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Design & Characterization of Tolcapone Floating Microspheres

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ABSTRACT:

Floating microspheres of Tolcapone was prepared by ionotropic gelation method with an aim of increasing the gastric residence time and for controlled release using different polymers like HPMC K4M and HPMC K15M as rate retarding agent in concept to optimize the formulation. The FTIR studies indicated no significant interaction observed between drug and excipients. The F12 formulation showed the excellent flow properties. % yield, % entrapment efficiency and swelling index of optimized formulation was found to be 98.45%, 98.02% and 98.50%, respectively. The %buoyancy was excellent with approximately 98.42% of the microspheres floating upto 24h. The Cumulative % drug released from F12 microspheres was found to be 98.26±5.05% with in 12h and compared with the marketed product 91.25±5.00%. The optimized formulation F12 best fitted into zero order and Higuchi kinetics indicating diffusion controlled drug release pattern. SEM studies showed spherical shape and revealed the presence of pores on the floating microspheres surface which was responsible for floating ability. From stability studies optimized microspheres were stable at for 6 months. The F12 formulation showed the better results with HPMC K15M compared with HPMC K4M as rate retarding polymer. These results indicated that the Tolcapone loaded microspheres could potentially be exploited as a delivery system with controlled drug release in the effective management of Parkinson's disease.

Keywords: Floating microspheres, Tolcapone, HPMC, %buoyancy, Release order kinetics.

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INTRODUCTION:

Oral delivery of drugs is by far the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation etc. From immediate release to site-specific delivery, oral dosage forms have really progressed. However, it is a well-accepted fact that it is difficult to predict the real *in vivo* time of release with solid, oral controlled release dosage forms. Thus, drug absorption in gastrointestinal (GI) tract may be very short and highly variable in certain circumstances [1,2]. Floating microspheres are gastro retentive drug delivery system based on non-effervescent approach. They are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting in increased gastric retention with reduced fluctuations in plasma drug concentration [3].

Tolcapone is a selective, reversible inhibitor of peripheral and central catechol-O-methyl transferase (COMT). Tolcapone is used to treat patients with Parkinson's disease. Parkinson's disease is a progressive brain disorder that causes shaking, slow movement and muscle stiffness. Tolcapone is eliminated quickly, with an elimination half-life of 1.6 to 3.4 h[4].

The short half-life of tolcapone necessitated for fabricating extended release microspheres to provide a therapeutic amount of drug and maintain the desired drug concentration. The objective of the present study was to develop tolcapone floating microspheres by ionotropic gelation method. The results indicate that the optimized formulation of tolcapone floating microspheres can be successfully used for the treatment of Parkinson's disease.

MATERIALS AND METHOD

Materials:

Tolcapone pure drug was procured from R A Chem Pharma Ltd, Hyderabad. Sodium alginate from Pruthvi Chemicals, Mumbai. Calcium chloride and Sodium bi carbonate from SD Fine ltd, Mumbai. HPMC K4M and HPMC K15M were gifted by Rubicon Labs, Mumbai. All other chemicals and solvents were of analytical grade.

Formulation of Tolcapone Floating microspheres

Floating microspheres of Tolcapone were prepared by ionotropic gelation technique using different proportion of polymers as shown in Table 1. Different concentrations of sodium alginate is prepared, weighed quantities of drug and other polymers were added to the 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 dessicater [5].

Table 1: Formulation trials of Tolcapone Floating microspheres:

Formulation code	Tolcapone (mg)	Sodium alginate	HPMC K4M (mg)	HPMC K15M (mg)	Sodium bi carbonate (mg)	Calcium chloride
F1	200	1.0%	40	-	25	1%
F2	200	1. 2%	55	-	50	1%
F3	200	1.4 %	70	-	75	1%
F4	200	1.6%	85	-	100	1%
F5	200	1.8 %	125	-	125	1%
F6	200	2.0%	150	-	150	1%
F7	200	2.2%	200	-	175	1%
F8	200	1.0%	-	40	25	1%
F9	200	1. 2%	-	55	50	1%
F10	200	1.4%	-	70	75	1%
F11	200	1.6%	-	85	100	1%
F12	200	1.8%	-	125	125	1%
F13	200	2.0%	-	150	150	1%
F14	200	2.2%	-	200	175	1%

