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Entacapone – Based Floating Microspheres by Ionotropic Gelation Technique-Morphology and Release Characteristics

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ABSTRACT

The main objective of the present investigation was to develop gastro retentive floating microspheres for Entacapone. These are prepared by ionotropic gelation method with an aim of increasing the gastric residence time and for controlled release. The polymeric mixture of Sodium alginate and HPMC K4, was used as polymers. Sodium bicarbonate was used as the gas-forming gent. Prepared 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 F14 was optimized. The % yield of F14 formulation was found to be 98.03%. Based on optical microscopy, the particle size was 65.23 ± 0.05µm. The % buoyancy, % entrapment efficiency and swelling index of F14 formulation was 98.16%, 97.54% and 97.67%, respectively. The cumulative % drug release of F14 formulation was 97.99 ± 5.05% in 12 h when compared with marketed product 95.12 ± 5.01 in 1 h. SEM studies showed the particles were in spherical shape. Hence the formulated and prepared floating Entacapone microspheres may establish to be potential candidate for safe and effective sustained drug delivery and improve the bioavailability in the management of Parkinson's disease.

Keywords: Entacapone, Floating microspheres, SEM, Release order kinetics.

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INTRODUCTION

The floating drug delivery system was first described by Davis (1968). Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems. FDDS are known as Hydro dynamically balanced systems or low-density system that has been made developed to increase the gastric transit time of drug. [1] Since the last three decades many drug molecules formulated as Gastroretentive Drug Delivery System (GRDDS) have been patented keeping in view its commercial success. Oral controlled release (CR) dosage forms have been extensively used

to improve therapy of many important medications. [2] These microspheres are characteristically free flowing powders consisting of natural or synthetic polymers and ideally having a particle size less than 200µm. Microspheres incorporating a drug dispersed or dissolved throughout particle matrix have the potential for the controlled release of drug. [3]

Floating microspheres are one of the multiparticulate drug delivery systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability and to target drug to specific sites. Floating microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency, and improving patient compliance. [4]

Entacapone is a selective, reversible catechol-O-methyl transferase (COMT) inhibitor. It is a member of the class of nitrocatechol. The chemical name of Entacapone is (2E)-2-cyano-3-(3, 4- dihydroxy-5-nitrophenyl)-N, N-diethylprop-2- enamide**.** Entacapone is rapidly absorbed (approx. 1 hour) and has an absolute oral bioavailability of 35%.

The aim of the present study is to develop Entacapone Floating microspheres by ionotropic gelation method to obtain an extended retention in the upper GIT, which may result in increased absorption and thereby improved bioavailability. The prepared microspheres were evaluated for different evaluation parameters and characterization.

MATERIALS AND METHODS

Materials

Entacapone procured from Hetero Drugs Ltd**,** Hyderabad. Sodium alginate was purchased from Pruthvi Chemicals, Mumbai. Calcium chloride received from SD Fine ltd, Mumbai. Sodium bicarbonate and HPMC K 4 M was received from Rubicon Labs, Mumbai. All other chemicals and solvents were of analytical grade.

Methods

Formulation of Entacapone Floating Microspheres

Floating microspheres of Entacapone were prepared by ionotropic gelation technique using different polymers listed in Table 1. A solution of sodium alginate is prepared, weighed quantity of drug and HPMC K4 was added to above solution. Sodium bicarbonate, a gas generating 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 dessicator. [5]

Evaluation of Entacapone Floating Microspheres

Micromeritic properties of Entacapone 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.

Table 1: Formulation trials of Entacapone Floating microspheres

Formulation code	Entacapone (mg)	Sodium alginate	HPMC K 4M (mg)	Sodium bi carbonate (mg)	Calcium chloride
F1	200	1%	50	25	7%
F2	200	1. 2%	75	50	7%
F3	200	1.4 %	100	75	7%
F4	200	1.6%	150	100	7%
F5	200	1.8 %	175	125	7%
F6	200	2.%	200	150	7%
F7	200	2.2%	200	175	7%
F8	200	1%	150	25	10%
F9	200	1. 2%	200	50	10%
F10	200	1.4%	250	75	10%
F11	200	1.6%	300	100	10%
F12	200	1.8%	350	125	10%
F13	200	2%	400	150	10%
F14	200	2.2%	450	175	10%

Determination of swelling index

For determining the swelling index, the accurately weighed quantities of Entacapone microspheres were suspended in 0.1 N HCl with pH 1.2 (simulated gastro intestinal fluids). Liquid droplets adhered to the surface of microspheres was removed by using blotting paper and then weighed it with the help of a microbalance. The swollen microspheres were dried in oven at 60°C for 5 h or until showed the constant weight. [11] The variation in swelling of microspheres before and after drying was used to calculate the % of swelling index. The following equation was used.

