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Formulation and evaluation of extended release trilayered matrix tablets of rasagiline mesylate by geomatrix

B. Prabhakar Reddy, D.V. R. N. Bhikshapathi[2*]

[1]*Research Scholar, Mewar University, Chittorgarh, Rajasthan, India*
[2]*Research Supervisor, Mewar University, Chittorgarh, Rajasthan, India*

***Corresponding Author: D.V. R. N. Bhikshapathi**
Email: dbpath@yahoo.com

ABSTRACT

The main objective of the present study was to prepare controlled release (CR) matrix trilayer tablet of rasagiline mesylate to achieve zero-order drug release for controlled plasma concentration. Twenty seven formulations (F1-F27) for middle layer were prepared by direct compression method using 3^3 response surface method (3 variables and 3 levels of polymers) by using design of experiment software with polymers like different HPMC grades. The barrier layers was formulated employing hydrophobic swellable polymer Polyox WSR 303, xanthan gum and EC. The procedure adopted to make the compacts was via direct compressions. The tablets were also evaluated for physicochemical characteristics and release kinetics and it was satisfactory. The developed drug delivery systems showed prolonged drug release rates over a period of 24 h. The release profile of the optimized formulation (HF17) was described by the zero-order and Higuchi model. These results also demonstrated the suitability of rasagiline mesylate three-layered tablet formulation of to provide controlled release for prolonged period of time and improved linearity for rasagiline mesylate in comparison to marketed product in the management of Parkinson's disease.

Keywords: Rasagiline mesylate, Parkinson's disease, HPMC, Xanthum gum, Geomatrix.

INTRODUCTION

Controlled release pharmaceutical systems have been developed and studied to improve the performance of drugs and in particular to increase their pharmacological effect and reduce any side effects[1]. The basic characteristic of the systems is that the rate of drug absorption may be adjusted through a controlled rate of drug release from the dosage forms [1].

A number of design options are available to control or modulate drug release from a drug delivery system. Most oral controlled release dosage forms fall in the category of matrix, reservoir or multi-layer systems. Lately, multi-layer matrix systems are gaining importance in the design of oral sustained drug delivery systems. A multi-layer system consists, usually, of a hydrophilic matrix core containing the active

ingredient and one or two impermeable or semi-permeable polymers (barrier-layer) applied on one or both faces of the core during tabletting .The barrier layers delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate. In the device, the polymeric layers prevent the water penetration through the protected core for some duration. After this phase during the subsequent dissolution process, the swollen barriers erode and the surface available for drug release slowly increases. In this way the decrease of delivery rate due to the increase in diffusion path length is counter balanced by the simultaneous increase of the area available for drug release [2,3].

Geomatrix technology

There have been different approaches to achieve zero-order drug release from dosage forms for controlled plasma concentration. Among different approaches to achieve zero-order release from hydrophilic matrix technologies, multilayer matrices have been widely evaluated and developed for commercial products under the trade name of Geomatrix. The technology makes use of bilayer or trilayer tablets to modulate the release and to achieve constant release [13]. 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 extended release matrix 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. Controlled release tablets are intended to take once daily, when compared with conventional dosage forms that may have to take three or four times daily to achieve the same therapeutic effect. The objective of the present study was to develop a trilayered tablet of rasagiline mesylate with different hydrophobic and hydrophilic polymers. The results indicate that the optimized trilayered rasagiline mesylate tablet can be successfully used for treatment of Parkinson's disease [4].

MATERIALS AND METHODS

Materials

Rasagiline mesylate pure drug was generous gift from Aurobindo Pharma Limited, Hyderabad, India. HPMC K 4 M, HPMC K 15 M & HPMC K 100 M was obtained from Rubicon labs, Mumbai. Xanthan gum and Polyox WSR 303 and ethyl cellulose were gifted from MSN Labs Ltd. Hyderabad. All other chemicals used were of analytical grade.

METHODS

Preparation of middle active layer

Twenty seven formulations (F1-F27) for active layer were prepared by direct compression method using 3[3] Response surface method (3 variables and 3 levels of polymers) by using Design of experiment software with polymers like different HPMC grades. All the formulations were varied in concentration of polymers, magnesium stearate constituted in all the formulations. These materials were screened through #60 and mixed together in motor by using pestle. Final mixtures were compressed by using 12 mm diameter flat punches on a sixteen station rotary tablet press. Formulation of active layer was depicted in **Table 1**. The prepared tablets were subjected to dissolution studies [5].

Table 1: Formulation trials of middle active layer of Rasagiline mesylate.