Evaluation of Tolcapone Floating Microspheres:

Micromeritic properties of Tolcapone microspheres:

Particle size [6], Angle of repose [7], Bulk density[8], Tapped density[8], Compressibility index[9] and Hausner's ratio[10] was evaluated according to the reported methods.

Microsphere size was determined using an optical microscope under regular polarized light. The mean microsphere size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer [6].

Swelling index:

Swelling index was determined by measuring the extent of swelling of microspheres in the given medium. Exactly weighed amount 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^{o} 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 [11].

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 spectrophotometrically at 257nm. Each batch should be examined for drug content in a triplicate manner [12].

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

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

Percentage buoyancy of Tolcapone floating microspheres:

In vitro floating ability can be determined by calculating percentage buoyancy and performed in USP type II dissolution test apparatus by spreading the floating microspheres in 0.1N HCL containing the surfactant, RPM was maintained at 100 at 37± 0.5° C. After specific intervals of time, both the fraction of microspheres (floating and settled microspheres) is collected and buoyancy of the floating microspheres is determined by using formula [13].

Weight of floating microspheres % Floating Microspheres = X 100 Initial weight of floating microspheres

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 was withdrawn and analyzed spectrophotometrically at 257nm.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 [14].

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. 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

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

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

Formulation of Tolcapone floating microspheres:

Fourteen different formulations floating Tolcapone microspheres were prepared (**Table 1**) by ionotropic gelation method and the microspheres are shown in Figure 1.

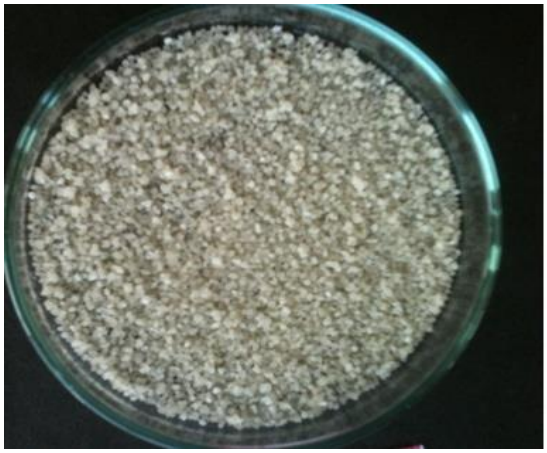

Figure 1: Tolcapone floating microspheres

All the formulations were evaluated for their various physical parameters like particle size, bulk density, tapped density, angle of repose, Carr's index and % buoyancy and found to be within the results and summarized in **Table 2**.

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. All the 14 formulations of floating

microspheres were exposed to buoyancy test. The formulation F12 shows highest buoyancy of 98.42% (**Table 2**). The entrapment efficiency, percentage yield and swelling index of all the formulations were shown in **Table 3.** The formulation F12 shows highest entrapment efficiency, percentage yield and swelling index of 98.02%, 98.45% and 98.50% respectively.

Table 2: Micromeretic properties of Tolcapone floating microspheres:

