CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.8283611

Available online at: http://www.iajps.com *Research Article*

FORMULATION, CHARACTERIZATION, AND *IN-VITRO* EVALUATION OF FLOATING MICROSPHERES OF RASAGILINE MESYLATE

Dr. H. Padmalatha, N.Jyothi Reddy, V. Meghana, B. Sandhya, Y. Vijaya Lakshmi, Y. Anusha, P.Anuradha

Gyana Jyothi College of Pharmacy, Gyana Jyothi Nagar, Uppal, Hyderabad, Telangana

Abstract:

Systematic studies were conducted using two different polymers in different concentrations to prepare Rasagiline Mesylate Floating Microspheres. All the prepared systems were evaluated for the different properties. From the Preformulation studies for drug excipients compatibility, it was observed that no physical incompatibility existed between the drug and excipients.

All the four different formulations prepared contain drug about 97%-102%.

In vitro drug release profile indicated that drug release was retarded due to the presence of higher concentration of polymer. Formulation F2 has only 68%drug release in 9 hrs due to higher ratio of the polymer. Formulated Microspheres gave satisfactory results for various evaluation parameters like Angle of Repose, Drug Entrapment Efficiency, Scanning Electronic Microscopy and in vitro drug release.Comparing the two different Polymers such as HPMC and Chitosan provided better-sustained release characteristics with excellent in-vitro drug release. From the above results also indicated that at higher viscosity grades of polymer concentrations drug release was retarded greatly.

Key words: Formulation, Characterization, Vitro Evaluation, Floating Microspheres, Rasagiline Mesylate.

Corresponding author:

Dr. H. Padmalatha,

Gyana Jyothi College of Pharmacy

Gyana Jyothi Nagar, Uppal, Hyderabad, Telangana

Email Id: Padmalatha.malthar@gmail.com

QR code

Please cite this article in press H. Padmalatha et al, ***Formulation, Characterization, And In-Vitro Evaluation Of Floating Microspheres Of Rasagiline Mesylate***, Indo Am. J. P. Sci, 2023; 10 (08).

INTRODUCTION:

The constraints associated with conventional dosage forms and classical oral drug delivery systems is leading the pharmaceutical community towards a new era of drug delivery systems i.e., Novel Drug Delivery Systems (NDDS). The concept of targeted drug delivery, indeed, as a subset of NDDS is being investigated substantially nowadays. However, the concept of targeting is not new to the drug delivery domain. It dates back to 1906, when sir Paul Ehrlich, postulated the concept of 'magic bullet' and laid down the foundation of a new paradigm in the field of drug delivery [1]. Thenceforth, the concept has been evolving continuously, with newer and innovative approaches adding on to the existing knowledge.

Targeting refers to the selective accumulation of cargo in organs, tissues, cells or intracellular structures by systemic or local drug delivery [2]. The preferential accumulation of the drugs at the targeted site spares the rest of the healthy tissues of the body and increases the therapeutic index of the drug, thus improving the overall treatment outcome [3]. Targeting a drug delivery system, either passively or by specific means requires the use of carriers such as nanoparticles, liposomes, micellar systems, microspheres etc [4].

The growing number of studies in the recent years, illustrating the potential use of microspheres as drug delivery carriers for targeted delivery has attracted the attention of researchers across the globe. Microspheres are free-flowing particles ranging between 1 μm and 1000μm and are capable of delivering the therapeutics with a satisfactory sustained release/controlled release profile [5]. They are matrix particles in which the actives are homogeneously distributed in the polymeric network. They are capable of encapsulating small molecules, proteins/peptides and nucleic acids [6]. The high translational efficiency and clinical success rate compared to nanoparticles give them an upper-hand over nanoparticulate drug delivery systems [7]. They provide several advantages over conventional dosage forms like enhanced solubility of poorly soluble drugs, protection of drugs from enzymatic and photolytic degradation, decreased dosing frequency, improved bioavailability, providing controlled release profile, reduction in dose and drug toxicities, etc [8]. They can be manufactured by various techniques including solvent evaporation [9,10], spray drying [11,12], phase separation [13] and polymerization [14].

The currently marketed microsphere formulations are available as long-acting injectable depots which provide controlled release of the encapsulated drug over a specific period of time. Most of these formulations contain hormonal analogues as the encapsulated drugs [15]. Apart from hormones, several other drugs acting on central nervous system and some opioid antagonists are also available as microsphere formulations for several applications [16]. Unfortunately, microspheres for targeted delivery of the drugs are not available in the market till date. However, a lot of research is currently in progress where these carriers are being explored for their applications in Targeted Drug Delivery System (TDDS). Indeed, several ongoing clinical trials on microspheres encapsulating anticancer drugs like doxorubicin (DOX) and irinotecan for colon cancer, rectal cancer and hepatocellular carcinoma are the proofs which showcase the potential of microspheres to be used in targeting drugs to desired locations [17,18].

The main objective of the study was to formulate and evaluate Floating microspheres of Rasagiline Mesylate which is expected to deliver the drug in controlled manner with reduced frequency of drug administration, improve patient compliance & bioavailability of Rasagiline Mesylate.

This study mainly deals in the design of a formulation which produces time controlled prolonged drug release and to enhance the bioavailability of the drug to about 90% and also to reduce the dosing interval of the drug.

To design, formulate & carryout the in-vitro evaluation studies on floating microspheres of Rasagiline Mesylate.

MATERIALS AND METHODS:

The following materials were used as supplied by the manufacturers.

