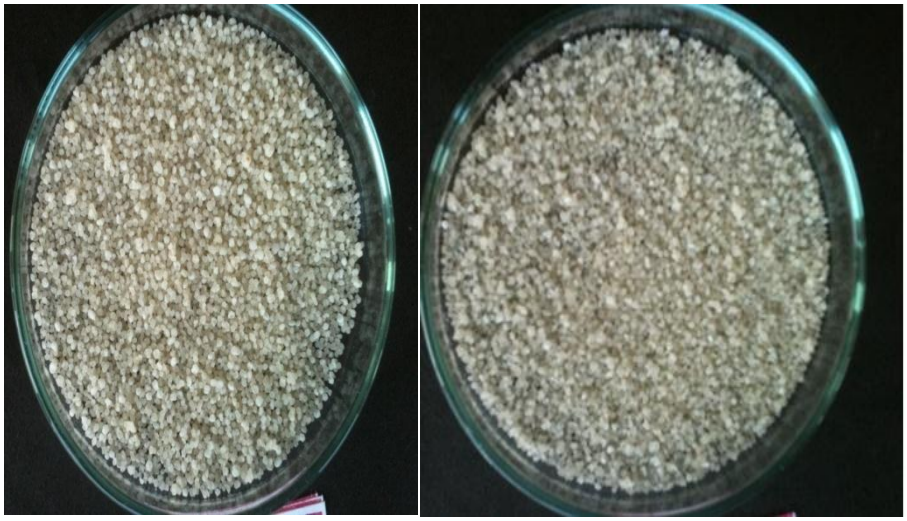

Figure 1: Pramipexole floating microspheres

Particle size was measured by using optical microscopy. All the formulations F1 to F14 varied from 65.12±0.04µm to 73.34±0.02µm. it is shown in Table 2

The bulk densities of all the formulations F1 to F14 were measured and they are ranged from 0.52±0.03g/cc³ to 0.62±0.03g/cc³.

The tapped densities of all the formulations F1 to F14 were measured and they are ranged from 0.62±0.03g/cc³ to 0.68±0.09g/cc³.

The compressibility index values were found to be in the range of 9.08 to 18.16 %. 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 20˚.10±0.02. having good flow property.

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 hrs in 0.1N HCL.

Percentage of floating microspheres = No. of floating microspheres /Initial no. of floating microspheres X 100.

All the 14 formulations of floating microspheres were exposed to buoyancy test. The formulation F12 shows the buoyancy of 98.12%.it is shown in Table 2 and Figure 2

Table 2: Micromeretic properties of Pramipexole floating microspheres

Formulation code	Particle size (µm)	Bulk density g/cc^3	Tapped density g/cc^3	Angle of repose	Carr's index	Buoyancy%
F1	67.45±0.09	0.57±0.09	0.64±0.05	23˚.36±0.05	11.56%	75.18%
F2	69.12±0.10	0.59 ±0.09	0.68±0.09	27˚.19±0.09	12.45%	84.50%
F3	68.29±0.09	0.54±0.05	0.66±0.05	29˚.22±0.10	18.16%	82.30%
F4	73.33±0.02	0.56±0.05	0.67±0.09	24˚.09±0.05	13.36%	91.45%
F5	72.35±0.02	0.62±0.03	0.65±0.05	25˚.45±0.05	10.25%	81.62%
F6	69.67±0.10	0.57±0.09	0.64±0.05	26.˚24±0.05	15.34%	89.40%
F7	67.45±0.09	0.54±0.05	0.66±0.05	24˚.48±0.05	11.95%	92.05%
F8	70.23±0.01	0.56±0.05	0.67±0.09	25˚.32±0.05	13.32%	72.50%
F9	72.67±0.02	0.54±0.05	0.64±0.05	27˚.25±0.09	12.90%	75.80%
F10	73.34±0.02	0.55±0.05	0.65±0.05	28˚.14±0.10	14.34%	72.14%
F11	69.15±0.10	0.53±0.03	0.66±0.05	24˚.15±0.05	11.90%	90.16%
F12	65.12±0.04	0.52±0.03	0.62±0.03	20˚.10±0.02	9.08%	98.12%
F13	68.23±0.09	0.55±0.05	0.64±0.05	25˚.25±0.05	11.26%	82.19%
F14	70.12±0.01	0.54±0.05	0.66±0.05	26˚.18±0.05	15.44%	78.22%