Formulation code	Particlesize (µm)	Bulk density g/cc^3	Tapped density g/cc^3	Angle of repose	Carr's index (%)	Buoyancy%
F1	70.02±0.01	0.56±0.05	0.67±0.06	28˚.96±0.07	11.60	84.20
F2	68.04±0.07	0.58±0.06	0.70±0.01	31 ˚.45±0.01	15.25	81.20
F3	63.69±0.04	0.61±0.01	0.69±0.07	27 ˚.72±0.07	14.56	75.48
F4	66.25±0.05	0.60±0.01	0.67±0.06	26 ˚.03±0.05	12.35	93.65
F5	68.56±0.07	0.59±0.07	0.72±0.01	30 ˚.04±0.01	13.99	72.54
F6	67.25±0.05	0.57±0.06	0.70±0.01	28 ˚.54±0.07	15.02	75.80
F7	64.90±0.04	0.58±0.06	0.71±0.01	27 ˚.91±0.07	14.12	76.40
F8	65.11±0.04	0.56±0.05	0.69±0.07	30 ˚.54±0.01	12.94	85.31
F9	66.18±0.05	0.57±0.06	0.66±0.05	31 ˚.25±0.01	13.56	92.21
F10	67.45±0.05	0.58±0.06	0.68±0.07	29 ˚.67±0.07	14.04	87.11
F11	65.56±0.04	0.56±0.05	0.69±0.07	27 ˚.58±0.07	13.54	89.40
F12	62.12±0.03	0.54±0.03	0.65±0.05	22 ˚.01±0.01	10.54	98.42
F13	64.66±0.04	0.59±0.07	0.68±0.07	26 ˚.44±0.05	12.25	94.22
F14	66.23±0.05	0.56±0.05	0.67±0.06	27 ˚.06±0.07	11.45	80.15

Table 3: Percentage yield, entrapment efficiency and Swelling Index of Tolcapone floating microspheres

Formulation code	Percentage Yield (%)	Entrapment efficiency (%)	Swelling index (%)
F1	88.30	91.25	75.65
F2	82.50	85.14	72.14
F3	81.25	75.37	85.20
F4	75.20	60.23	83.65
F5	71.65	83.77	86.98
F6	74.98	79.35	65.23
F7	78.62	89.45	89.99
F8	65.44	83.56	76.23
F9	89.77	81.80	79.65
F10	85.60	81.88	82.15
F11	77.20	76.54	86.46
F12	98.45	98.02	98.50
F13	72.54	72.15	90.12
F14	79.86	75.85	84.89

In vitro drug release studies:

In vitro drug release studies of Tolcapone floating microspheres were carried out and depicted in Table 4 & 5 and Figure 3 & 4. Among all the formulations F12 showed best drug release of 98.26% within 12 h when compared with other formulations.