Table 1: Materials Used

S. No.	Chemicals	Supplied by
1	Rasagiline Mesylate	Microlabs, Bangalore
2	HPMC	Oxford Laboratories, Mumbai
3	Chitosan	Central Institute of Fisheries, Kerala
4	Sodium Alginate	S.D. Fine Chem. Ltd, Mumbai
5	Sodium Bicarbonate	S.D. Fine Chem. Ltd, Mumbai
6	DichloroMethane	S.D. Fine Chem. Ltd, Mumbai
7	Ethanol	S.D. Fine Chem. Ltd, Mumbai
8	Petroleum Ether	S.D. Fine Chem. Ltd, Mumbai
9	-hexane	S.D. Fine Chem. Ltd, Mumbai

Rasagiline is an irreversible inhibitor of monoamine oxidase used for the symptomatic management of idiopathic Parkinson's disease as initial monotherapy and as adjunct therapy to levodopa. The precise mechanisms of action of rasagiline is unknown. One mechanism is believed to be related to its MAO-B inhibitory activity, which causes an increase in extracellular levels of dopamine in the striatum. The elevated dopamine level and subsequent increased dopaminergic activity are likely to mediate rasagiline's beneficial effects seen in models of dopaminergic motor dysfunction.

PRE-FORMULATION STUDY

Prior to the development of the dosage forms the Preformulation study was carried out. Hence Infrared spectra of the physical mixture of the drug and the polymers chosen were taken. The infra-red spectra of the drug and polymers were also taken.

The application of infra-red spectroscopy lies more in the qualitative identification of substances either in pure form or in the mixture and as a tool in establishment of the structure. Since I.R. is related to covalent bonds, the spectra can provide detailed information about the structure of molecular compounds. In order to establish this point, comparisons can be made between the spectrum of the substance and the drug.

STANDARD PLOT FOR ESOMEPRAZOLEMAGNESIUM TRIHYDRATE

Standard Graph by usin:g Phosphate Buffer (pH 7.4)

Accurately weighed 10 mg of Rasagiline Mesylatewas dissolved in 100 ml of 7.4 pH buffer solution to form 100 µg/ml stock solutions.

From this stock solution aliquots of 2.5 ml, 5 ml, 7.5 ml, 10 ml, 12.5 ml, 15 ml, 17.5ml, 20 ml, 22.5 ml, 25 ml were pipette out into a series of 50 ml in order to get a concentration ranging from 5-50µg/ml.

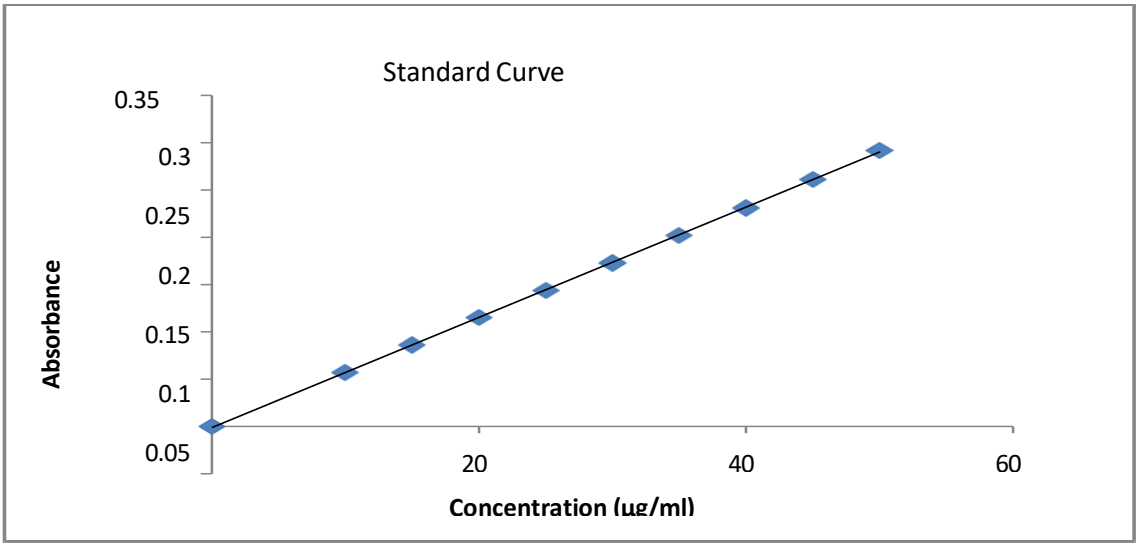
The absorbance of the resulting solution was then measured at 301 nm using UV spectrophotometer against respective parent solvent as a blank. The standard curve was obtained by plotting absorbance Vs. concentration µg/ml.

Table No. 2: Standard Calibration Curve of Rasagiline Mesylate

SL. No	CONCENTRATION(µg/ml)	ABSORBANCE
1	**10**	**0.057**
2	**15**	**0.086**
3	**20**	**0.115**
4	**25**	**0.144**
5	**30**	**0.173**
6	**35**	**0.202**
7	**40**	**0.231**
8	**45**	**0.261**
9	**50**	**0.292**

Graph No.1

Standard Calibaration Curve of Rasagiline Mesylate



b) SOLUBILITY STUDIES:

Table No.3
Solubility studies of Rasagiline Mesylate

S. No.	Solvents	Observed
1	PBS-7.4(pH)	Freely soluble
2	Ethanol	Freely soluble
3	Dichloro Methane	Freely soluble

***FT-IR* SPECTRA OF RASAGILINE MESYLATE**

The *FT-IR* analysis of the Rasagiline Mesylatewas carried out for qualitative compound identification. The *FT-IR* spectra for pure drug and with other excipients was obtained by placing the drug directly into the cavity and was determined by *FT-IR* spectrophotometer in the wave number region of 4000-400 cm^{-1}.