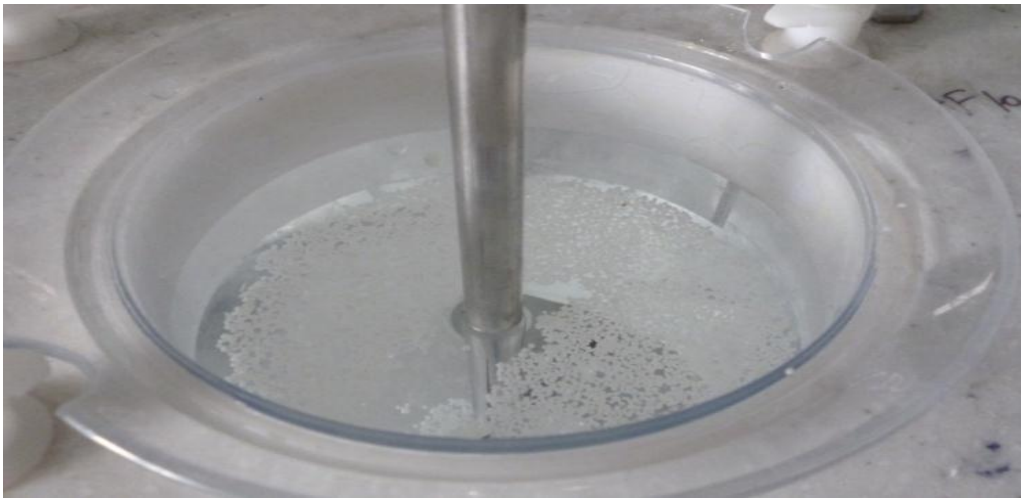

Figure 2: In vitro buoyancy study of Pramipexole floating microspheres (F12)

The formulation F12 shows the good percentage yield and entrapment efficiency the values were 98.58% and 96.56%.it is shown in **Table 3.**

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

Formulation code	Percentage Yield	Entrapment efficiency	Swelling index
F1	76.03%	78.09%	76.76%
F2	81.12%	82.23%	79.78%
F3	83.23%	84.56%	83.34%
F4	86.87%	77.28%	85.23%
F5	89.30%	90.20%	87.34%
F6	89.30%	91.10%	89.78%

F7	96.10%	94.30%	89.06%
F8	86.42%	84.30%	82.23%
F9	94.50%	92.56%	91.10%
F10	89.76%	88.78%	88.45%
F11	81.56%	84.89%	84.34%
F12	98.58%	96.56%	97.10%
F13	85.30%	84.16%	83.89%
F14	92.29%	92.18%	91.45%

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 was 98.3±5.10% within 12 h.

Table 4: In vitro cumulative % drug release of Pramipexole 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	18.25±0.99	19.63±0.99	14.56±0.95	15.66±0.96	17.60±0.99	21.45±1.20	20.18±1.29
2	23.45±1.31	24.67±1.34	22.75±1.32	25.67±1.35	21.63±1.30	30.67±2.08	31.45±2.09
4	30.46±2.08	32.18±2.01	34.67±2.02	35.19±2.05	36.70±2.05	40.98±2.40	42.18±2.46
6	55.67±2.89	54.18±2.88	58.67±2.98	55.78±2.89	56.40±2.90	57.42±2.91	52.19±2.85
8	72.16±3.82	75.56±3.91	68.45±3.20	67.12±3.18	64.33±3.14	75.5±03.81	76.45±3.82
10	82.16±4.82	81.98±4.81	79.67±3.95	75.46±3.91	76.82±3.92	83.45±4.84	80.42±4.82
12	90.23±5.01	92.46±5.02	87.56±4.97	89.65±4.99	88.49±4.98	91.67±5.01	93.44±5.03

Table 5: In vitro cumulative % drug release of Pramipexole floting microspheres:

Time	F8	F9	F10	F11	F12	F13	F14	Marketed product
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	24.86±1.32	25.46±1.36	27.6±1.39	23.46±1.31	28.15±1.50	22.15±1.30	20.18±1.29	10.12±0.69
2	32.19±2.01	35.67±2.03	36.8±2.05	35.98±2.03	39.18±2.39	33.12±2.02	32.56±2.01	19.18±0.99
4	42.19±2.46	43.26±2.50	44.52±2.50	41.06±2.41	47.19±2.51	44.16±2.50	46.98±2.50	28.16±1.50
6	52.19±2.85	56.14±2.90	55.98±2.89	53.29±2.87	59.16±2.92	52.2±2.85	54.12±2.88	35.26±2.03
8	68.19±3.87	69.16±3.89	72.15±3.93	66.32±3.87	70.18±3.89	65.19±3.86	64.18±3.85	45.89±2.50
10	79.8±3.95	78.67±3.94	81.26±4.59	84.62±4.66	85.19±4.75	82.36±4.62	85.16±4.75	69.3±3.98
12	88.9±4.89	89.99±4.98	90.63±5.01	91.46±5.01	98.3±5.10	93.67±5.05	92.15±5.02	90.45±5.01