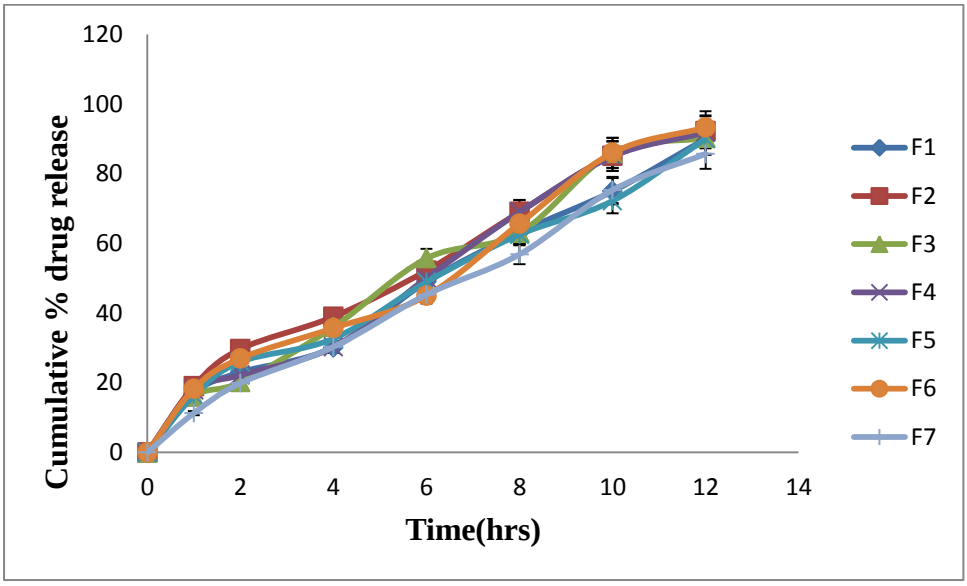

Figure 3: In vitro cumulative % drug release of Tolcapone floting microspheres

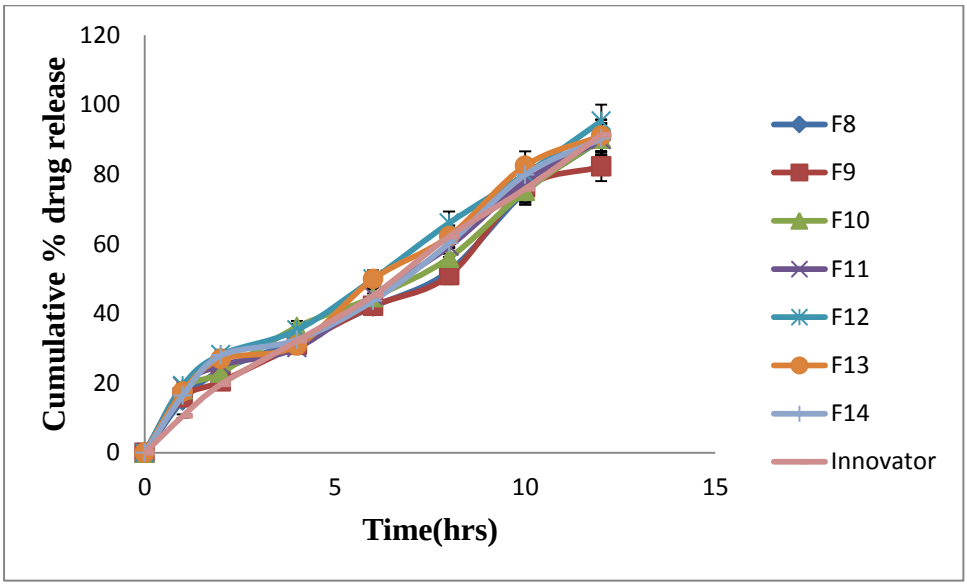

Figure 4: In vitro cumulative % drug release of Tolcapone floating microspheres

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

Time (h)	F1	F2	F3	F4	F5	F6	F7
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	16.89±0.96	18.99±0.98	15.98±0.95	17.89±0.97	16.27±0.96	18.25±0.98	11.26±0.93
2	22.97±1.32	29.67±1.40	20.15±1.28	22.19±1.2	25.98±1.33	26.98±1.36	19.89±0.99
4	30.12±2.18	38.94±2.40	35.96±2.15	30.25±2.18	32.65±2.10	35.67±2.15	30.29±2.18
6	48.97±2.85	52.16±2.85	55.67±2.89	49.99±2.86	48.90±2.85	44.96±2.64	45.28±2.65
8	63.12±3.12	68.99±3.85	62.98±3.11	68.97±3.85	62.52±3.11	65.66±3.115	56.84±2.89
10	74.96±3.81	85.13±4.85	85.96±4.89	84.98±4.88	72.19±3.82	85.98±4.98	75.29±3.81
12	89.96±4.99	92.15±5.02	90.25±5.01	91.84±5.01	89.99±4.99	93.26±5.03	85.67±4.89

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

Time (h)	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	14.99±0.93	15.86±0.94	18.18±0.98	19.01±0.99	19.26±0.99	17.54±0.97	16.45±0.96	10.54±0.90
2	23.65±1.33	20.45±1.01	22.98±1.32	25.16±1.33	28.19±1.39	26.89±1.36	27.98±1.39	19.65±0.99
4	32.18±2.10	30.98±1.98	36.12±2.16	30.12±1.98	35.27±2.25	30.78±1.98	32.45±2.10	32.16±2.01
6	41.97±2.46	42.13±2.47	44.68±2.64	45.12±2.65	49.89±2.78	49.87±2.78	43.65±2.64	45.16±2.65
8	52.19±2.85	50.98±2.80	55.98±2.84	59.27±2.95	65.99±3.45	62.19±3.12	60.18±3.09	62.13±3.15
10	74.98±3.80	76.13±3.82	75.16±3.81	77.89±3.90	79.98±3.95	82.45±4.58	79.86±3.95	75.82±3.81
12	89.99±4.99	82.19±4.85	90.15±5.00	89.90±4.99	98.26±5.05	91.06±5.01	90.22±5.00	91.25±5.00