Table No.4
Comparison of I.R. Spectra of Rasagiline Mesylate and in Combination with Polymers

S. No	Sample	C=O (cm^{-1})	-CC (cm^{-1})	-CH (cm^{-1})
1	Rasagiline Mesylate	3182	1462	919
2	RM + HPMC	3183	1458	915
3	RM + Chitosan	3182	1462	919
4	RM + Na_2CO_3	3182	1495	919
5	RM + HPMC+ Chitosan	3182	1462	919

Preparation of Microspheres:

In the present study, microspheres are prepared using ***Emulsion-Polymerization*** method. In this method, polymeric drug solution i.e., drug + polymer and solvent system (DicloroMethane + Ethanol) of 10 ml is added to 10 % solution of egg albumin. This polymeric phase is stirred continuously to form a uniform dispersion. In another beaker 86 ml of coconut oil containing 1 ml of 0.5% Sodium Lauryl Sulphate is taken which forms the organic phase. The polymeric phase is added drop wise using needle into the organic phase. It is continuously stirred for 2 hrs with a speed of 700 rpm using stirrer. After stirring 1 ml of formaldehyde is added and obtained microspheres are washed thrice with 20 ml of □–hexane and the obtained final microspheres are stored in a dessicator.

Table No. 5
Formulation Design For Floating Microspheres of Rasagiline Mesylate

Formulation No.	Drug in mg	HPMC (mg)	Chitosan (mg)	Sodium Bicarbonate (% W/V)	Sodium Alginate (% W/V)
F_1 (1:1)	50	50	-	1 %	2 %
F_2 (1:1.5)	50	75	-	1 %	2 %
F_3 (1;1)	50	-	50	1 %	2 %
F_4 (1;1.5)	50	-	75	1 %	2 %

PARTICLE SIZE DETERMINATION

The particle size of a pharmaceutical preparation is strictly maintained in order to get optimal biological activity.

Methods to estimate particle size are

a. Optical Microscopy
b. Sieving Method
c. Sedimentation Method
d. Elutriation Method
e. Centrifugal refractometry
f. Permeability Method
g. Light scattering Method

Table No. 6
Common techniques for measuring fine particles of various sizes

S. No.	Technique	Particle sizes in (µm)
1	Optical Microscopy	1-100 µm
2	Sieving	> 50 µm
3	Sedimentation	> 1 µm
4	Elutriation	1-50 µm
5	Centrifugation	< 50 µm
6	Permeability	> 1 µm
7	Light Scattering	0.5-50 µm

RESULTS:

SCANNING ELECTRON MICROSCOPY

Procedure

Morphology details of the specimens were determined by using a Scanning Electron Microscope (SEM), Model JSM 35CF, JEOL, Japan.

The samples were dried thoroughly in Vaccum dessicator before mounting on brass specimen studies. The samples were mounted on specimen studies using Double sided adhesive tape. The sputtering was done for nearly 3 minutes to obtain uniform coating on the sample to enable good quality SEM images. The SEM was operated at low accelerating voltage.

The condenser lens position was maintained between 4.4-5.1. The objective lens aperture has a diameter of 240 microns and the Working Distance WD is 39 mm.

Fig No.2
SEM of Prepared Microspheres Under Low Magnification

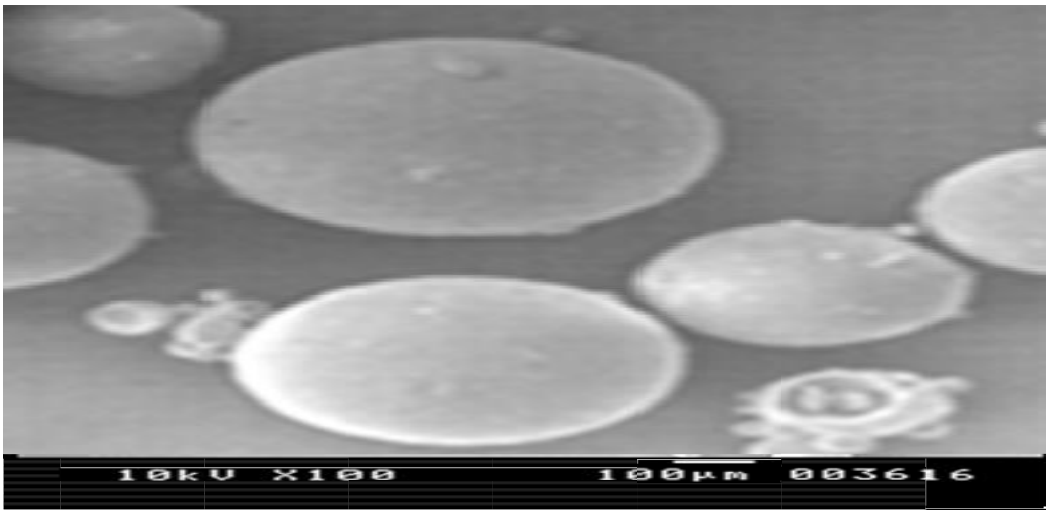
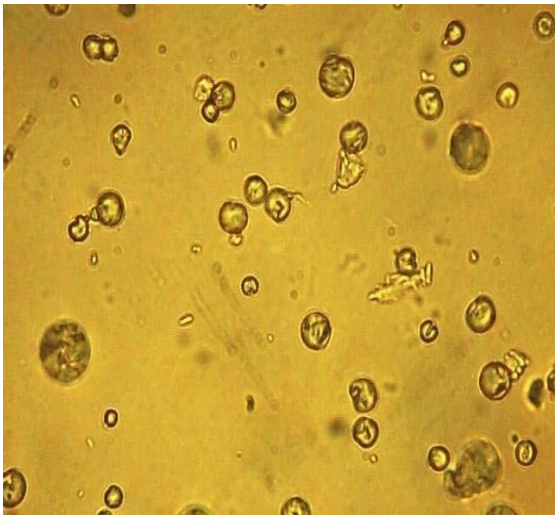