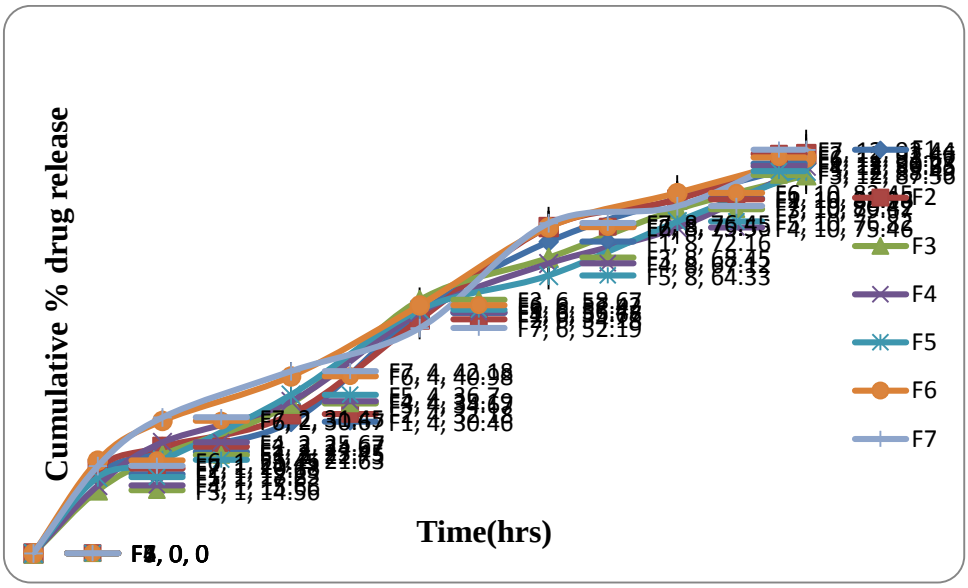

Figure 3: In vitro cumulative % drug release of Pramipexole floating microspheres (F1-F7)

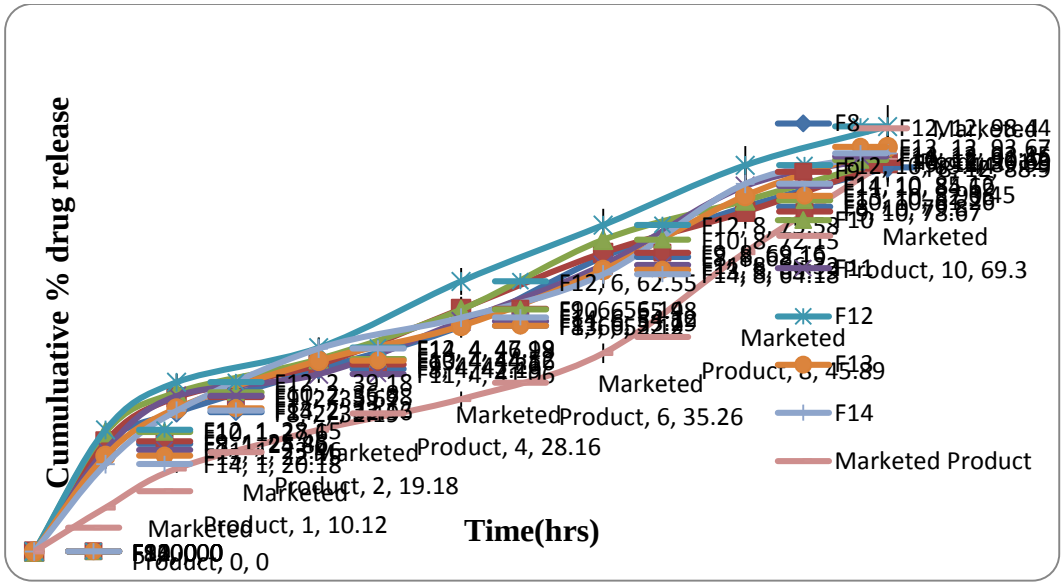

Figure 4: In vitro cumulative % drug release of Pramipexole floating microspheres(F8-F14)

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.991 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. 0.984 starting that the release from the matrix was through

diffusion. Further the n value obtained from the Korsmeyer plots i.e. 0.484 suggest that the drug release from floating microspheres was anomalous Non fickian diffusion.it is shown in **Table 6** and **Figure 5 -8**

In vitro drug release order kinetics for optimized floating microspheres

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

Formula Code	Zero Order		First Order		Higuchi		Korsmeyer	
	R^2	K	R^2	K	R^2	K	R^2	N
F12	0.991	4.710	0.8002	0.136	0.984	26.47	0.974	0.484
Marketed product	0.965	6.831	0.6711	0.122	0.869	24.10	0.964	0.818

