ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2016; 2(10): 47-53
www.allresearchjournal.com
Received: 14-08-2016
Accepted: 15-09-2016

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Formulation and evaluation of Rasagiline floating tablets using HPMC

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Abstract
The aim of the present work was to develop a gastro retentive drug delivery system of Rasagiline with the objective of retarding the drug release when the dosage form is exposed to gastrointestinal fluid. Floating tablets of Rasagiline were developed using a HPMC K 250 PH PRM, HPMC K750 PH PRM, and HPMC K1500 PH PRM. The prepared tablets were evaluated in terms of their pre compression parameters, physical characteristics, *In Vitro* buoyancy, *In Vitro* drug release and release order kinetics. The results of *In Vitro* release studies showed that optimized formulation (F19) could sustain drug release (98.92%) for 24 h and remain buoyant for 24 h. The optimized formulation was subjected to various release kinetic investigations and it was found that the mechanism of drug release was predominantly diffusion with a minor contribution from polymeric relaxation. Floating tablets of Rasagiline were successfully formulated with the ability of providing controlled release and non-Fickian transport of the drug from tablets was confirmed.

Keywords: Rasagiline, Floating tablets, HPM

Introduction
Oral delivery of the drug is the most preferable route of drug delivery due to the ease of administration, patient compliance, and flexibility in the formulations [1] To prolong the residence time of dosage forms within gastrointestinal tract until all drug is released at desired rate is one of the real challenges for oral controlled release drug delivery system [2] In the present era, gastro-retentive dosage forms (GRDF) receive great attention because they can improve the performance of controlled release systems. An optimum GRDF system can be defined as a system which remains in the stomach for a sufficient time interval against all the physiological barriers, releases active moiety in a controlled manner, and finally is easily metabolized in the body. Physiological barriers like gastric motility and gastric retention time (GRT) act as obstacles in developing an efficient GRDF [3Several technical approaches are currently utilized in the prolongation of gastric residence time, including high density, swelling and expanding, polymeric mucoadhesive, ion-exchange, raft forming, magnetic and floating drug delivery systems (FDDS), as well as other delayed gastric emptying devices [4Since decade or two, the development of floating drug delivery systems becomes a significant and novel tool as having low density than gastric content [5]
Rasagiline mesylate is a propargylamine and an irreversible inhibitor of monoamine oxidase (MAO). MAO, a flavin-containing enzyme, regulates the metabolic degradation of catecholamines and serotonin in the CNS and peripheral tissues it is used in the treatment of Parkinson's disease. The short half-life of Rasagiline mesylate necessitated for fabricating floating release tablets to provide a therapeutic amount of drug and maintain the desired drug concentration i.e. the drug- delivery system should deliver drug at a rate dictated by the needs of the body over a specific period of time.

Materials and Methods
Materials
Rasagiline mesylate pure drug was generous gift from Aurobindo Pharma Limited, Hyderabad, India. HPMC K 250 PH PRM, Carnauba wax, Sodium Bicarbonate, MCC, HPMC K 750 PH PRM, HPMC K 1500 PH PRM, was obtained from Rubicon labs,

Mumbai. Xanthan gum and Polyox WSR 303 ere gifted from MSN Labs Ltd. Hyderabad. All other chemicals used were of analytical grade.

Methods

Micromeritic Studies of Rasagiline Mesylate

Angle of repose

A funnel was fixed at a height approximately 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the tip of powder cone so formed just touched the tip of funnel stem**.** Angle of repose was then determined by measuring the height of the cone of powder and radius of the circular base of powder heap.

Density analysis

The volume of powder packing was determined on an apparatus consisting of a graduated cylinder mounted on a mechanical tapping device that has a specially cut rotating cam. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel [6] Initial volume of powder was noted and the sample subjected to tapping (500, 750 or 1250 tappings) until no further reduction in volume was noted or the percentage of difference in volume was not more than 2%. A sufficient number of taps should be employed to assure reproducibility for the material in question. The tapping should not produce particle attrition or a change in the particle size distribution of the material being tested.

Compressibility index and Hausner ratio

In recent years compressibility index and the closely related Hausner ratio have become the simple, fast and popular methods of predicting powder flow characteristics. Compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and Hausner ratio are determined by measuring both bulk density and the tapped density of a powder.