Drug release order kinetics for optimized floating microspheres F12:

From the results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.983 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 values are shown in **Table 6**. 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. 0.951 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer plots i.e. 0.63 suggest that the drug release from floating tablet was anomalous Non fickian diffusion (**Figure 5, 6, 7 and 8**).

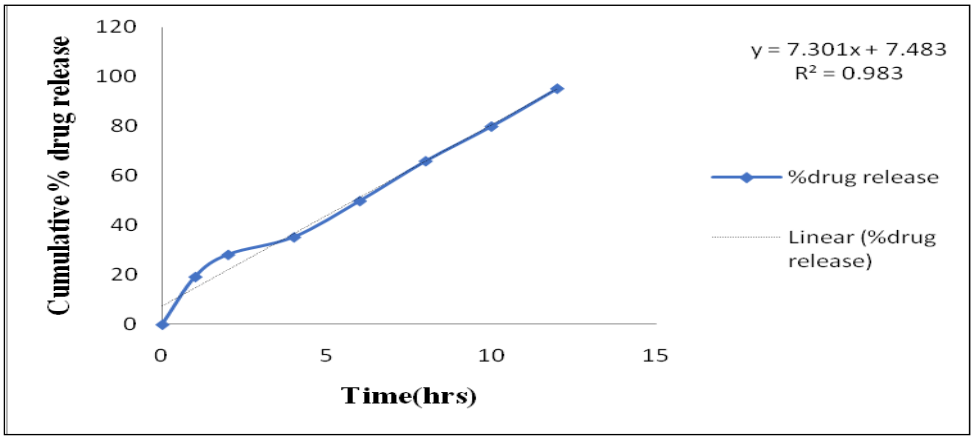

Figure 5: Zero order plots for the optimized formulation of floating microspheres F12

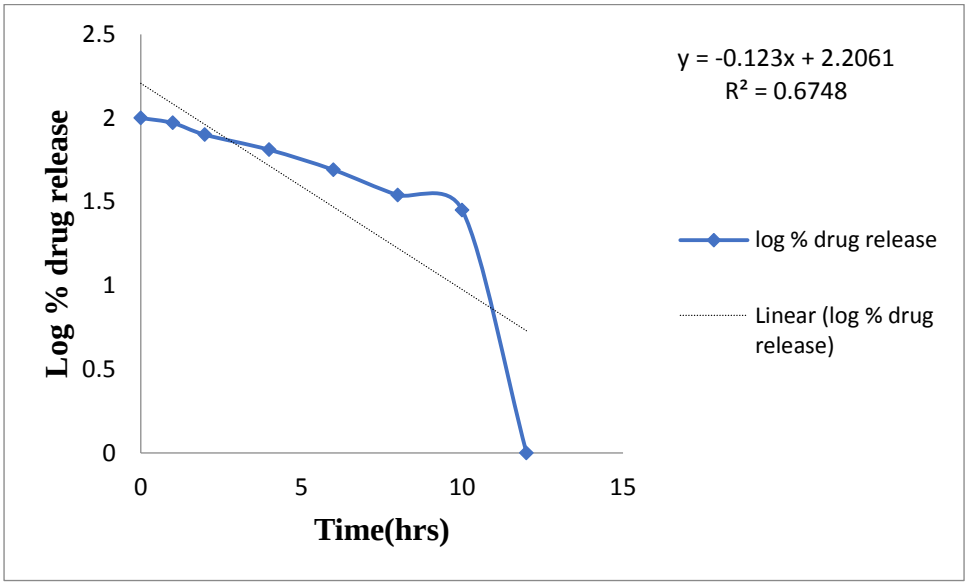

Figure 6: **First order plot for the optimized formulation of floating microspheres. F12**