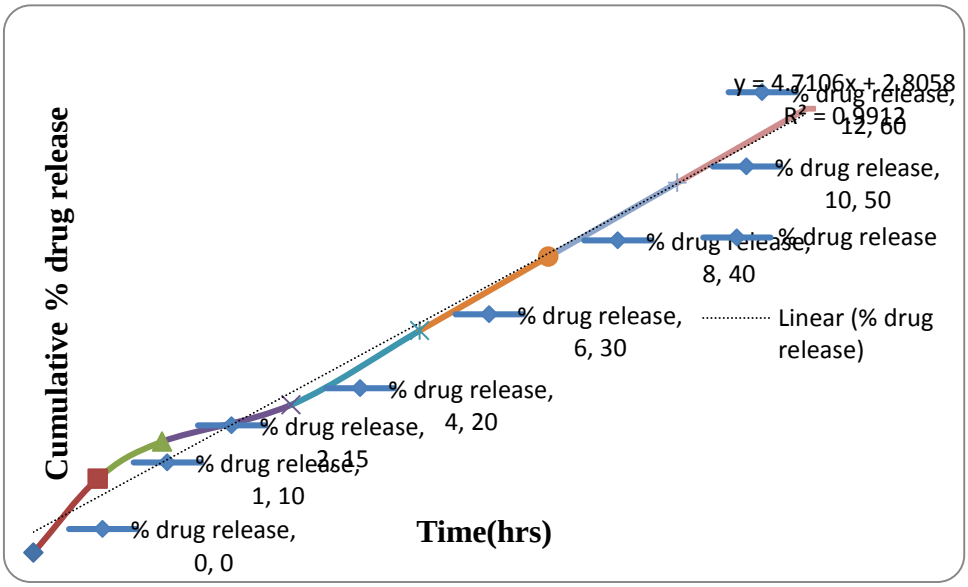

Figure 5: Zero order plots for the optimized formulation of floating microspheres F12

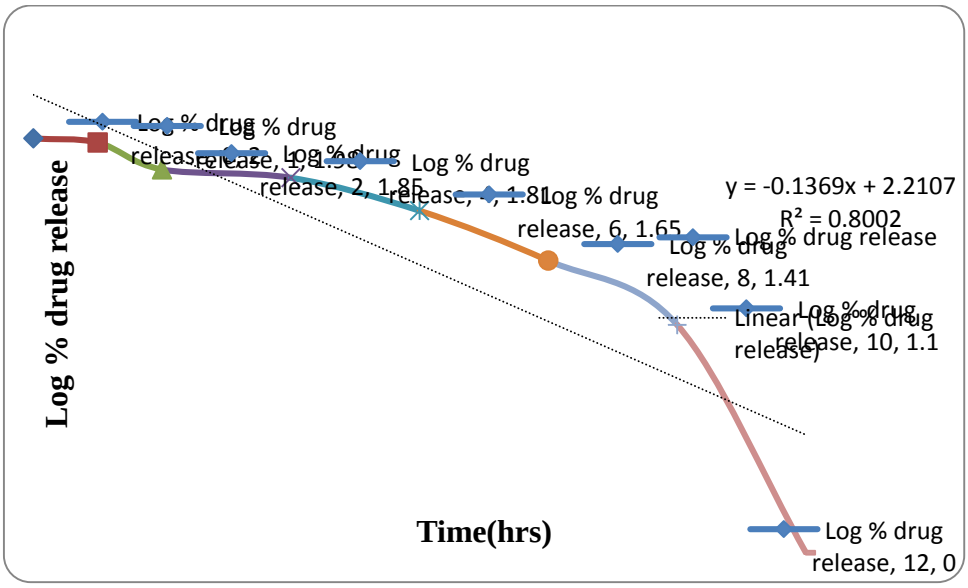

Figure 6: **First order plot for the optimized formulation of floating microspheres. F12**