Fig No. 3
Microscopic Pictures of Rasagiline Mesylate Floating Microspheres



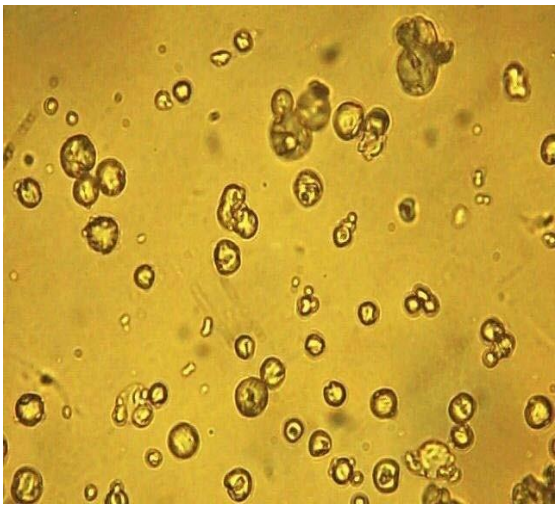


Table No.7

Relation between Angle of Repose and Flow of the Particles

Angle of repose (º) (degrees)	Type of flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

Table No.8
Angle of Repose of Microparticles

S. No.	Formulation	Angle of repose
1	F1	25º70’
2	F2	28º29’
3	F3	29º74’
4	F4	30º96’

DRUG ENTRAPMENT EFFICIENCY

Drug entrapment efficiency of Rasagiline Mesylate was performed by accurately weighing 100 mg of microparticles and suspend in 100 ml of simulated intestinal fluid of pH 7.4±0.1 and it was kept for 12 hrs. Next day it was stirred for 15 min, and subjected for filtration. After suitable dilution, Rasagiline Mesylate content in the filtrate was analyzed Spectrophotometrically at 301 nm using Shimadzu 1201 UV-visible spectrophotometer.

The absorbance found from the UV-Spectrophotometer was plotted on the standard curve to get the concentration of the entrapped drug. Calculating this concentration with the dilution factor we get the percentage drug encapsulated in microparticles.

Table No.9
Drug Entrapment Efficiency of Microparticles

Formulation	Absorbance at 301 nm	Theoretical yield (mg)	Practical yield (mg)	Drug Entrapment Efficiency
F1	0.059	50	20.34	79.66
F2	0.054	50	18.62	81.38
F3	0.032	50	11.03	88.97
F4	0.0481	50	16.58	83.42

***In-vitro* Dissolution Studies**

A drug is expected to release from the solid dosage forms (granules, tablets, capsules etc) and immediately go into molecular solution. This process is called as Dissolution.

Drug release studies

The method specified in USP for the drug release study was followed.

Apparatus

USP XXIII dissolution test apparatus employing the round bottom dissolution vessel and rotating basket assembly.

Buffer stage

900 ml of pH 7.4 intestinal fluid (phosphate buffer) is used as dissolution media.

Time

At every 1 hr interval upto 12 hours.

Procedure

In-vitro release profile of the microparticles was evaluated using rotating basket dissolution apparatus. 900 ml of phosphate buffer (pH 7.4) maintained at 37±0.5ºC is used as dissolution Media, and the basket was rotated at a constant speed of 75 rpm. Accurately weighed amount of microparticles were placed in the baskets.

Aliquots of samples were withdrawn at the interval of 1 hour for 9 hours in phosphate buffer pH 7.4. The samples withdrawn were filtered, diluted suitably and analyzed at 301 nm spectrophotometrically for drug release.

Table No. 10

***In-vitro* Dissolution Profile for Formulation F_1**

Time (hrs)	Absorbance	Concentration	Cumulative % Drug Released
1	0.08	0.275	9.931
2	0.12	0.413	14.89
3	0.18	0.620	22.34
4	0.22	0.758	27.31
5	0.25	0.862	31.03
6	0.29	1.031	36.01
7	0.35	1.206	43.44
8	0.43	1.482	53.37
9	0.57	1.965	70.75
10	0.65	2.241	80.68
11	0.71	2.448	88.13
12	0.75	2.586	93.10