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

% yield of microspheres

The prepared Entacapone microspheres were collected and weighed. The actual weight of obtained microspheres divided by total weight of added drug and polymer was used for the calculation of % yield and mentioned below. [12]

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

Entrapment efficiency

Entacapone incorporation efficiency was analyzed by weighing 10 mg of floating microspheres then dissolved in methanol. The above solution was agitated to solubilize the drug and polymers and to extract the drug. Then solution was filtered using membrane filter (0.45µm) to separate shell fragments. The drug was determined using spectrophotometer (Shimadzu, UV-1800) at the λ_{max} of 377 nm. [13] The encapsulation efficiency was determined using the following equation.

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

Test for buoyancy

Buoyancy test was carried out by weighing 100 mg of the microspheres and transferred to a USP type II dissolution test apparatus containing 900 ml of simulated gastric fluid (0.1N HCl) at 37°C. The content of the beakers was stirred at 100 rpm. Then microspheres were separated at different time intervals

and dried until a constant weight obtained. [14] The % of buoyancy is calculated by using following equation.

$$\text{Buoyancy (\%)} = \frac{\text{Weight of floating microspheres}}{\text{Initial weight of floating microspheres}} \times 100$$

In vitro drug release studies

Release rate of drug from sodium alginate microspheres was carried out using USP type II dissolution apparatus with 0.1N HCl (pH 1.2) of 900 ml as dissolution medium. 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. 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 377 nm. The amount of drug released was calculated from the calibration curve of the same dissolution medium.

Table 2: Formulated Entacapone Floating microspheres- Micromeritic properties

Formulation code	Particle size (µm)	Bulk density (g/cc³)	Tapped density (g/cc³)	Angle of repose	Carr's index	Buoyancy %
F1	70.12 ± 0.01	0.61 ± 0.02	0.69 ± 0.10	25˚.60 ± 0.04	11.05	71.23
F2	71.46 ± 0.02	0.57 ± 0.08	0.67 ± 0.08	28 ˚.35 ± 0.07	13.25	78.36
F3	67.16 ± 0.08	0.60 ± 0.02	0.64 ± 0.05	30˚.60 ± 0.01	15.69	75.32
F4	74.66 ± 0.05	0.58 ± 0.08	0.65 ± 0.07	26 ˚.63 ± 0.05	10.45	82.54
F5	69.09 ± 0.10	0.59 ± 0.09	0.66 ± 0.08	27 ˚.35 ± 0.05	12.50	90.36
F6	70.16 ± 0.01	0.61 ± 0.02	0.68 ± 0.09	28 ˚.14 ± 0.06	13.81	79.22
F7	73.03 ± 0.02	0.60 ± 0.02	0.69 ± 0.10	24 ˚.60 ± 0.04	12.05	70.98
F8	72.35 ± 0.02	0.59 ± 0.10	0.65 ± 0.07	28 ˚.56 ± 0.06	11.01	79.58
F9	70.33 ± 0.01	0.57 ± 0.08	0.64 ± 0.05	25 ˚.15 ± 0.04	13.98	72.15
F10	68.40 ± 0.10	0.56 ± 0.07	0.69 ± 0.10	29 ˚.45 ± 0.09	14.59	78.56
F11	71.23 ± 0.01	0.59 ± 0.09	0.67 ± 0.08	25 ˚.82 ± 0.04	12.02	81.65
F12	69.15 ± 0.10	0.58 ± 0.08	0.66 ± 0.08	26 ˚.25 ± 0.05	10.89	94.02
F13	70.67 ± 0.01	0.57 ± 0.08	0.65 ± 0.07	24 ˚.09 ± 0.04	11.56	96.26
F14	65.23 ± 0.05	0.54 ± 0.03	0.62 ± 0.03	21 ˚.05 ± 0.01	9.52	98.16

Table 3: Percentage yield, entrapment efficiency and swelling index of Entacapone microspheres

Formulation code	Percentage Yield (%)	Entrapment Efficiency (%)	Swelling index (%)
F1	78.36	81.03	79.62
F2	72.19	78.21	89.66
F3	65.24	65.23	65..13
F4	82.19	89.67	86.35
F5	77.65	74.52	72.15
F6	62.39	73.69	75.85
F7	90.25	88.45	92.42
F8	93.65	72.64	81.46
F9	65.89	79.13	65.85
F10	82.36	69.98	79.85
F11	72.45	76.33	75.67
F12	70.98	82.98	71.22
F13	82.15	80.22	72.98
F14	98.03	97.54	97.67

Table 4: *In vitro* cumulative % drug release of Entacapone 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	18.95 ± 0.98	12.45 ± 0.94	11.56 ± 0.93	17.25 ± 0.97	14.85 ± 0.94	15.65 ± 0.95
2	25.67 ± 1.33	26.89 ± 1.36	22.85 ± 1.20	20.18 ± 1.98	23.45 ± 1.33	27.36 ± 1.38	21.99 ± 1.31
4	38.16 ± 2.40	32.65 ± 2.10	34.89 ± 2.14	33.86 ± 2.11	35.89 ± 2.15	36.70 ± 2.16	38.99 ± 2.40
6	54.14 ± 2.87	52.16 ± 2.85	49.67 ± 2.86	49.99 ± 2.86	51.16 ± 2.84	53.98 ± 2.86	50.46 ± 2.87
8	65.16 ± 3.15	60.32 ± 3.10	59.85 ± 2.91	58.96 ± 2.90	62.85 ± 3.11	61.98 ± 3.12	59.99 ± 2.92
10	82.19 ± 4.85	85.69 ± 4.98	72.18 ± 3.82	75.19 ± 3.81	83.18 ± 4.86	82.19 ± 4.85	85.96 ± 4.98
12	92.13 ± 5.02	93.16 ± 5.03	88.54 ± 4.98	89.98 ± 4.99	92.99 ± 5.02	91.89 ± 5.01	90.25 ± 5.00