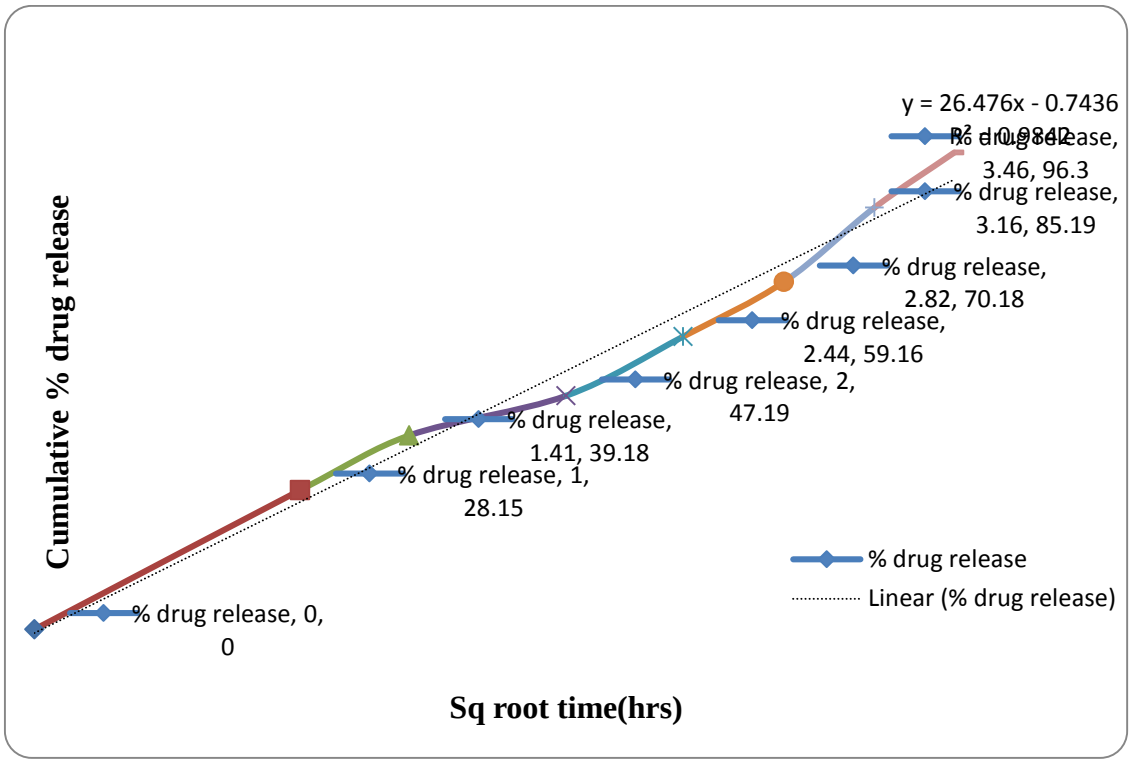

Figure 7: Higuchi plot for the optimized floating microspheres formulation F12

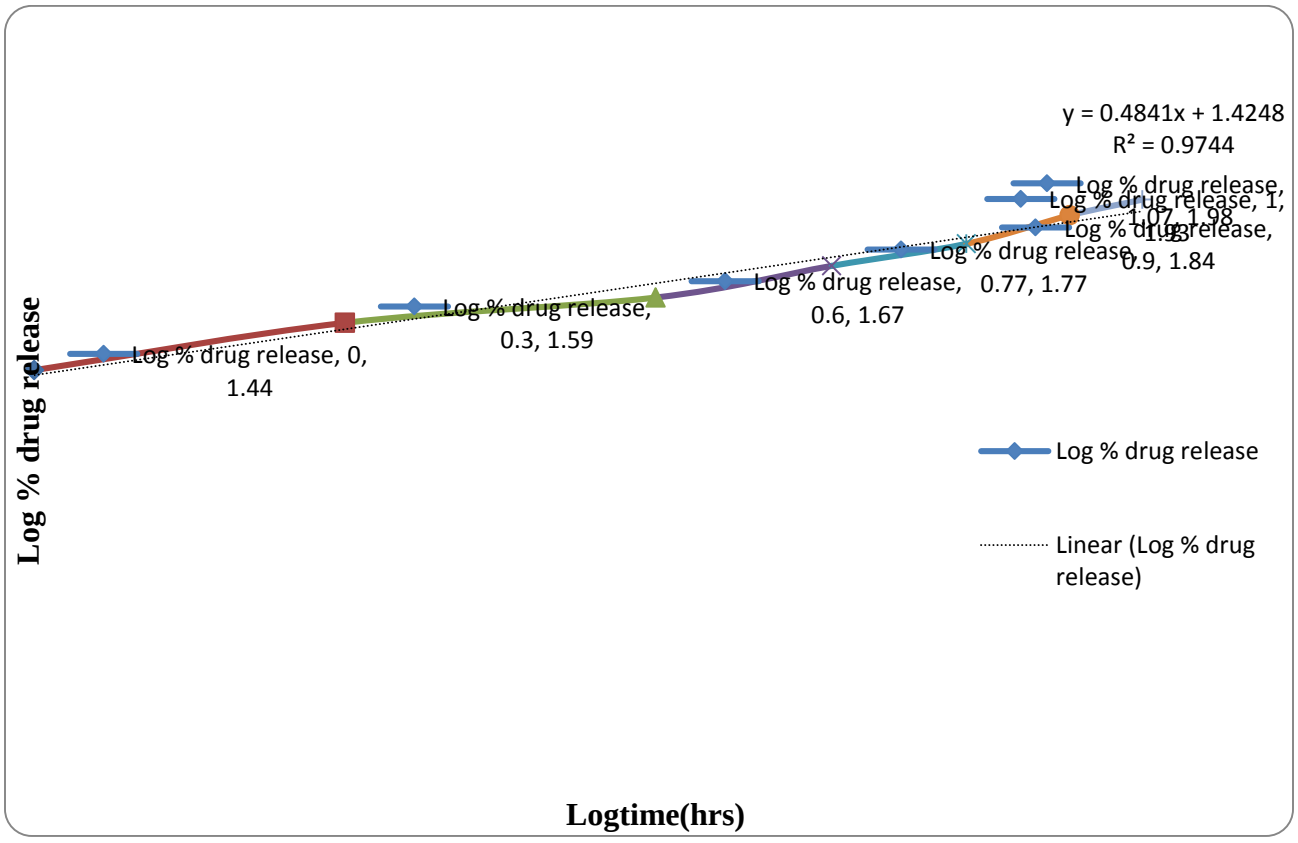

Figure 8: Korsmeyer-Peppas plot for the optimized floating microspheres formulation F12