Graph No 4
Cumulative % Drug Release Vs Time

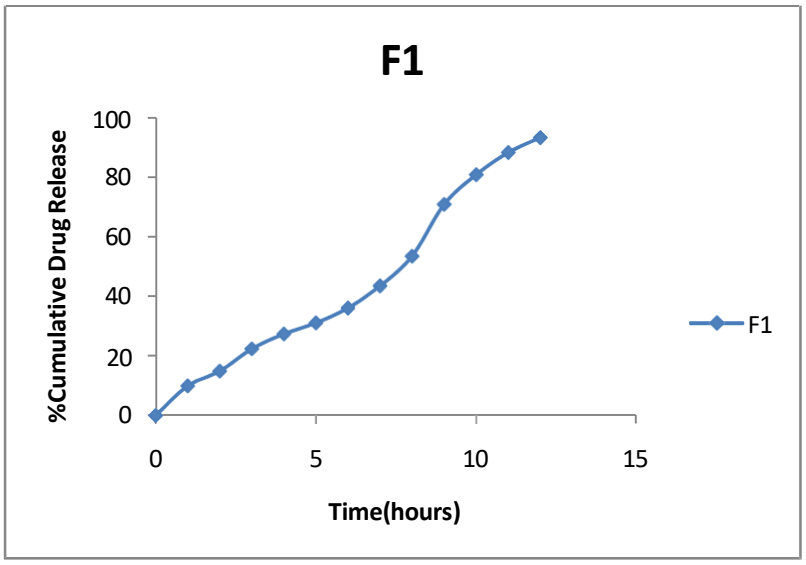


Table No.11

***In-vitro* Dissolution Profile for Formulation F_2**

Time (hrs)	Absorbance	Concentration	Cumulative % Drug Released
1	0.07	0.214	8.68
2	0.09	0.310	11.17
3	0.13	0.448	16.13
4	0.15	0.517	18.62
5	0.21	0.724	26.03
6	0.28	0.965	34.75
7	0.34	1.172	42.20
8	0.37	1.275	45.93
9	0.44	1.517	54.62
10	0.48	1.655	59.58
11	0.54	1.862	67.03
12	0.74	2.551	91.86

Graph No 5

Cumulative % Drug Release Vs Time

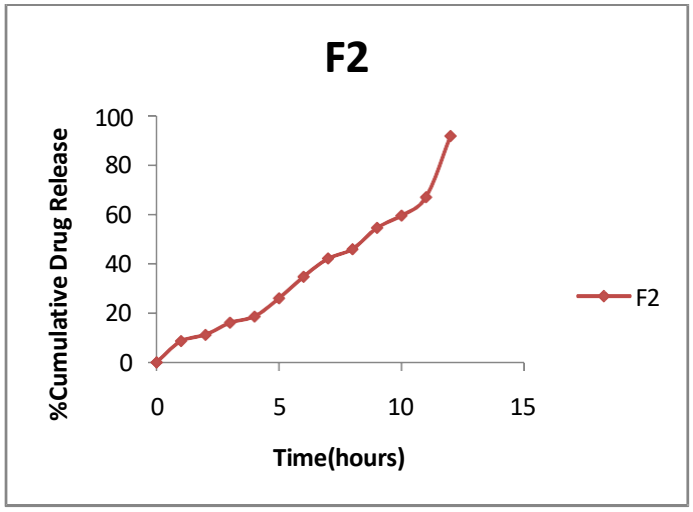


Table No.12

***In-vitro* Dissolution Profile for Formulation F_3**

Time (hrs)	Absorbance	Concentration	Cumulative % Drug Released
1	0.09	0.31	11.17
2	0.13	0.044	16.13
3	0.23	0.724	26.06
4	0.25	0.852	31.03
5	0.29	1.068	38.48
6	0.34	1.172	42.20
7	0.41	1.413	50.88
8	0.53	1.827	65.79
9	0.58	2.006	72.28
10	0.62	2.137	76.96
11	0.68	2.379	85.65
12	0.78	2.689	96.82

Graph No 6

Cumulative % Drug Release Vs Time

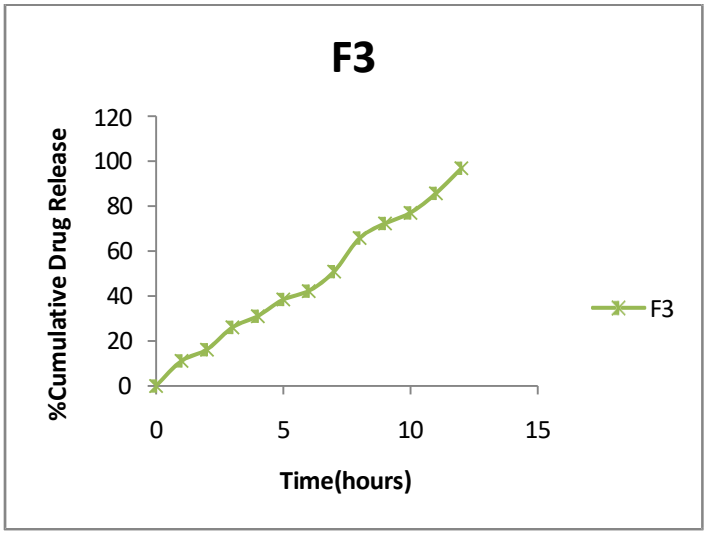


Table No.13

***In-vitro* Dissolution Profile for Formulation F_4**

Time (hrs)	Absorbance	Concentration	Cumulative % Drug Released
1	0.07	0.241	8.6
2	0.12	0.413	14.9
3	0.19	0.655	23.5
4	0.23	0.793	28.55
5	0.31	1.068	38.48
6	0.38	1.310	47.17
7	0.46	1.586	57.10
8	0.53	1.827	65.79
9	0.59	2.034	73.24
10	0.63	2.172	78.20
11	0.65	2.241	80.68
12	0.76	2.620	94.34