Table 5: *In vitro* cumulative % drug release of Entacapone 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	18.25 ± 0.98	16.58 ± 0.95	17.35 ± 0.97	15.96 ± 0.94	14.99 ± 0.93	19.86 ± 0.99	20.22 ± 1.01	95.12 ± 5.01
2	28.32 ± 1.39	27.12 ± 1.38	26.89 ± 1.36	26.19 ± 1.34	25.16 ± 1.33	30.26 ± 1.98	38.58 ± 2.30	
4	43.18 ± 2.64	45.98 ± 2.65	43.56 ± 2.64	40.25 ± 2.45	42.16 ± 2.47	44.12 ± 2.64	49.16 ± 2.78	
6	55.67 ± 2.84	54.19 ± 2.83	57.98 ± 2.93	58.19 ± 2.94	52.18 ± 2.85	56.18 ± 2.85	65.58 ± 3.45	
8	66.19 ± 3.45	69.53 ± 3.50	62.98 ± 3.12	65.18 ± 3.45	69.98 ± 3.56	68.19 ± 3.55	72.18 ± 3.78	
10	80.19 ± 3.96	79.98 ± 3.95	75.67 ± 3.81	82.19 ± 4.58	79.15 ± 3.95	75.14 ± 3.81	88.16 ± 4.98	
12	90.16 ± 5.00	91.36 ± 5.01	88.45 ± 4.98	93.68 ± 5.03	92.35 ± 5.02	89.19 ± 4.99	97.99 ± 5.05	

Table 6: Release order kinetics of optimized formulation of floating microspheres F14

Formula Code	Zero Order		First Order		Higuchi		Korsmeyer	
	R^2	K	R^2	K	R^2	K	R^2	N
F14	0.998	5.564	0.589	0.116	0.990	28.08	0.981	0.598

Table 7: Stability studies of optimized Floating Microspheres

Retest Time For optimized formulation	Percentage yield	Entrapment efficiency	*In-vitro* drug release profile (%)
0 days	98.03	97.54	97.99
30 days	97.62	96.58	96.23
60 days	96.22	95.22	95.03
120 days	95.21	94.05	94.88
180 days	94.03	93.66	94.33

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 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.

Drug-excipient compatibility studies

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR technique can be used to recognize the functional groups in the pure drug and drug-excipient compatibility. Pure Entacapone FTIR spectra and optimized formulation were recorded by using FTIR (SHIMADZU). Weighed quantity of KBr and excipients were taken in the ratio 100: 1 and mixed by mortar. [15] The samples were made into pellet by the application of pressure. Then the FTIR spectra were recorded between 4000 - 400 cm^{-1}

SEM studies

Surface nature of microspheres includes size and shape was examined with the help of Scanning Electron Microscope (HITACHI, S-3700N). The microspheres were dried completely prior to analysis and SEM was carried out at various magnifications. [16]

Stability studies

Optimized formulation such as F14 floating microspheres were subjected to stability testing at 40°C ± 2°C/75% RH ± 5% RH for 6months using stability chamber (Thermo Lab, Mumbai). Samples were withdrawn at predetermined intervals 0, 30, 60, 120, and 180 days period according to ICH guidelines. Parameters like % yield, entrapment efficiency and *in vitro* release studies were determined. [17]

RESULTS AND DISCUSSION

Formulation of Entacapone Floating microspheres

Entacapone floating microspheres are shown in Figure 1. Floating microspheres of Entacapone were formulated by ionic gelation method, using different polymers like sodium alginate, HPMC K4M, sodium bicarbonate and calcium chloride in different concentration and the formulation codes F1 - F14 were prepared. All the formulations were evaluated for their various micromeritic properties and found to be within the limits, which are shown in Table 2.

In vitro buoyancy studies of floating microspheres

All the 14 formulations of floating microspheres were exposed to buoyancy test. The formulation F14 shows the buoyancy of 98.16%, shown in Table 2 and Figure 2. The percentage yield, entrapment efficiency and swelling index of all the formulation were measured and found to be within the limits (Table 3).

In vitro drug release studies

In vitro drug release studies were carried out and depicted in Table 4 & 5 and Figure 3 & 4. Among all the formulations F14 showed best drug release of 97.99% within 12 h when compared with other formulations.

Kinetic modeling of drug release

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e. 0.998 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. 0.982 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer plots i.e. 0.598 suggest that the drug release from floating tablet was anomalous Non fickian diffusion are shown in Table 6 and Figures 5, 6, 7 & 8.