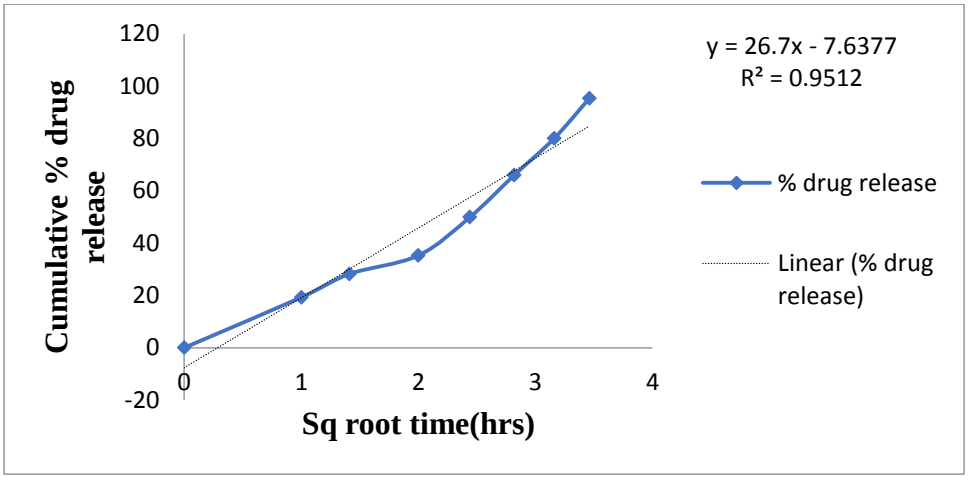

Figure 7: Higuchi plot for the optimized floating microspheres formulation F12

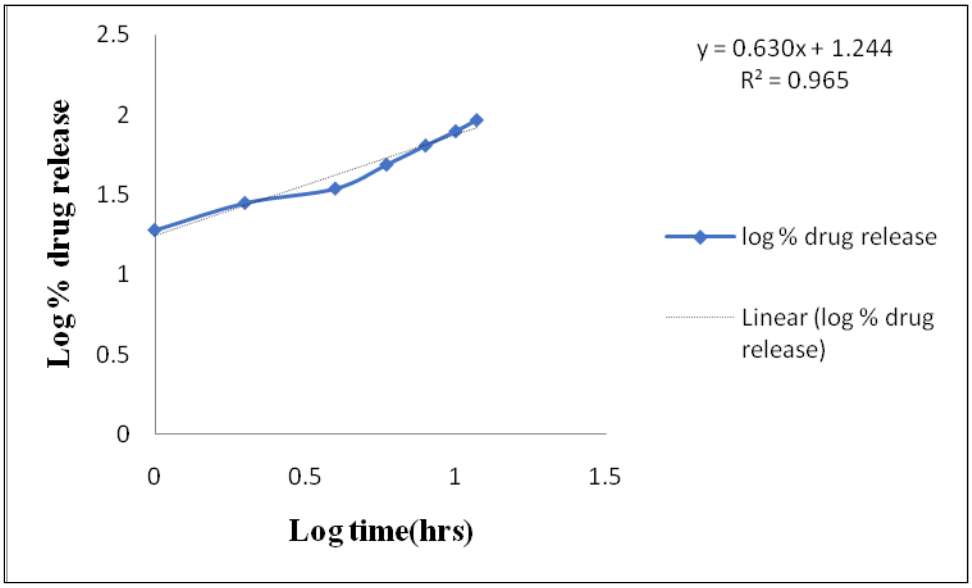

Figure 8: Korsmeyer-Peppas plot for the optimized floating microspheres formulation F12

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

Formula Code	Zero Order		First Order		Higuchi		Korsmeyer Peppas	
	R^2	K	R^2	K	R^2	K	R^2	N
F12	0.983	7.301	0.674	0.123	0.951	26.7	0.965	0.63