Graph No 7
Cumulative % Drug Release Vs Time

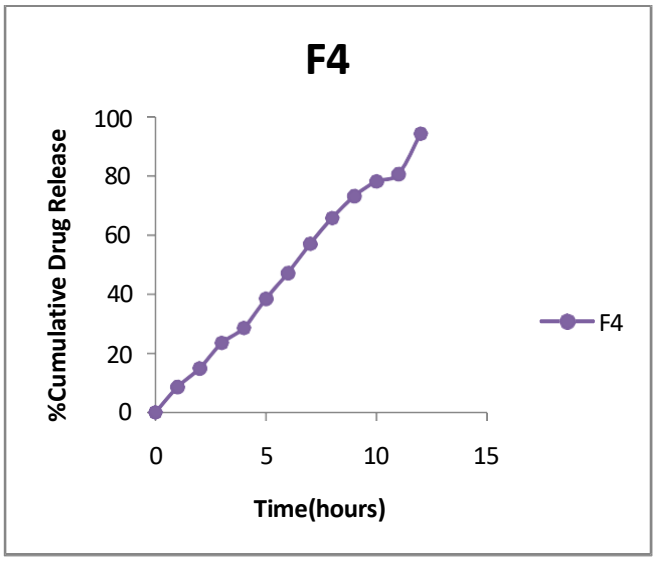


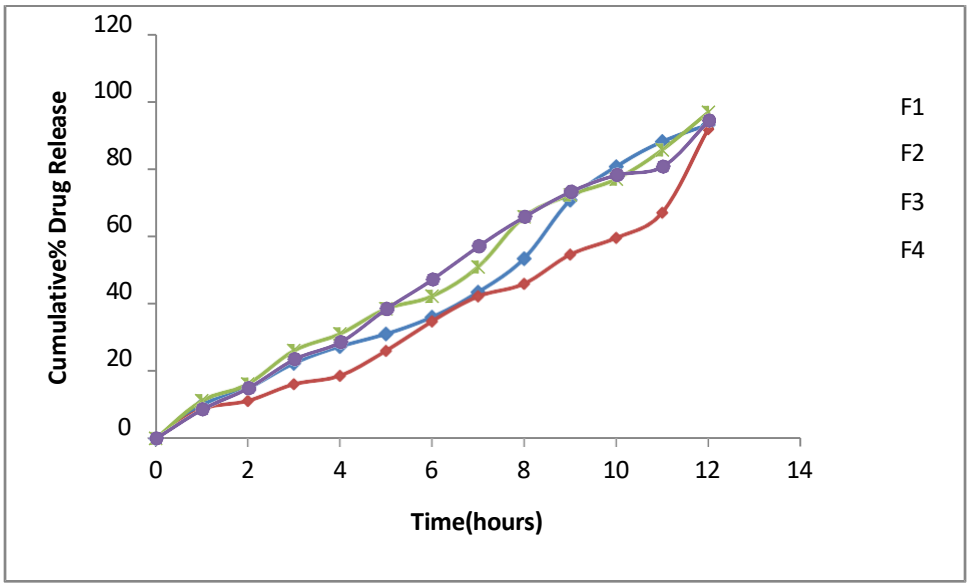
Table No.14

Cumulative % Drug Release Vs Time

	Cumulative % Drug Release			
Time (hrs)	**F_1**	**F_2**	**F_3**	**F_4**
1	9.931	8.68	11.17	8.6
2	14.89	11.17	16.13	14.9
3	22.34	16.13	26.06	23.5
4	27.31	18.62	31.03	28.55
5	31.03	26.03	38.48	38.48
6	36.01	34.75	42.20	47.17
7	43.44	42.20	50.88	57.10
8	53.37	45.93	65.79	65.79
9	70.75	54.62	72.28	73.24
10	80.68	59.58	76.96	78.20
11	88.13	67.03	85.65	80.68
12	93.10	91.86	96.82	94.34