Fig. 1: Entacapone Floating Microspheres

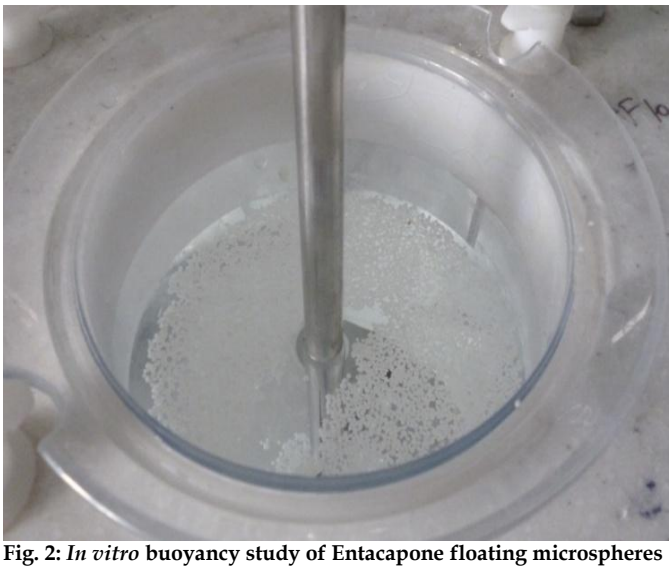

Fig. 2: *In vitro* buoyancy study of Entacapone floating microspheres (F14)

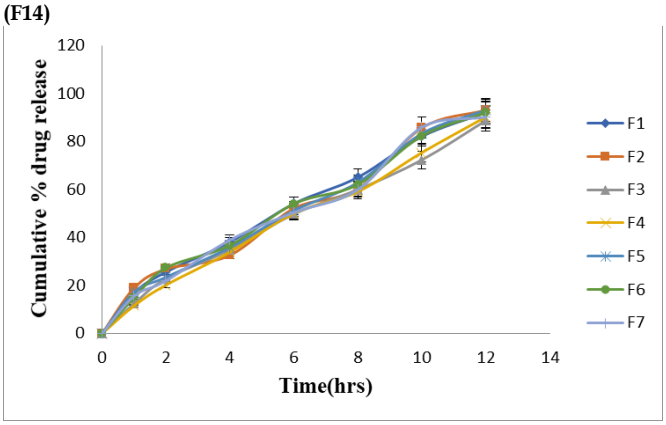

Fig. 3: *In vitro* cumulative % drug release of Entacapone floting microspheres

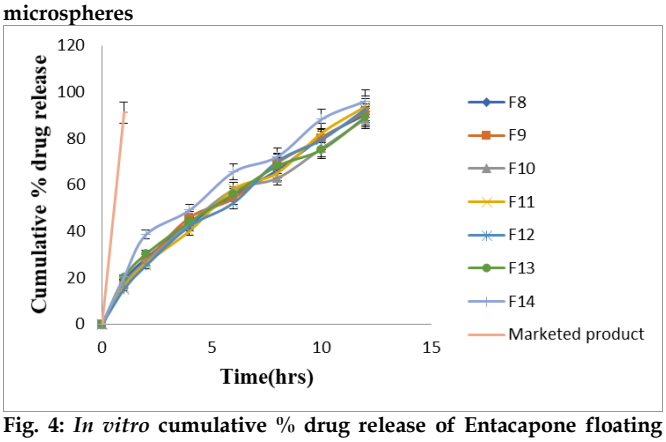

Fig. 4: *In vitro* cumulative % drug release of Entacapone floating microspheres

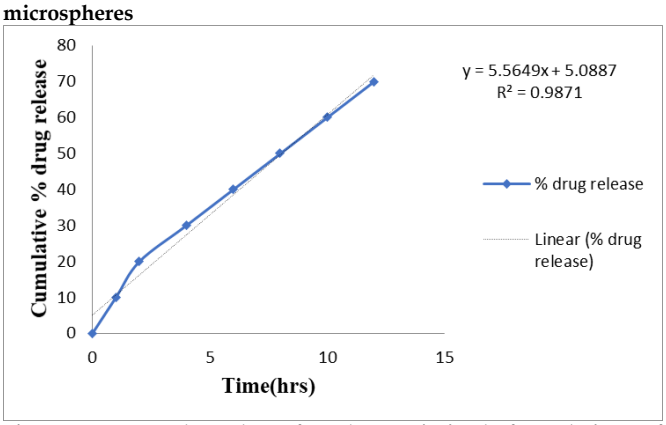

Fig. 5: Zero order plots for the optimized formulation of Entacapone floating microspheres F14