Marketed product

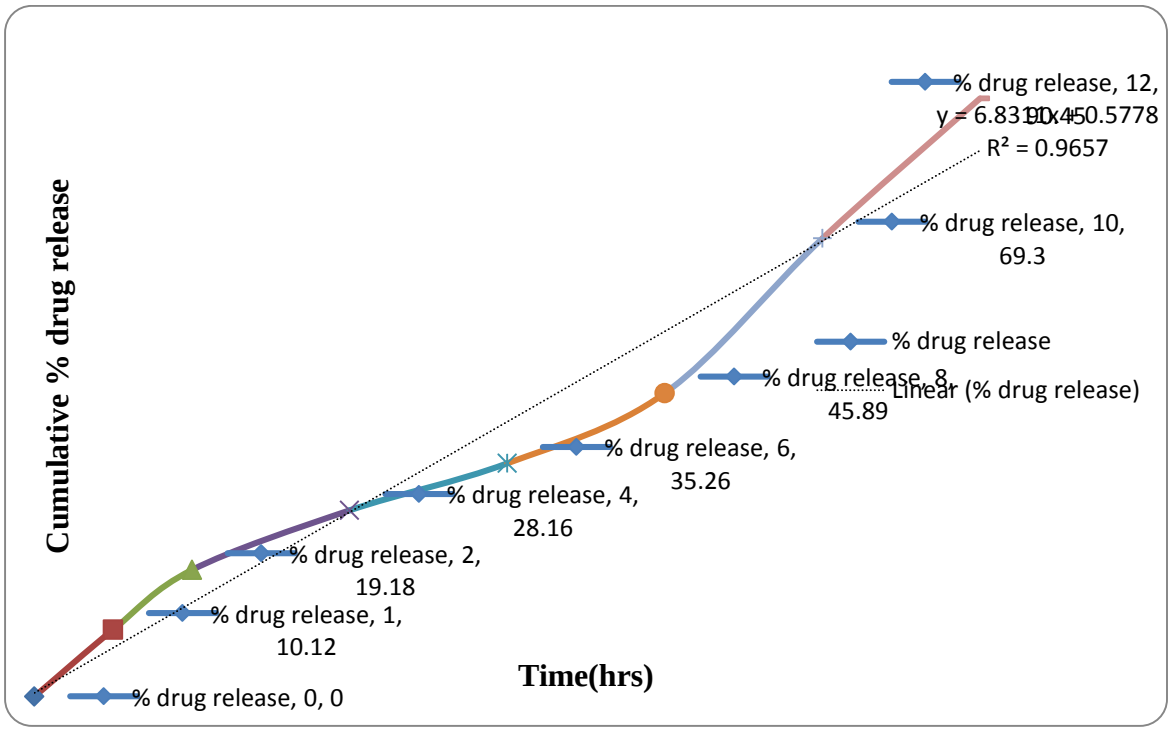

Figure 9: Zero order plot for the Marketed product

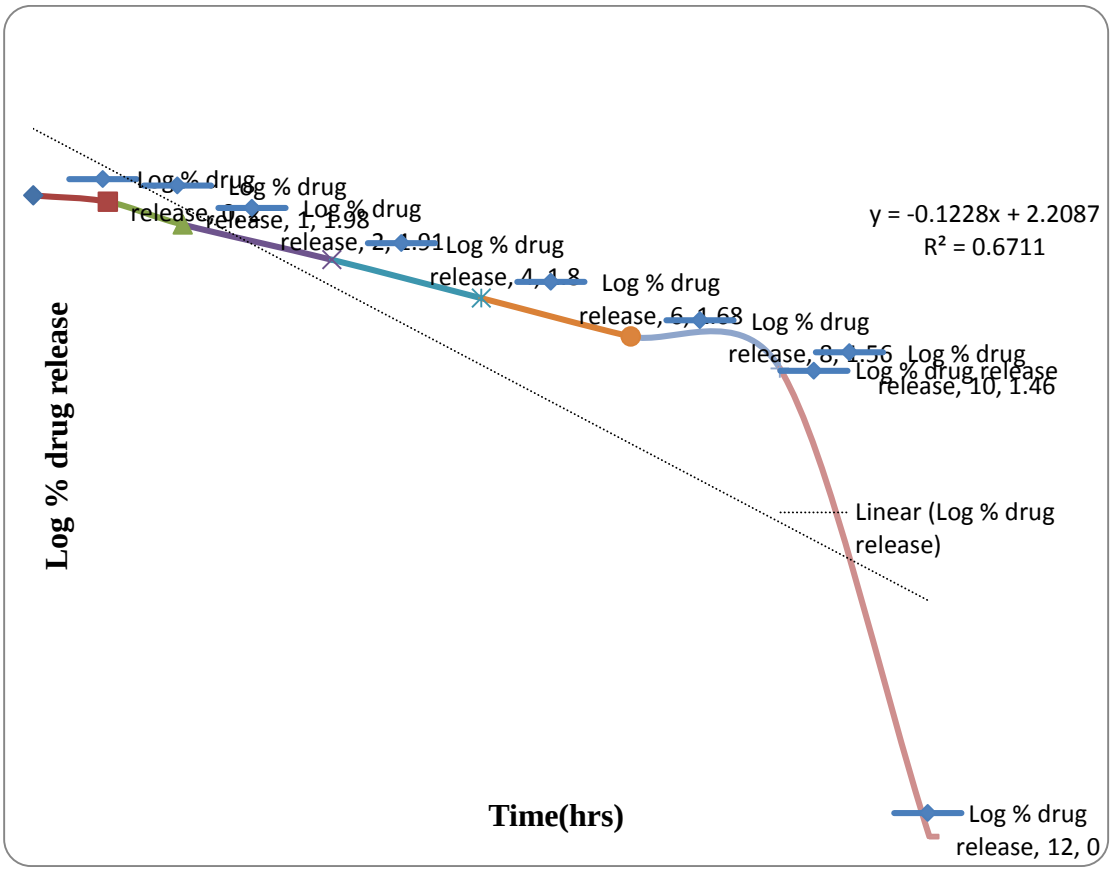

Figure 10 : First order plot for the Marketed product

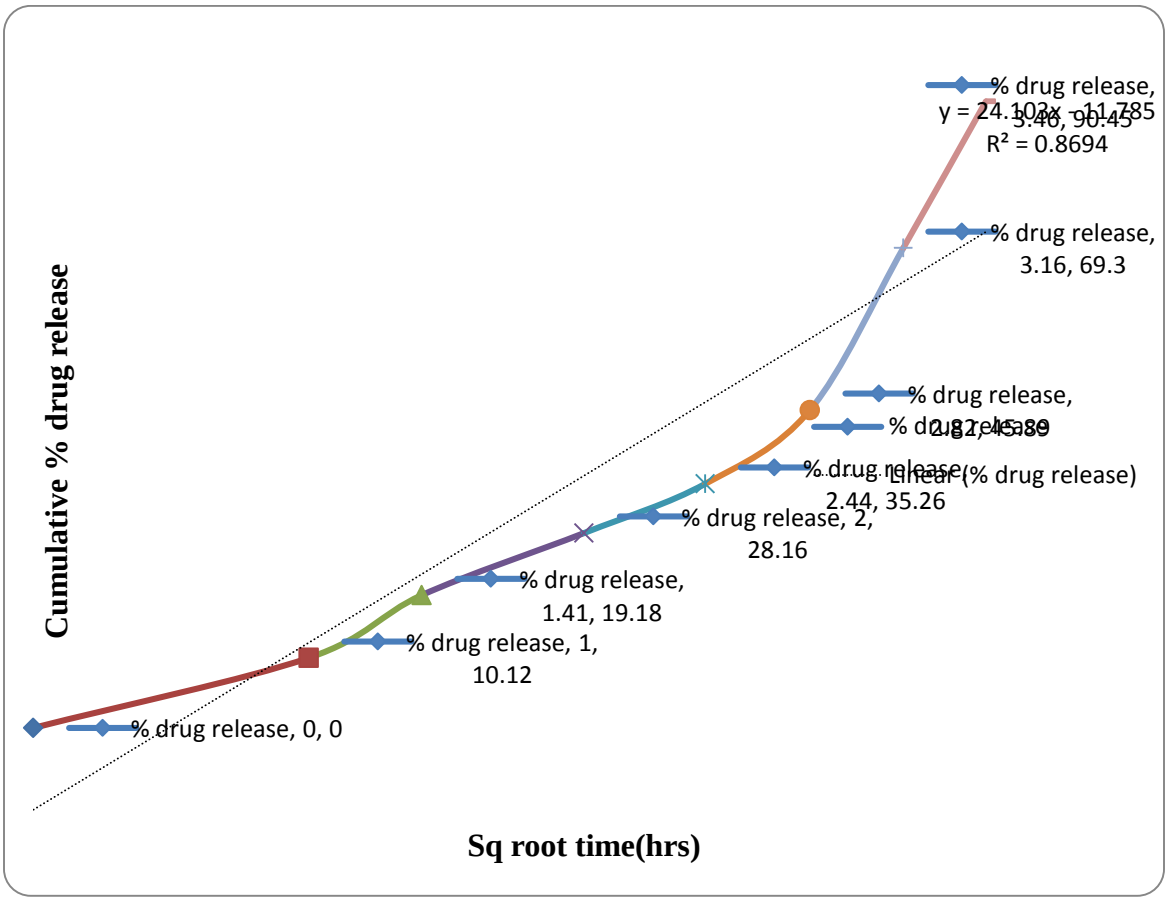

Figure 11 : Higuchi plot for the Marketed product

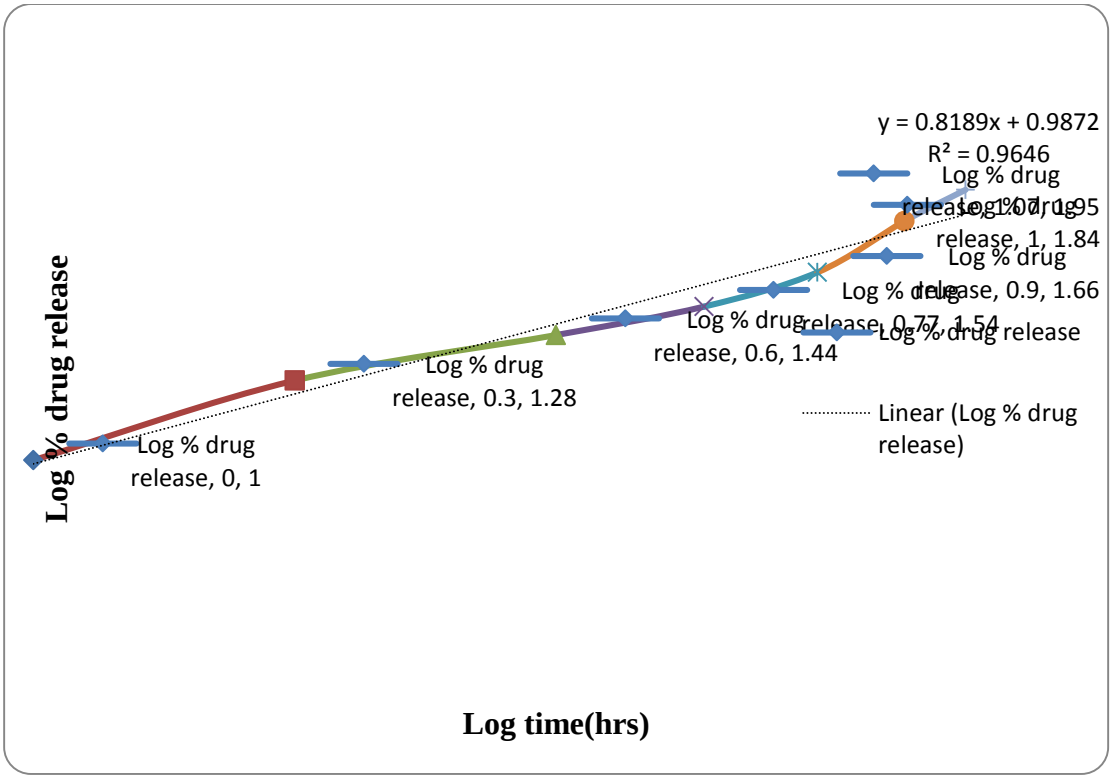

Figure 12: Korsmeyer-peppas plot for the Marketed product

Stability studies:

Optimized formulation was selected for stability studies on the basis of 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.**

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	98.30
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

CONCLUSION

Floating microspheres were prepared by ionotropic gelation technique for prolonged as well as stomach specific delivery of Pramipexole which showed the good floating ability. The formulation of Pramipexole loaded sodium alginate and HPMC K4 sodium bicarbonate, Olibanum gum and gum Kondagogu microspheres was effectively prepared. Various investigation son formulation, characterization, *in-vitro* release study were carried out and performance of theformulation was evaluated. Comparatively, F12 formulation displayed better results than marketed product. Hence it clearly indicated floating microspheres was a successful way to sustained drug release.

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