S.NO	Rasagiline Mesylate (mg)	HPMC K4M (mg)	HPMC K15M (mg)	HPMC K100M (mg)	PVP K-30 (mg)	MCC (mg)	Mg Stearate (mg)	Total (mg)
F1	1	20	30	18	4	25	2	100
F2	1	24	30	18	4	21	2	100
F3	1	20	34	18	4	21	2	100

F4	1	24	34	18	4	17	2	100
F5	1	20	30	22	4	23	2	100
F6	1	24	30	22	4	17	2	100
F7	1	20	34	22	4	17	2	100
F8	1	24	34	22	4	13	2	100
F9	1	20	34	22	4	17	2	100
F10	1	24	32	20	4	17	2	100
F11	1	20	30	20	4	23	2	100
F12	1	22	34	20	4	17	2	100
F13	1	22	32	18	4	21	2	100
F14	1	22	32	22	4	17	2	100
F15	1	22	30	20	4	21	2	100
F16	1	22	34	22	4	15	2	100
F17	1	24	34	22	4	13	2	100
F18	1	22	34	20	4	17	2	100
F19	1	24	30	20	4	19	2	100
F20	1	22	34	18	4	19	2	100
F21	1	24	32	18	4	19	2	100
F22	1	24	32	20	4	17	2	100
F23	1	22	32	20	4	19	2	100
F24	1	20	32	20	4	21	2	100
F25	1	24	32	18	4	19	2	100
F26	1	20	32	18	4	23	2	100
F27	1	22	32	18	4	21	2	100

Preparation of upper and lower layers of rasagiline mysylate trilayered tablets

The barrier layers was formulated employing hydrophobic swellable polymer natural wax i.e. polyox WSR 303 the swelling erosion modeling fillers which include water soluble MCC, EC and Xanthan gum. The procedure adopted to make the compacts was via direct compressions. For the first procedure the wax, xanthan gum and the filler was mixed in mortar and lubricated with magnesium stearate. Formulation of upper and lower layers was depicted in **Table 2.**

Formulation of extended release tryilayered matrix tablets of rasagiline mesylate

The trilayered matrix tablets of Rasagiline mesylate were prepared by direct compression method. The first step in the formulation was to develop the middle active layer so as to give at least 90%drug release during 12hours. The release profile of this layer might not be of constant rate type but would be preferably of constantly falling rate type. This layer would then be sandwiched between barrier layers (Upper & Lower layers) so as to continue the drug release for 24 h.

Table 2: Composition of Rasagiline mesylate trilayer matrix tablets

INGREDIENTS	AF17	BF17	CF17	DF17	EF17	FF17	GF17	HF17
MIDDILE ACTIVE LAYAER (F17) (100 mg)								
Rasagiline Mesylate	1	1	1	1	1	1	1	1
HPMC K 4 M	24	24	24	24	24	24	24	24
HPMC K 15 M	34	34	34	34	34	34	34	34

HPMC K 100 M	22	22	22	22	22	22	22	22
PVP K30	04	04	04	04	04	04	04	04
Micro Crystalline Cellulose	13	13	13	13	13	13	13	13
Magnesium stearate	02	02	02	02	02	02	02	02
UPPER AND LOWER LAYER (100 mg)								
Polyox WSR 303	15	20	25	30	35	40	45	50
Xanthan gum	50	45	40	35	30	25	20	15
Ethyl cellulose	12	12	12	12	12	12	12	12
Micro Crystalline Cellulose	19	19	19	19	19	19	19	19
Magnesium stearate	2	2	2			2	2	2
Talc	2	2	2			2	2	2

Evaluation of Rasagiline mesylate trilayer matrix tablets

The tablets were also evaluated for physicochemical characteristics and release kinetics such as weight variation [7] tests, thickness [8], hardness [9], friability [10], content uniformity [11], *in vitro* swelling studies [12].

In Vitro drug dissolution study [13]

In vitro drug release studies for developed trilayer matrix tablets were carried out by using dissolution apparatus II paddle type (Electrolab TDL-08L). The drug release profile was studied in 900ml Phosphate buffer pH 6.8 at 37± 0.5^0C temperature at 100RPM. The amount of drug release was determined at different time intervals of 1, 2, 3, 4, 6, 8, 12, 16. 20 & 24h by UV Visible spectrophotometer (Shimadzu UV 1800) at 265nm.

Kinetic model fitting [14]

The model dependent methods all rely upon a curve fitting procedure. Different mathematical functions have been used to model the observed data. Both the linear and non-linear models are being used in practice for dissolution modeling. Linear models include Zero order, Higuchi, Hixon – Crowell, Quadratic and Polynomials, where as the nonlinear models include First order, Weibull, KorsMeyer – Peppas, Logistic etc.

Introduction to Design of Experiments (DOE) [15]

DOE is an essential piece of the reliability program pie. It plays an important role in Design for Reliability (DFR) programs, allowing the simultaneous investigation of the effects of various factors and thereby facilitating design optimization. This article introduces the concept of DOE. Future articles will cover more DOE fundamentals in addition to applications and discussion of DOE analyses accomplished with a soon-to-be-introduced ReliaSoft software product.