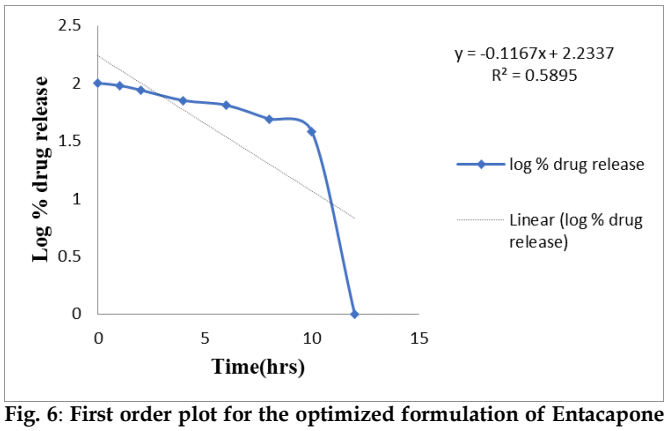

Fig. 6: First order plot for the optimized formulation of Entacapone floating microspheres. F14

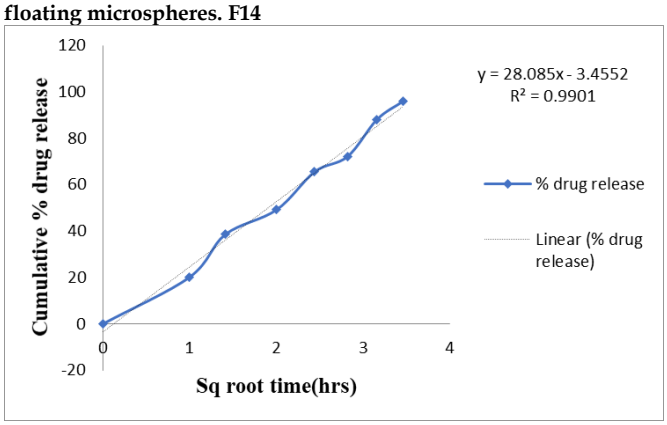

Fig. 7: Higuchi plot for the optimized Entacapone floating microspheres formulation F14

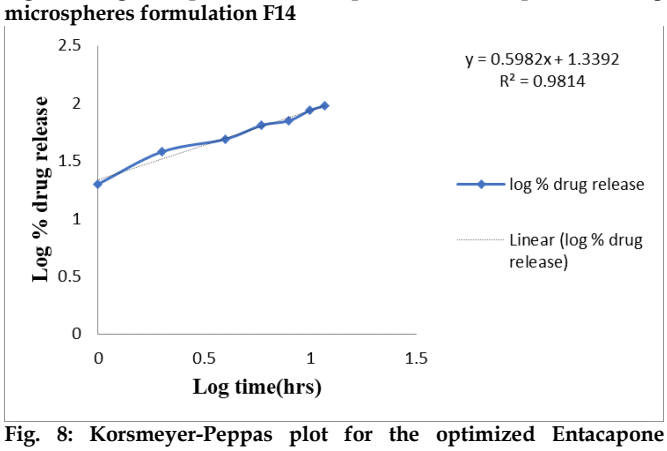

Fig. 8: Korsmeyer-Peppas plot for the optimized Entacapone floating microspheres formulation F14

Drug Excipient Compatability Studies

FT-IR studies

The FTIR spectrum of Entacapone pure drug (Figure 9), Entacapone physical mixture and optimized formulation F14 are shown in Figures 9, 10 & 11. There was no alteration in peaks of pure drug and optimized formulation suggesting that there was no interaction between drug & excipients.

Scanning Electron Microscopy

The external and internal morphology of controlled release microspheres were studied by Scanning Electron Microscopy are shown in Figure 12, the particles are surface is rough and small pores are seen which are responsible for controlled release of the drug from the microspheres.