Table 7: Stability studies of optimized Tolcapone Floating Microspheres F12:

Retest Time For Optimized formulation	Percentage yield	Entrapment efficiency	*In-vitro* drug release (%)
0 days	98.45	98.02	98.26
30 days	97.12	97.27	97.88
60 days	96.49	96.11	97.17
120 days	95.77	95.55	96.74
180 days	95.14	94.82	96.15

Characterization work

CHARECTERIZATION

FTIR:

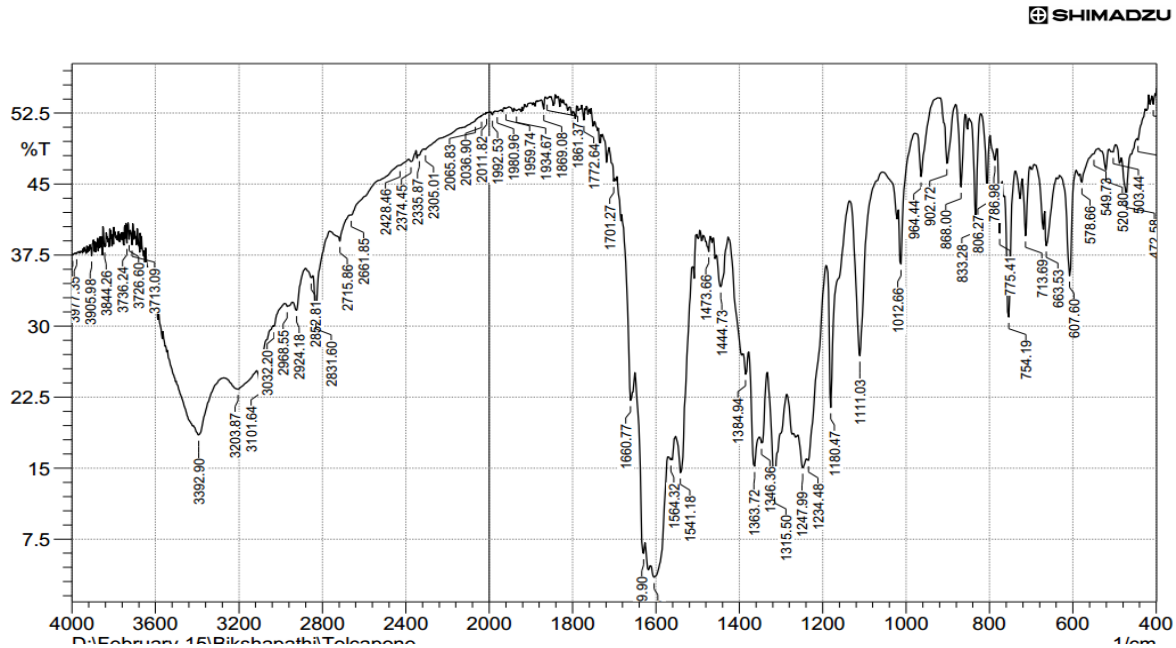

Figure 9: FT-IR spectrum of pure drug Tolcapone

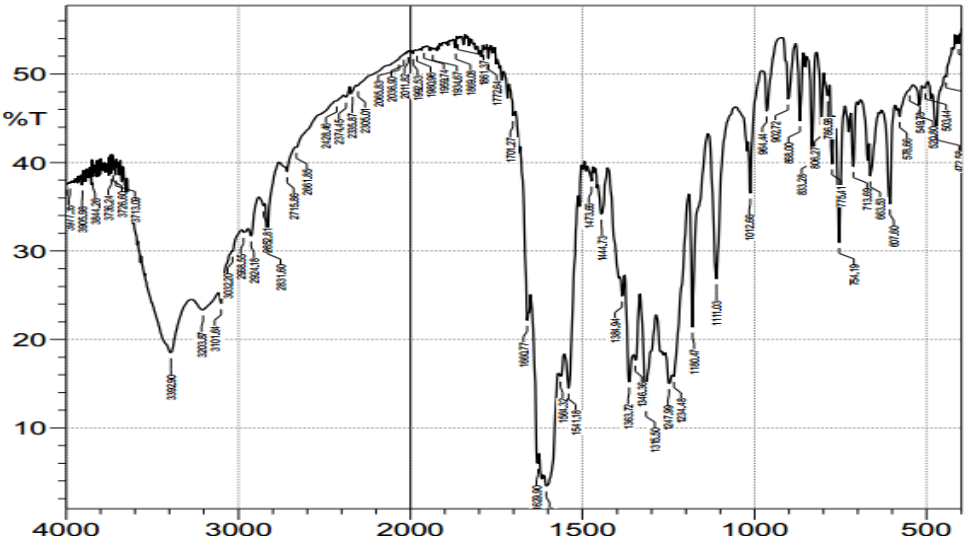

Figure 10: FT-IR spectrum of Tolcapone optimized formulation F12

There was no alteration in peaks of Tolcapone pure drug (**Figure 9**) and optimized formulation (**Figure 10**), suggesting that there was no interaction between drug & 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 studies of Tolcapone floating microspheres:

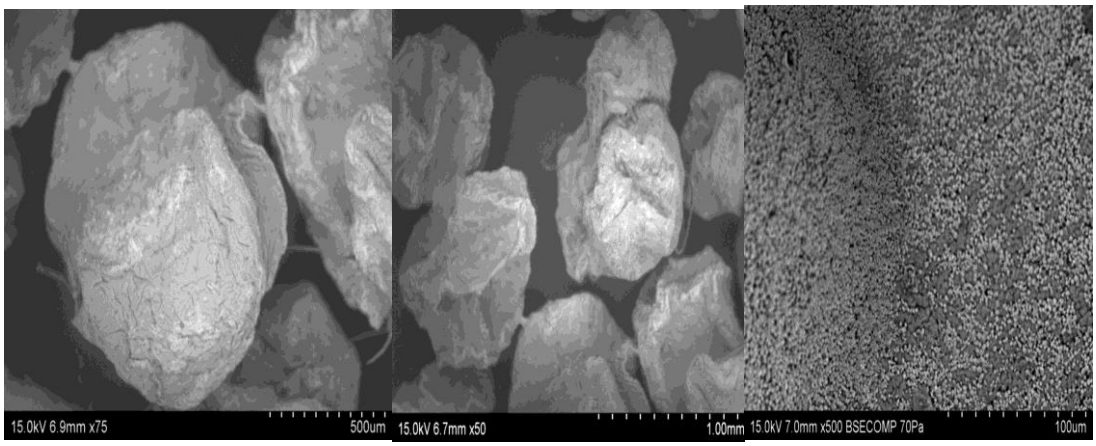

Figure 11: Scanning electron micrographs of Tolcapone optimized floating microspheres F12

The SEM of optimized floating microspheres shows a hollow spherical structure with a rough surface morphology. Some of microsphere showed dented surface structure but they showed good floating ability on medium indicated intact surface. The shell of microspheres also showed some porous structure it may be due to release of carbon dioxide (**Figure 11**).

Stability studies:

Optimized formulation (F12) of Tolcapone microspheres 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 **Table7**

CONCULSION

Tolcapone loaded floating microspheres were prepared by ionotropic gelation method. From the results it was concluded that formulation F12 was found to be optimized formulation based on the evaluation parameters like % buoyancy (98.42%), swelling index (98.50%) and highest *in vitro* drug release of 98.26±5.05% in a sustained manner with constant fashion over extended period of time for 12h compared with marketed product 91.25±5.00 in 12h. From FTIR studies it was found that drug and polymers were compatible, no interaction takes place. Drug release from Tolcapone 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 with stability studies for 6 months. The formulations have shown good drug release in controlled manner for prolonged period, which is the desired for drug absorption. In addition, the release continues at a constant rate in this medium.

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