Sieve analysis

The procedure involves the electromagnetic sieve shaking of the sample through the series of successively arranged sieves (sieve no. 20, 30, 60, 80 and 100 and receiver), and weighing of the portion of the sample retained on each sieve and calculating percentage retained on each sieve.

Evaluation of Final Blend

The Final blend of all formulations was evaluated for Bulk density, Tapped density, Compressibility Index (CI), Hausner ratio and Angle of repose[7].

Formulation Method

Accurately weighed quantities of polymers and MCC were taken in a mortar and mixed geometrically, to this required quantity of Rasagiline was added and mixed slightly with pestle. Accurately weighed quantity of Sodium bicarbonate was taken separately in a mortar and powdered with pestle. The powder is passed through sieve no 40 and mixed with the drug blend which is also passed through sieve no 40. The whole mixture was collected in a plastic bag and mixed for 3 minutes. To this Magnesium stearate was added and mixed for 5 minutes, later Talc was added and mixed for 2 minutes [7The mixture equivalent to 300mg was compressed into tablets with 10mm round concave punches at a hardness of 6 kg/cm^2.

Table 1: Composition of floating tablets of Rasagiline with HPMC K 250 PH PRM

Ingredients (weight in mg)	Formulations						
	F1	F2	F3	F4	F5	F6	F7
Rasagiline	1	1	1	1	1	1	1
HPMC K 250 PH PRM	45	50	55	60	65	70	75
Carnauba wax	25	22	17	17	14	15	10
POLYOX WSR 303	20	20	20	20	20	20	20
Sodium Bicarbonate	10	11	12	13	14	15	16
MCC	43	40	39	33	30	25	22
Talc	4	4	4	4	4	4	4
Magnesium Stearate	2	2	2	2	2	2	2
Total Weight	150	150	150	150	150	150	150

Table 2: Composition of floating tablets of Rasagiline with HPMC K 750 PH PRM

Ingredients (weight in mg)	Formulations						
	F8	F9	F10	F11	F12	F13	F14
Rasagiline	1	1	1	1	1	1	1
HPMC K 750 PH PRM	45	50	55	60	65	70	75
Carnauba wax	25	22	17	17	14	12	10
POLYOX WSR 303	20	20	20	20	20	20	20
Sodium Bicarbonate	10	11	12	13	14	15	16
MCC	43	40	39	33	30	26	22
Talc	4	4	4	4	4	4	4
Magnesium Stearate	2	2	2	2	2	2	2
Total Weight	150	150	150	150	150	150	150

Table 3: Composition of floating tablets of Rasagiline with HPMC K 1500 PH PRM

Ingredients (weight in mg)	Formulations						
	F15	F16	F17	F18	F19	F20	F21
Rasagiline	1	1	1	1	1	1	1
HPMC K 1500 PH PRM	45	50	55	60	65	70	75
Carnauba wax	25	22	17	17	14	12	10
POLYOX WSR 303	20	20	20	20	20	20	20
Sodium Bicarbonate	10	11	12	13	14	15	16
MCC	43	40	39	33	30	26	22
Talc	4	4	4	4	4	4	4
Magnesium Stearate	2	2	2	2	2	2	2
Total Weight	150	150	150	150	150	150	150

Evaluation of Floating Tablets of Rasagiline

Weight Variation

Twenty (20) tablets from each batch were individually weighed in grams on an analytical balance. The average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same and compared with average weight.

Thickness

The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using Vernier Calipers. The average thickness and standard deviation were reported.

Hardness

Tablet hardness was measured using a Monsanto hardness tester. The crushing strength of the 10 tablets with known weight and thickness of each was recorded in kg/cm^2 and the average hardness, and the standard deviation was reported.

Friability

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche Friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as per weight loss from the original tablets [8].

***In Vitro* buoyancy studies**

The *In Vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100ml beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as floating lag time [9]. The duration of time for which the dosage form constantly remained on the surface of medium was determined as the total floating time.

Drug Content

Twenty tablets were taken, powdered. The powder equivalent to one dose each was transferred to a 100 ml volumetric flask and 0.1N HCl was added. The volume was then made up to the mark with 0.1N HCl. The solution was filtered and diluted suitably and drug content in the samples was estimated using UV-spectrophotometer at 265nm [10].