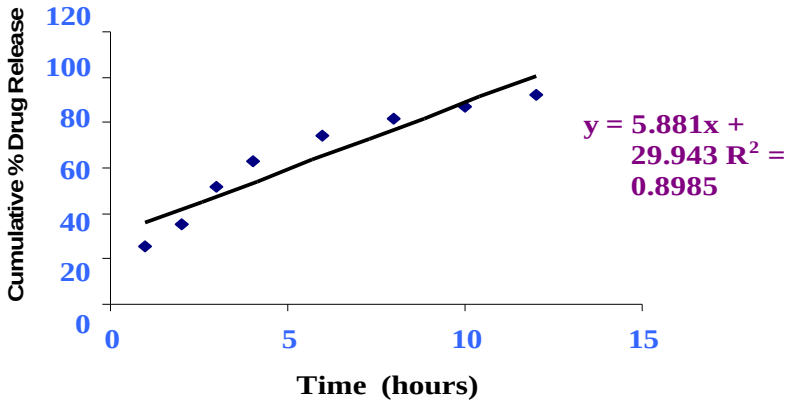
Graph No.8

Percentage Cumulative Percentage Drug Release Vs Time



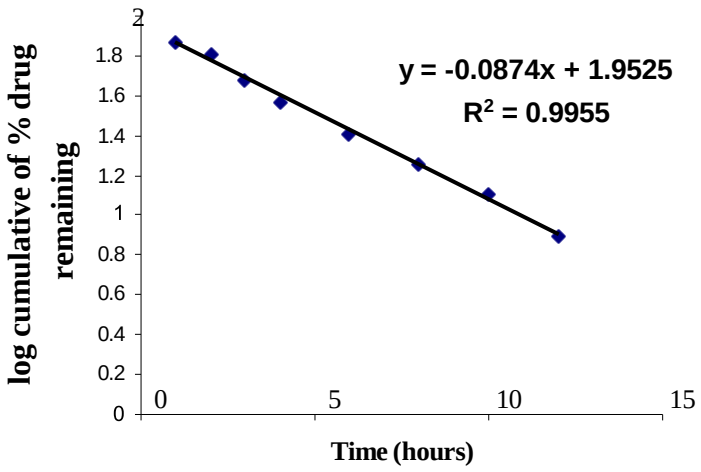
Graph No 9

Zero Order Release Model Of Formulation F3



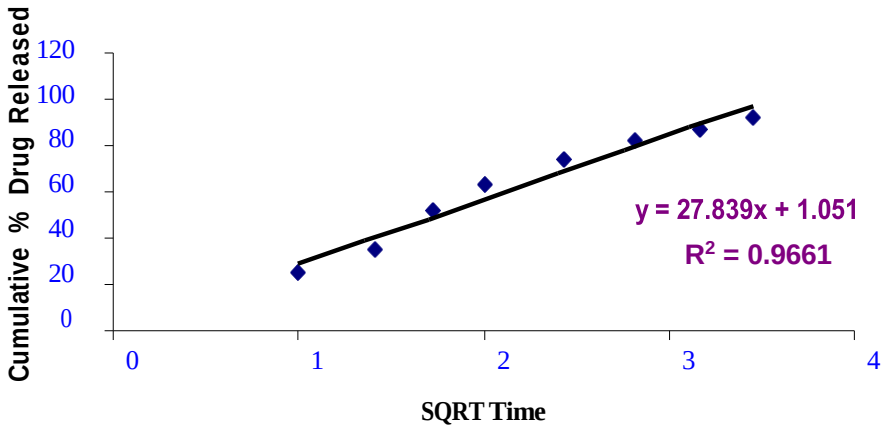
Graph No 10

First order Release Model Of Formulation F3



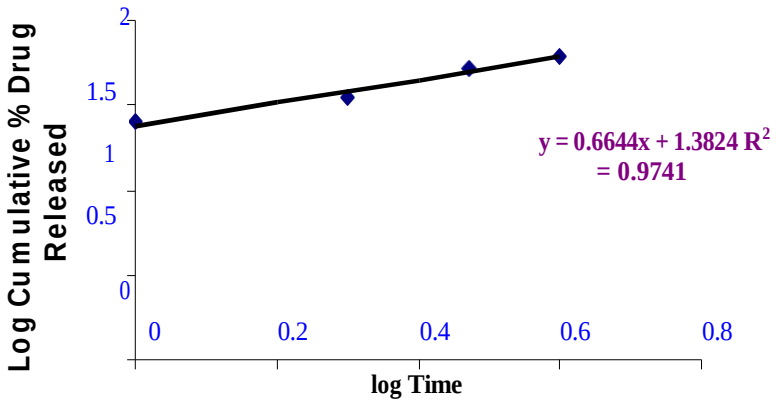
Graph No 11

Higuchi release model for formulation F3



Graph No 12

Korsmeyer-Peppas release model for formulation F3



Accelerated Stability Studies

The formulations were stored in an oven at 37±1°c and 60±1°c for a period of six weeks. The samples were analyzed for drug content every week by Spectrophotometer at 301nm.

Method

Microspheres were individually wrapped in aluminium foil and packed in amber colured screw capped bottle and put under specified condition in incubator for 3 months. After 3 months the microspheres were evaluated for *In-vitro* drug release.

Table No.16
Results of Assay of Formulation After Accelerated Stability Studies

Days	37°C	60°C
1	82.13	81.08
7	82.08	80.35
14	81.05	79.01
21	80.92	78.03
28	79.87	78.26
35	77.86	77.22
42	76.26	76.28

DISCUSSION:

Floating Microspheres of Rasagiline Mesylate were prepared by emulsion polymerization technique and various evaluation parameters were assessed, with a view to obtain oral controlled released of Rasagiline Mesylate.

The prepared microparticles were then subjected to granulometric study, angle of repose, scanning electron microscopy, drug entrapment efficiency, *in-vitro* dissolution and stability studies.

A standard calibration curve for the drug was obtained by measuring absorbance at 301 nm, and by plotting the graph of absorbance Vs concentration.

Angle of Repose

Acceptable range of angle of repose is 22º61' to 31º60'. All the formulations showed an angle of repose within the range.

Formulations F_1 to F_4 showed an angle of repose in the acceptable range, which indicates a good flow property.

The drug entrapment efficiency of all the formulations were in the range between 78.62 % to 91.25%.

The dissolution studies were conducted by using dissolution medias, a pH 7.4.

The data obtained in the in-vitro dissolution studies were grouped according to modes of data treatment as follows:

- Cumulative percent drug release Vs. Time (Zero-order).
- Cumulative percent drug retained Vs. Square root of Time (Higuchi Model).
- Log Cumulative percent drug retained Vs. Time (First-order).
- Cumulative percent drug release in (mg) Vs. Time (Korsmeyer-Peppas Model).

The results of the in-vitro dissolution studies of formulation F_1 to F_4 are shown in **Table.** The plots of Cumulative percentage drug release Vs. Time, is drawn and represented graphically.

Morphology of the microparticles were investigated by Scanning Electron Microscopy. The photographs of formulations taken by Scanning Electron Microscope are shown in the **Figure.**

Stability study was carried out for the formulation F_3 at 40ºC ± 1ºC for a period of 45 days.

SUMMARY:

Systematic studies were conducted using two different polymers in different concentrations to prepare Rasagiline Mesylate Floating Microspheres. All the prepared systems were evaluated for the different properties.