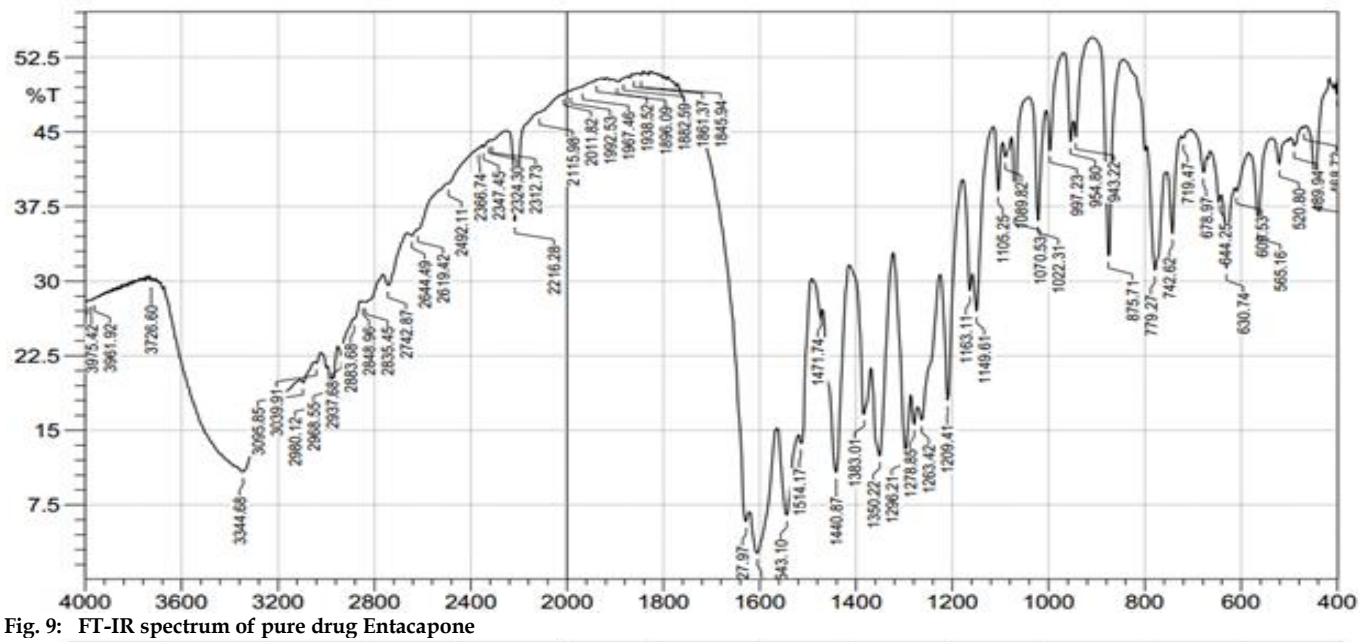

Fig. 9: FT-IR spectrum of pure drug Entacapone

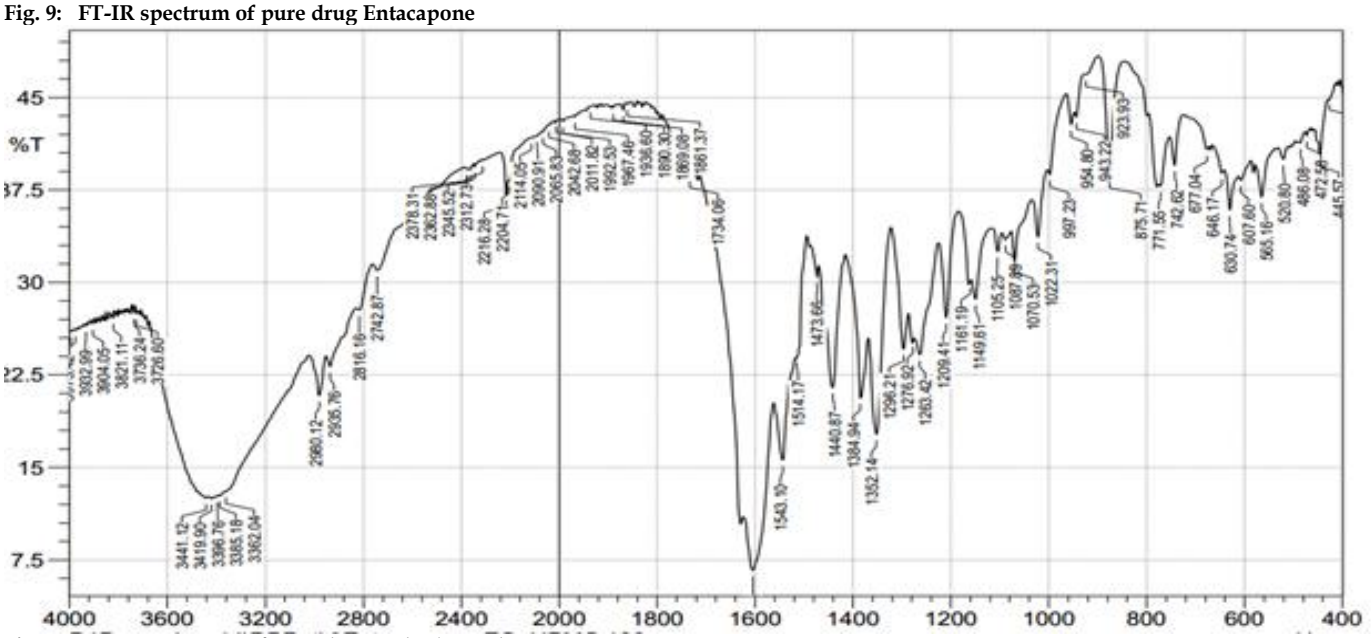

Fig. 10: FT-IR spectrum of pure drug and other polymers

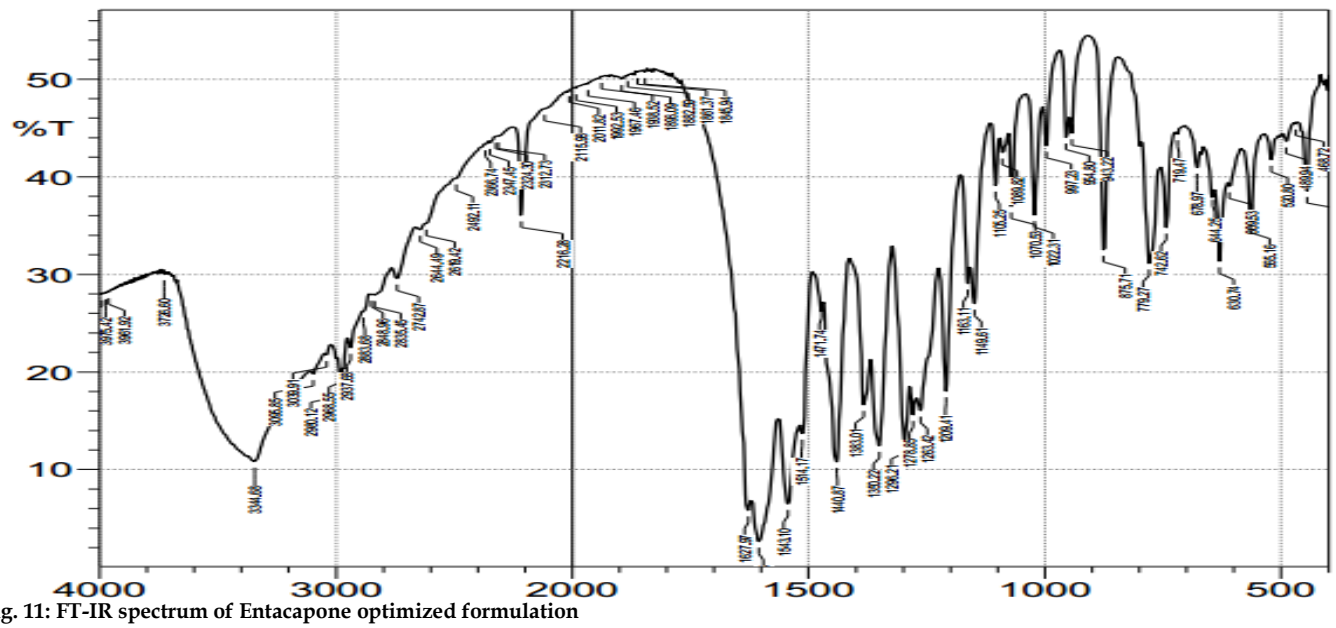

Fig. 11: FT-IR spectrum of Entacapone optimized formulation

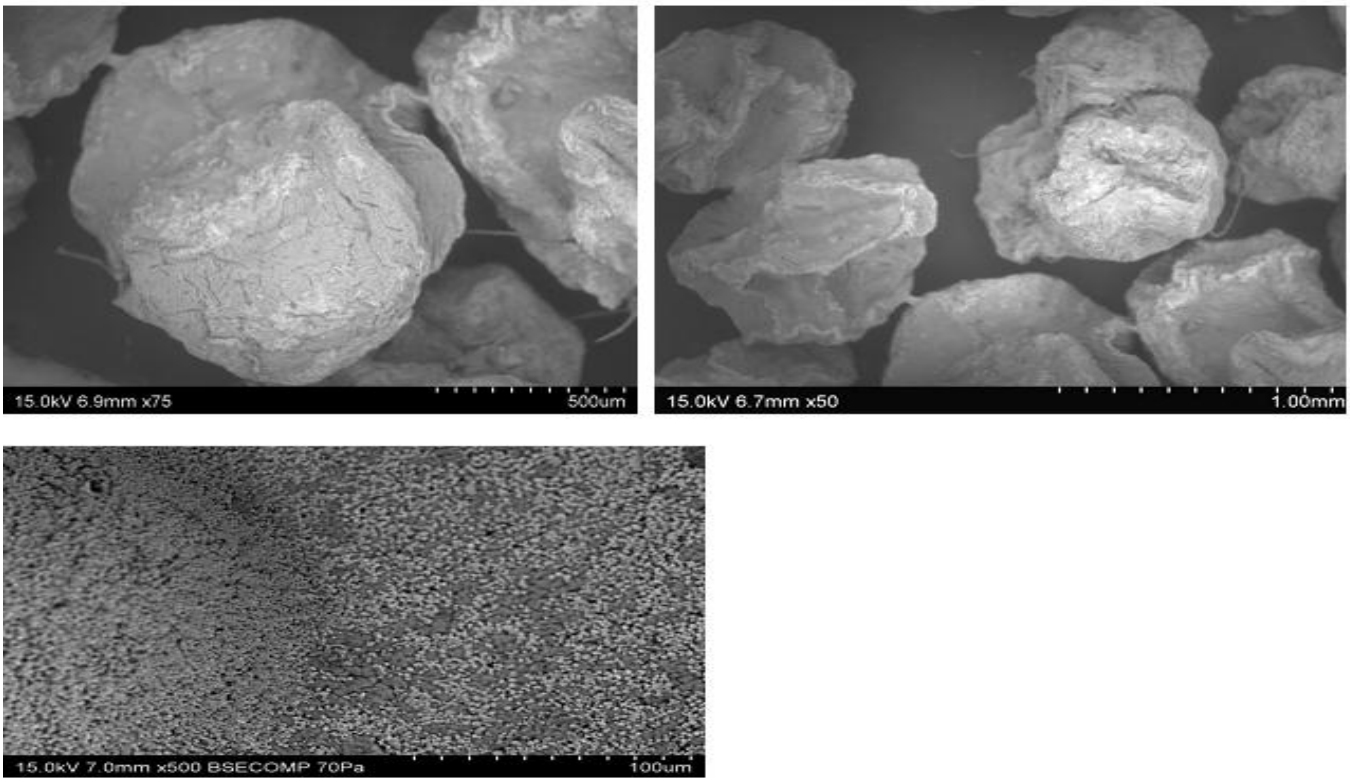

Fig. 12: Scanning electron micrographs of Entacapone floating microspheres

Stability studies

Optimized formulation F14 was selected for stability studies based on high cumulative % drug release and other parameters. 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 was depicted in Table 7.