Drug-excipient compatibility studies

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The samples were dispersed in KBr and compressed into disc/pellet by application of pressure. The pellets were placed in the light path for recording the IR spectra. The scanning range was 400-4000 cm^{-1} and the resolution was 1 cm^{-1}.

SEM studies

The surface and shape characteristics of Tablets 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 formulated trilayer tablets were carried out under different conditions according to ICH guidelines using stability chamber (REMI make). Accelerated Stability studies were carried out at 40 ^{0}C / 75 % RH for the best formulations for 6 months. The tablets were characterized for the hardness, friability, drug content and cumulative % drug released during the stability study period.

Results & Discussion

Design of Experiment

This method is mainly used to explain the effect of one factor on other factor. Whether this effect is significant or not, if significant how it influence the response. In this present work the effect of one factor (HPMC K 100M) on other two factors (HPMC K 4M, HPMC K 15M) is explained.

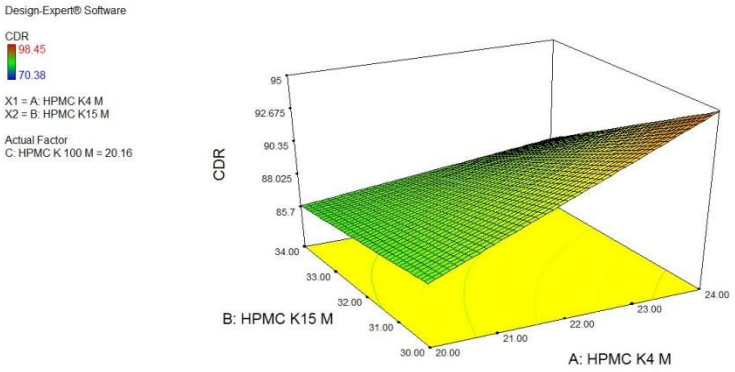

Fig 1: Response surface plot showing the influence of amount of polymer on the release profile of Rasagiline mesylate for Cumulative % Drug Released.

In the above graph the effect of HPMC K100M on % cumulative drug release is examined and it clearly indicates that there is a very significant effect of HPMC K100M on % cumulative drug release. The formulations with all 3 factors shown % drug release in between 70.38-98.48 but when Guar Gum is removed from the formulations the maximum % CDR is near 70.38 .This is the effect of factor (HPMC K100M**)** on response.

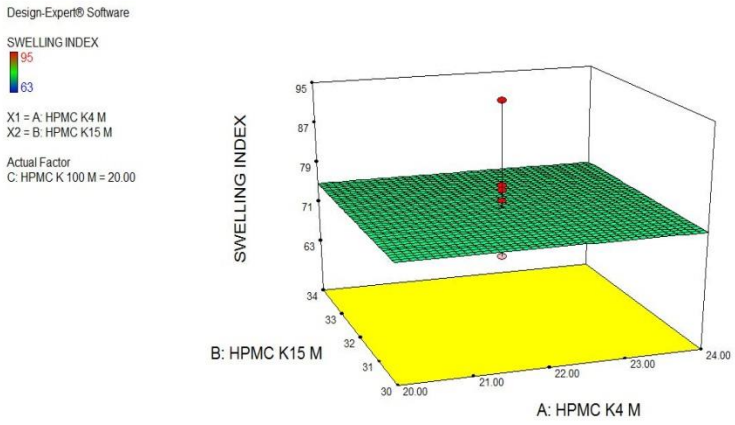

Fig 2: Response surface plot showing the influence of amount of polymer on Swelling Index of Rasagiline mesylate

There is a negligible effect on Swelling Index of formulations because all formulations have excellent Swelling property and there is slightly influence on Swelling Index by HPMC K 100M (Fig 1 &2) (Table 3).

In vitro drug release profile for prepared middle active layer of Rasagiline mesylate

Among all the formulations the formulation F17 was decided as optimized formulation for active layer based on the highest drug release i.e. 98.54±1.15 within 12 hrs when compared with other preparations (**Figure 3, 4, 5 & 6**). Formulation F17 was chosen as active layer for further studies.