***In vitro* drug release studies**

The *In Vitro* drug release study was performed for the single- & multiple-unit tablets using USP Type II dissolution apparatus using 900ml of 0.1N HCl at a temperature of 37±0.5 2 ºC at 50 rpm. 5 ml of sample was collected at 0, 2, 4, 6, 8, 12, 16, 20, 24 hours and the same volume of fresh media was replenished [11]. The drug content in the samples was estimated using UV visible spectrophotometer at 265 nm.

Analysis of *In Vitro* drug release kinetics and mechanism

The *In Vitro* release data from several microspheres' formulations containing Rasagiline was determined kinetically using different mathematical models like Zero order, First order, Higuchi, and Korsmeyer–Peppas model**.**

Drug-excipient compatibility studies

Fourier transform infrared spectroscopy (FTIR)

The spectral analysis can be used to identify the functional groups in the pure drug and drug-excipient compatibility. Pure Rasagiline FTIR spectra, physical mixtures and optimized formulation were recorded by using FTIR (SHIMADZU). Weighed quantity of KBr and drug-excipients were taken in the ratio 100: 1 and mixed by mortar. The samples were made into pellet by the application of pressure [12]. Then the FTIR spectras were recorded in the wavelength region between 4000 and 400 cm^{-1}.

Stability studies

Stability testing was conducted at 40˚C ± 2˚C/75% RH ± 5% RH for 3 months using stability chamber (Thermo Lab, Mumbai). Samples were withdrawn at predetermined intervals 0, 30, 60- and 90-days period according to ICH guidelines [13]. Various *In Vitro* parameters like % yield, entrapment efficiency and *In Vitro* release studies were evaluated.

Results and Discussion

Physical parameters of prepared powder blends Rasagiline

Table 4: Physical properties of prepared powder blends of Rasagiline

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (Ɵ)	Carr's index (%)	Hausner ratio
F1	0.58±0.04	0.59±0.01	25.34±0.4	11.23±0.8	1.13±0.02
F2	0.56±0.14	0.60±0.04	26.67±0.3	12.23±1.0	1.12±0.07
F3	0.53±0.04	0.64±0.05	26.54±0.1	11.12±0.7	1.13±0.09
F4	0.52±0.06	0.54±0.03	26.56±0.2	12.74±1.0	1.11±0.06
F5	0.61±0.02	0.65±0.02	25.56±0.1	11.23±0.8	1.13±0.05
F6	0.52±0.21	0.66±0.12	26.30±0.1	10.23±0.5	1.12±0.06
F7	0.58±0.04	0.63±0.04	26.89±0.2	11.34±0.6	1.16±0.03
F8	0.57±0.01	0.68±0.03	25.67±0.3	12.11±0.8	1.12±0.03
F9	0.56±0.01	0.61±0.01	26.56±0.3	11.45±0.7	1.13±0.02
F10	0.53±0.13	0.67±0.06	26.66±0.2	11.45±0.5	1.15±0.01
F11	0.53±0.09	0.68±0.12	25.34±0.2	12.23±0.5	1.13±0.01
F12	0.55±0.04	0.56±0.07	25.09±0.2	11.88±0.4	1.11±0.03
F13	0.52±0.01	0.67±0.04	25.14±0.3	10.67±0.4	1.13±0.02
F14	0.55±0.06	0.64±0.21	27.99±0.5	11.34±0.5	1.12±0.01
F15	0.53±0.01	0.63±0.04	25.78±0.4	10.45±0.3	1.13±0.02
F16	0.55±0.02	0.61±0.07	26.45±0.4	10.68±0.2	1.13±0.02
F17	0.61±0.24	0.68±0.03	25.09±0.3	11.47±0.8	1.12±0.02
F18	0.59±0.08	0.67±0.08	26.05±0.2	11.99±0.3	1.14±0.02
F19	0.58±0.01	0.61±0.12	25.06±0.2	11.45±0.6	1.13±0.01
F20	0.53±0.08	0.64±0.1	24.78±0.1	12.12±0.5	1.14±0.01
F21	0.54±0.03	0.56±0.03	23.04±0.6	09.10±0.4	1.10±0.02

Above parameters are communicated as Average ± Standard Deviation; (n=3)

The results of bulk densities formulations bearing F1 to F21 were reported to be in the range of 0.50g/cc to 0.61g/cc.