From the Preformulation studies for drug excipients compatibility, it was observed that no physical incompatibility existed between the drug and excipients.

All the four different formulations prepared contain drug about 97%-102%.

In vitro drug release profile indicated that drug release was retarded due to the presence of higher concentration of polymer.

Formulation F2 has only 68%drug release in 9 hrs due to higher ratio of the polymer.

Formulated Microspheres gave satisfactory results for various evaluation parameters like Angle of Repose, Drug Entrapment Efficiency, Scanning Electronic Microscopy and *in vitro* drug release.

Comparing the two different Polymers such as HPMC and Chitosan provided better-sustained release characteristics with excellent in-vitro drug release. From the above results also indicated that at higher viscosity grades of polymer concentrations drug release was retarded greatly.

CONCLUSION:

Floating microspheres of Rasagiline Mesylate can be formulated as an approach to increase residence time and thereby improve its bioavailability. Formulation F3 gave better-controlled drug release in comparison to the other formulations. Among the polymers used to improve the gastric residence, Chitosan showed better control over drug release.

The drug release pattern from the optimized formulations was best fitted to Korsmeyer-Peppas model and zero order kinetics. Drug – excipients interaction of optimized formulations was carried out by using FTIR studies. In this analysis drug – excipients compatibility interactions were not observed.

In conclusion, very promising in vitro drug release results were observed with Floating microspheres of Rasagiline Mesylate, further there is a scope to conduct the bioavailability studies in human volunteers to know the exact pharmacokinetics of the developed floating microspheres of Rasagiline Mesylate.

REFERENCES:

1. Reddy BV, Krishnaveni K. Formulation and evaluation of efavirenz microspheres. Der Pharmacia letters. 2015; 7(6):1-9.
2. Thanoo BC, Sunny MC, Jayakrishnan A. Cross-linked chitosan microspheres: preparation and evaluation as a matrix for the controlled release of pharmaceuticals. Journal of pharmacy and pharmacology. 1992 Apr; 44(4):283-6.
3. Sahil K, Akanksha M, Premjeet S, Bilandi A, Kapoor B. Microsphere: A review. Int. J. Res. Pharm. Chem. 2011;1(4):1184-98.
4. Virmani T, Gupta J. Pharmaceutical application of microspheres: an approach for the treatment of various diseases. Int J Pharm Sci Res. 2017; 8(8):3253-60.
5. Li SP, Kowarski CR, Feld KM, Grim WM. Recent advances in microencapsulation technology and equipment. Drug Development and Industrial Pharmacy. 1988 Jan 1; 14(2-3):353-76.
6. Kreuter J, Nefzger M, Liehl E, CzokR VR. Microspheres–A Novel Approach in Drug Delivery System. J Pharm sci. 1983; 72:1146.
7. Margel S, Wiesel E. Acrolein polymerization: monodisperse, homo, and hybrido microspheres, synthesis, mechanism, and reactions. Journal of Polymer Science: Polymer Chemistry Edition. 1984 Jan; 22(1):145-58.
8. Wakiyama N, Juni K, Nakano M. Preparation and evaluation in vitro of polylactic acid microspheres containing local anesthetics. Chemical and Pharmaceutical Bulletin. 1981 Nov 25; 29(11):3363-8.
9. Patel NR, Patel DA, Bharadia PD, Pandya V, Modi D. Microsphere as a novel drug delivery. International Journal of Pharmacy & Life Sciences. 2011 Aug 1; 2(8).
10. Toshio Y, Mitsuru H, Shozo M, Hitoshi S. Specific delivery of mitomycin c to the liver, spleen and lung: Nano-and m1crospherical carriers of gelatin. International Journal of Pharmaceutics. 1981 Apr 1;8(2):131-41.
11. Patel NR, Patel DA, Bharadia PD, Pandya V, Modi D. Microsphere as a novel drug delivery. International Journal of Pharmacy & Life Sciences. 2011 Aug 1;2(8).
12. Herfarth H, Obermeier F, Andus T, Rogler G, Nikolaus S, Kuehbacher T, Schreiber S. Improvement of arthritis and arthralgia after treatment with infliximab (Remicade) in a German prospective, open-label, multicenter trial in refractory Crohn's disease. The American journal of gastroenterology. 2002 Oct 1;97(10):2688.
13. Kavita K, Ashvini VR, Ganesh NS. Albumin microspheres. Unique system as drug delivery carriers for non steroidal anti-inflammatory drugs. Int J Pharm Sci Rev Res. 2010; 5(2):10.
14. Virmani T, Gupta J. Pharmaceutical application of microspheres: an approach for the treatment of various diseases. Int J Pharm Sci Res. 2017; 8(8):3253-60.
15. Gullotti E, Yeo Y. Extracellularly activated nanocarriers: a new paradigm of tumor targeted

drug delivery. Molecular pharmaceutics. 2009 Aug 3; 6(4):1041-51.
16. Alagusundaram M, Chetty MS, Umashankari K, Badarinath AV, Lavanya C, Ramkanth S. Microspheres as a novel drug delivery system: A review. Int J Chem Tech Res. 2009 Jul; 1(3):526-34.
17. Rathore B, Yadav A, Nayak G, Saraogi GK, Singhai AK. A review on microspheres as drug delivery carriers for management of diabetes mellitus. International journal of pharmacy & life sciences. 2012 Oct 1; 3(10).
18. Prasad BS, Gupta VR, Devanna N, Jayasurya K. Microspheres as drug delivery system-a review. J Glob Trends Pharm Sci. 2014; 5(3):1961-72.