Entacapone loaded floating microspheres were prepared by ionotropic gelation method. From the results it was concluded that formulation F14 was found to be optimized formulation based on satisfactory results in terms of excellent Micromeretic properties, particle size (65.23 ± 0.05µm), yield of microsphere (98.03%), Entrapment efficiency (97.54%), % buoyancy (98.16%), swelling index (97.67%) and highest *in vitro* drug release of 97.99 ± 5.05% in a sustained manner with constant fashion over extended period for 12 h compared with marketed product 95.12 ± 5.01 in 1 h. The drug and excipients were compatible, studied by using FTIR. Drug release from Entacapone 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. From stability studies the optimized formulation F14 was stable up to 6 months. Hence the formulated and prepared floating Entacapone microspheres may establish to be potential candidate for safe and effective sustained drug delivery and improve the bioavailability in the management of Parkinson's disease.

REFERENCES

1. Roy P, Shahiwala A. Multiparticulate formulation approach to pulsatile drug delivery: A current perspectives. Journal of Controlled Release. 2009; 134(2): 74-80.
2. Dehghan MHG, Khan FN. Gastroretentive Drug Delivery Systems: A Patent Perspective. International Journal of Health Research. March 2009; 2(1): 23-44.
3. Nayak AK, Maji R, Das B. Gastro retentive drug delivery systems: A review. Asian Journal of Pharmaceutical and Clinical Research. 2010; 3(1): 1-10.
4. Emeje MO, Kunle OO, Ofoefule SI. Compaction characteristics of ethyl cellulose in presence of some channeling agent: technical note. AAPS PharmSciTech. 2006 Sep; 7(3): E18–E21.
5. Najmuddin M, Hafiz RF, Nizamuddin M, Khalid MS. Development and evaluation of ketoprofen mini-matrices as sustained release formulation. Int. J. Chem. Sci. 2009; 7(3): 2122-2134.
6. Trivedi P, Verma AML, Garud N. Preparation and characterization of aceclofenac microspheres. Asian Journal of Pharmaceutics. 2008; April: 110-115.
7. Caroter SJ. Tutorial pharmacy Power flow and Compaction: 1st edition, CBS publishers and distributors, New Delhi, India, 1986, Chapter 19.
8. Haznedar MM, Buchsbaum MS, Hazlett EA, Shihabuddin L, New A, Siever LJ. Cingulate gyrus volume and metabolism in the schizophrenia spectrum. Schizophrenia Research. 2004; 71:249–262.
9. Banker GS, Rhodes CT. Modern Pharmaceutics: 3rd edition, Marcel Dekker Inc, New York. 2002:333-394.
10. Rockville. The United States Pharmacopoeia XX/ National Formulary XV: 15th edition. US Pharmacopoeia Convention MD. 1980:958-990.
11. Pandya N, Pandya M, Bhaskar VH. Preparation and *in vitro* Characterization of Porous Carrier-Based Glipizide Floating Microspheres for Gastric Delivery. J Young Pharm. 2011 Apr; 3(2):97-104.
12. Kampanart H, Katsuhide T, Sriamornsak P, Nunthanid J. Advanced technologies for assessment of polymer swelling and erosion behaviors in pharmaceutical aspect. Eur J Pharm Biopharm. 2013; 83: 315-321.

13. Yasunori S, Yoshiaki K, Hirofumi T, Hiromitsu Y. *In vitro* evaluation of floating and drug releasing behaviors of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method. Eur J Pharm Bio pharm. 2004; 57: 235–243.
14. Saravanan M, Anupama B. Development and evaluation of ethylcellulose floating microspheres loaded with ranitidine hydrochloride by novel solvent. Carbohydr Polymer. 2011; 85: 592–598.
15. Ninan M, Lu X, Qifang W, Xiangrong Z. Development and evaluation of new sustained-release floating microspheres. Int J Pharm. 2008; 358: 82–90.
16. Garg S, Gupta GD. Progress in controlled gastro retentive delivery systems. Trop. J Pharm Res. 2008; 7(3): 1055-66.
17. Shi G, Cai Q, Wang C, Lu N, Wang S, Bei J. Fabrication and biocompatibility of cell scaffolds of poly (L-lactic acid) and poly (L-lacticco- glycolic acid). Polym. Adv. Technol. 2002; 13: 227–232.

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