The findings of tapped density formulations F1 to F21were reported to be in the range of 0.54g/cc to 0.68g/cc.

The angle of repose of all the formulations was found to be satisfactory. The formulation F19 was had angle of repose value of 20.04, thus indicating good flow property.

The compressibility index values were found to be in the range of 9 to 12%. These findings indicated that the all the batches of formulations exhibited good flow properties.

The Hausner's ratio values in the space of 1.10 to 1.16%. These findings designated that the all the batches of formulations exhibited good flow criteria.

Table 5: Physicochemical parameters of Rasagiline floating tablets

F. No	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm^2)	#Friability (%)	#Content uniformity (%)	Floating Lag time (sec)	Total floating time (hrs)
F1	151.75±1.2	4.3±0.12	6.3±0.12	0.57±0.01	95.23±0.63	55	>24
F2	150.59±1.8	4.4±0.06	6.1±0.06	0.55±0.02	97.04±0.06	52	>24
F3	148.14±1.5	4.4±0.06	6.1±0.06	0.63±0.03	95.56±0.14	50	>24
F4	151.15±1.0	4.2±0.12	6.2±0.12	0.72±0.01	98.11±1.01	47	>24
F5	150.34±1.4	4.4±0.11	6.3±0.00	0.62±0.02	94.23±1.08	44	>24
F6	150.48±1.4	4.2±0.10	7.1±0.06	0.66±0.01	95.45±0.31	42	>24
F7	151.25±1.3	4.2±0.10	6.3±0.10	0.53±0.02	98.91±0.49	40	>24

F8	149.47±1.2	4.1±0.25	6.3±0.40	0.69±0.01	97.23±0.51	57	>24
F9	153.36±1.3	4.1±0.06	6.3±0.06	0.58±0.00	96.13±0.56	55	>24
F10	153.29±1.2	4.2±0.20	6.2±0.42	0.79±0.02	95.23±0.24	52	>24
F11	151.13±1.4	4.2±0.06	6.3±0.06	0.76±0.01	97.97±0.21	49	>24
F12	152.38±1.3	4.2±0.00	6.4±0.06	0.73±0.02	98.45±0.76	46	>24
F13	153.14±1.2	4.3±0.26	6.8±0.35	0.72±0.02	97.45±0.48	43	>24
F14	151.57±1.3	4.1±0.21	6.4±0.21	0.54±0.03	98.98±0.23	42	>24
F15	151.15±1.2	4.4±0.06	7.0±0.23	0.75±0.02	96.45±0.36	58	>24
F16	150.35±1.3	4.2±0.25	6.4±0.23	0.78±0.01	96.45±0.69	55	>24
F17	152.29±1.4	4.5±0.15	6.8±0.32	0.79±0.01	96.34±0.35	53	>24
F18	151.77±1.1	4.4±0.25	6.7±0.35	0.82±0.01	97.56±0.23	50	>24
F19	150.15±1.2	4.4±0.06	7.0±0.23	0.75±0.02	96.45±0.36	47	>24
F20	151.12±1.2	4.2±0.12	6.5±0.2	0.63±0.03	97.18±0.81	45	>24
F21	151.16±1.8	4.0±0.10	6.2±0.21	0.52±0.89	99.18±0.13	36	>24

The Weight variation of all formulations witnessed to be in the limit allowed that is ± 7.5% of total tablet weight.

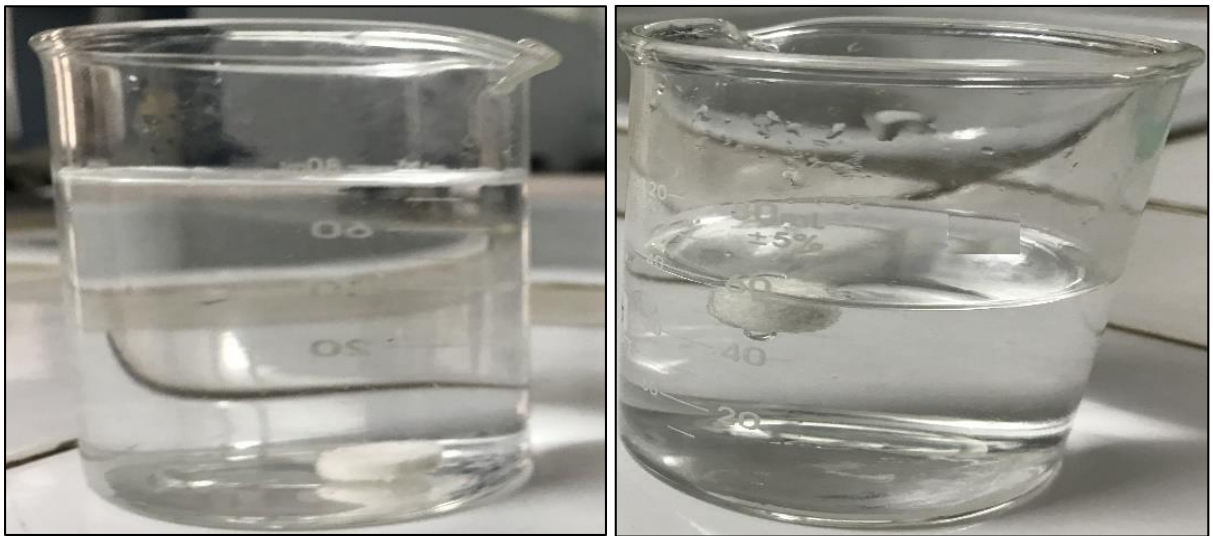
The suitable hardness for compressed tablets is considered as a vital function for the end user. The deliberated crushing strength of fabricated tablets of formulations F1-F21 trended between 6.0-7.0kg/cm^2.

The thickness of all the formulations ranges from 4-4.5 mm.

The friability of all prepared formulation between 0.52-0.84.the friability properties limits are in between 0-1%.

The drug content of all formulation is in between 94.11-99.78%, drug content depends on the angle of repose since the angle of repose indicates uniform flow nature of powder blend which makes the drug to evenly distribute in all the formulation and to maintain content uniformity in all batches.

Tablets of all batches had floating lag time below 3 minutes regardless of viscosity and content of HPMC because of evolution of CO_2 resulting from the interaction between sodium bicarbonate and dissolution medium; entrapment of gas inside the hydrated polymeric matrices enables the dosage form to float by lowering the density of the matrices. Total Floating time for the HPMC formulations were between 12 to 24 hrs.



At time 0 After 36 sec

Fig 1: *In Vitro* buoyancy lag time of the optimized formulation F19

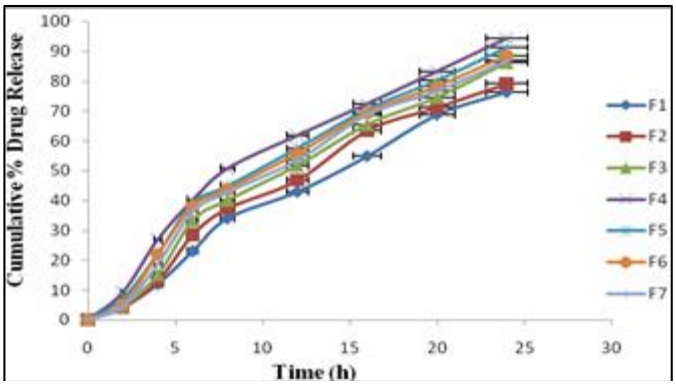


Fig 2: *In Vitro* Drug Release Profile of Rasagiline floating tablets F1-F7

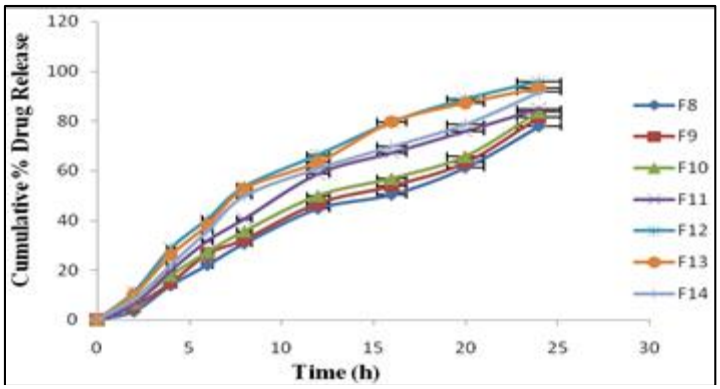


Fig 3: *In Vitro* Drug Release Profile of Rasagiline floating tablets F8-F14

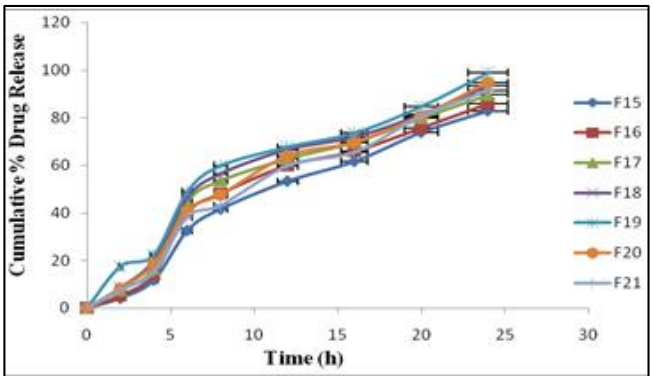


Fig 4: *In Vitro* Drug Release Profile of Rasagiline floating tablets F15-F21

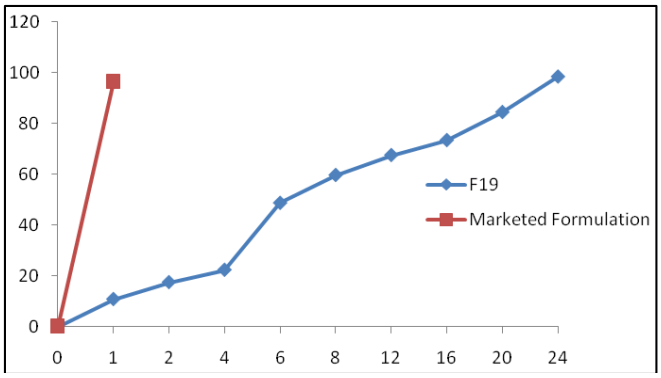


Fig 5: Comparison of marketed product of Rasagiline with optimized formulation (F19)

From the above figures (Fig. 2, 3 and 4) it can be observed that the polymer HPMC K 1500 PH PRM has controlling effect on the release of drug from the floating matrix tablet of Rasagiline compared to HPMC K 250 PH PRM and HPMC K 750 PH PRM. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer HPMC K 1500 PH PRM. The concentration of polymer was added in increasing order to check its drug release retarding ability and F19 was considered as best formulation among the all the formulations. F19 showed good buoyancy properties and controlled the drug release for desired period of time (24hrs). The release profiles from all these formulations followed diffusion-controlled release, complying with higher correlation coefficient values of Higuchi and Peppas equations.

In Vitro drug release studies for optimized formulation (F19) and marketed product

An *In Vitro* release profile of Rasagiline and marketed product was conducted; the optimized formulation F19 was shown drug release of 98.92% within 24h and 94.76% of the drug was released from the marketed product within 1h.

Mathematical modeling of optimized formula (F19) of Rasagiline floating tablets

In the present study drug release mechanism of optimized Rasagiline tablets F19 were best fitting to zero order and Higuchi model because regression coefficient was seen closest to 1. Thus the mechanism of drug release is by diffusion. Further the n value obtained from the Korsmeyer-Peppas plots i.e. 0.833 indicating non Fickian (anomalous) transport. Thus the active ingredient is being released by coupled diffusion and erosion. The reference standard (marketed product) drug release was explained by first order kinetics as the plot showed highest linearity as the drug release was best fitted in first order kinetics. The results are summarized in Table 6.

Table 6: Release order kinetics of F19 and Marketed Product

Formulation Code	Zero Order		First Order		Higuchi		Korsmeyer Peppas	
	R^2	N	R^2	n	R^2	n	R^2	n
Marketed	0.927	8.642	0.994	0.061	0.954	24.76	0.971	0.833
F19	0.999	8.741	0.748	0.151	0.937	29.62	0.959	0.825

Drug excipient interactions by FTIR

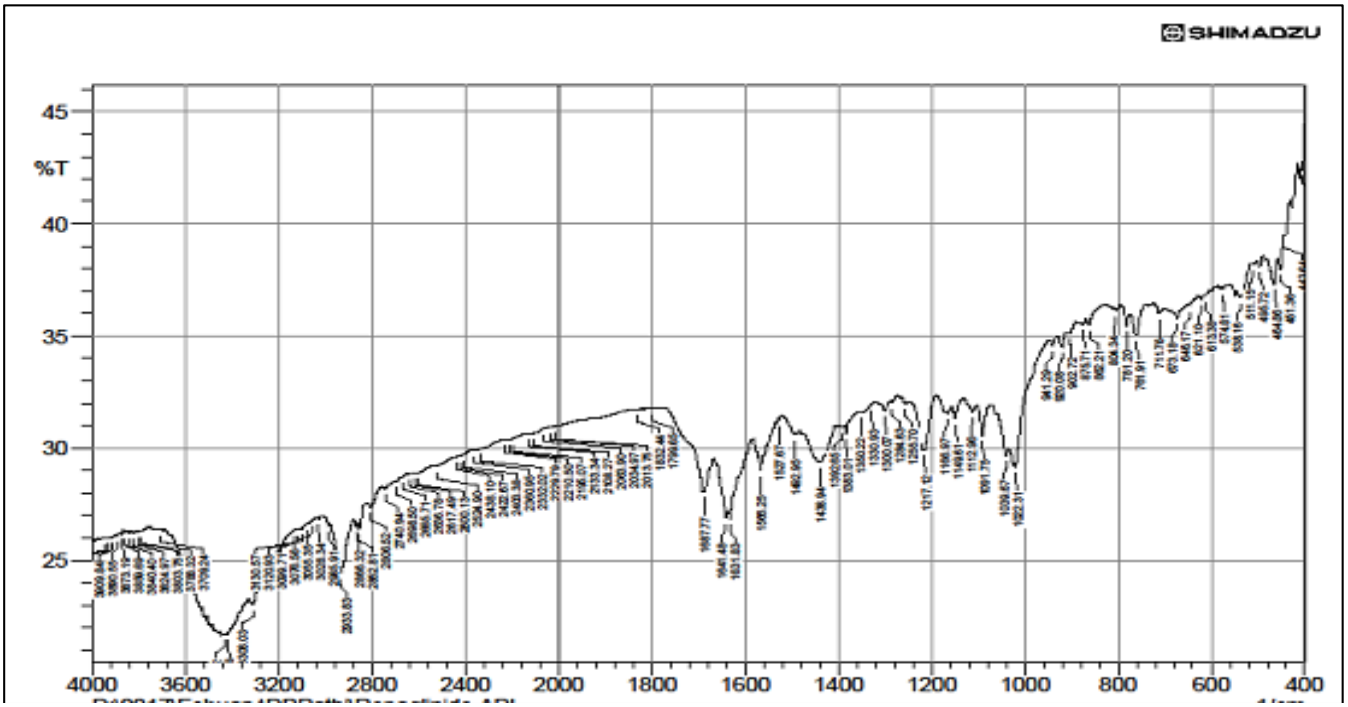


Fig 6: FTIR Spectroscopy of Rasagiline pure drug

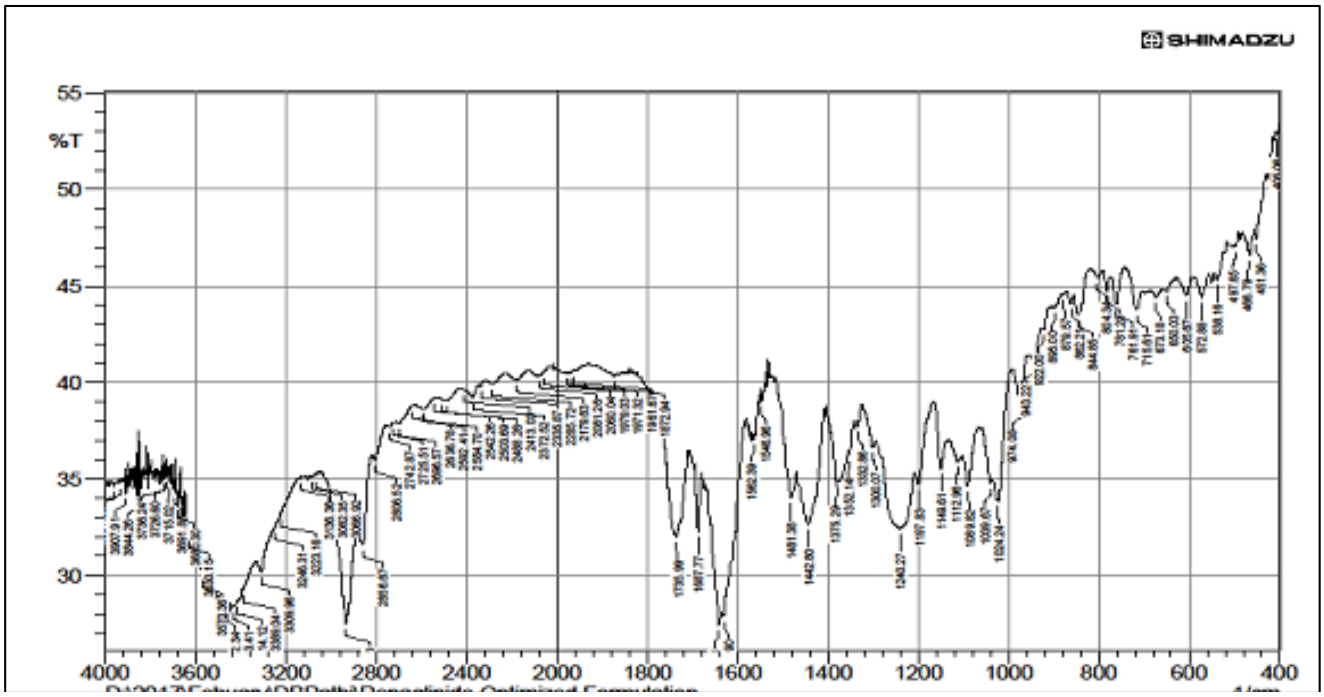


Fig 7: FTIR Spectroscopy of Rasagiline optimized formulation F19

Interpretation of FTIR Data

FT-IR spectrums are mainly used to determine if there is any interaction between the drug and any of the excipients used. The presence of characteristic absorption bands of Rasagiline pure drug and optimized floating tablet (F19) containing Rasagiline suggest that there was no interaction between the drug and excipients used in the formulation figures showed in fig. 6 and fig. 7.

Stability studies

Table 7: Parameters after Accelerated Stability Study of optimized Formulation F19

Parameter	Temperature Maintained at 40±2 ^{0}C; Relative Humidity (RH) Maintained at 75%±5%RH			
	Initial	After 1 Month	After 3 Months	After 6 Months
Drug Content (%)	99.18±0.13	98.96±0.68	98.13±0.37	97.12±0.22
***In Vitro* Drug Release (%)**	98.92±1.19	98.10±1.53	97.82±1.42	97.50±1.35
Floating lag time	36	38	39	42

There were no changes observed in % drug content, *In Vitro* drug release studies and floating lag time during storage of the optimized formulation and the results are tabulated in Table 7. Hence the optimized formulation was found to be stable.

Summary and Conclusion

In the present work, it can be concluded that the Rasagiline floating tablets can be an innovative and promising approach for the delivery of Rasagiline for the treatment of Parkinson's disease. The optimized formulation F19 containing HPMC K 1500 PH PRM, Caurnaba wax, Polyox WSR 303 and a gas-generating agent. *In-vitro* release profile of Rasagiline and marketed product when compared, the optimized formulation F19 showed drug release of 98.92±1.19% within 24h whereas 94.76±1.26% of the drug was released from the marketed product within 1h. The major mechanism of drug release follows zero order kinetics and non fickian transport by coupled diffusion and erosion. This means that water diffusion and also the polymer rearrangement have an essential role in the drug release. The release rate constant of optimized formulation F19 was low enough prolonging drug delivery.

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