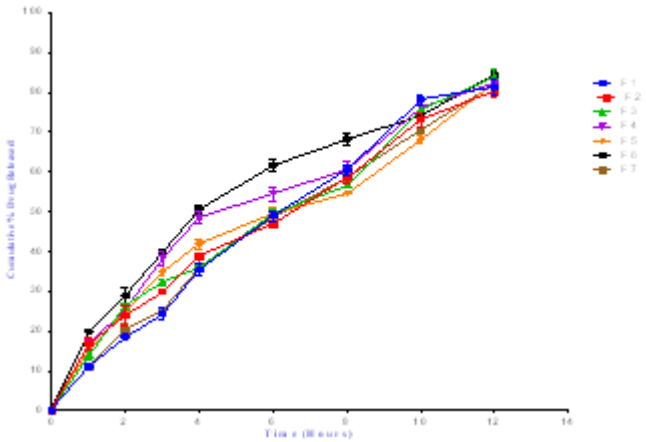

Fig 3: *In vitro* Drug Release Profile for Prepared middle active layer of Rasagiline mesylate tablets (F1-F7)

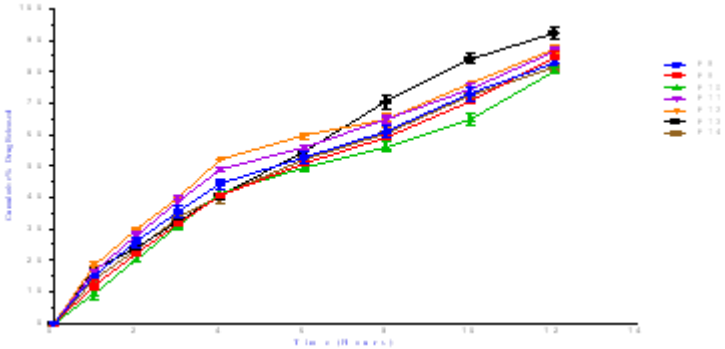

Fig 4: *In vitro* Drug Release Profile for Prepared middle active layer of Rasagiline mesylate tablets (F8-F14)

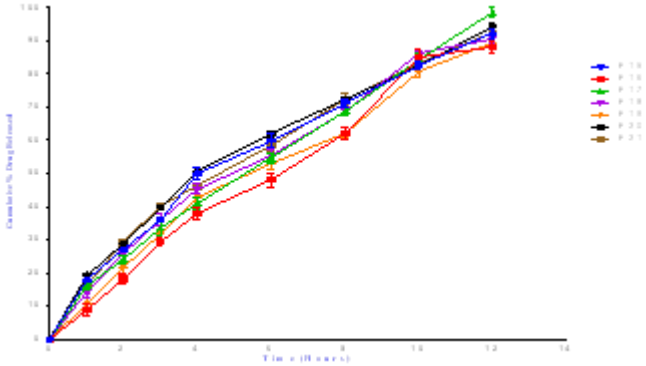

Fig 5: *In vitro* Drug Release Profile for Prepared middle active layer of Rasagiline mesylate tablets (F15-F21)

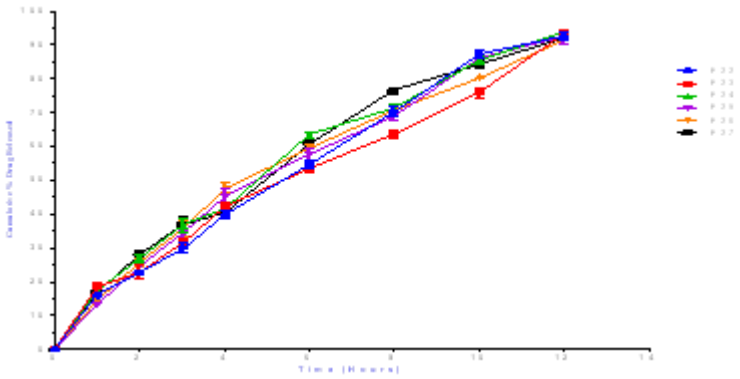

Fig 6: *In vitro* Drug Release Profile for Prepared middle active layer of Rasagiline mesylate tablets (F22-F27)

Table 3: Physical evaluation of middle active layer of Rasagiline mesylate tablets (F1-F27)

F.Code	Swelling index (%)
F1	84±0.76
F2	86±0.72
F3	82±0.64
F4	83±0.21
F5	80±1.03
F6	85±0.84
F7	87±0.33
F8	86±0.11
F9	88±0.68
F10	85±0.43
F11	83±0.64
F12	84±0.81
F13	81±1.03
F14	85±0.84
F15	84±0.18
F16	86±0.79
F17	97±0.64
F18	87±0.72
F19	85±0.64
F20	94±0.81
F21	80±1.03
F22	85±0.84
F23	8740.68
F24	83±0.59
F25	88±0.37
F26	85±0.22
F27	84±0.23

In phosphate buffer pH 6.8, HPMC polymers showed good swelling property. In middle layer of Rasagiline mesylate, among all the formulations F26 showed highest degree of swelling index 97.0%, where as in F5 showed leased swelling with a swelling index of 80.0%.

Evaluation of trilayer matrix tablets of Rasagiline mesylate

Fig7: Rasagiline mesylate trilayer matrix tablet

Table 4: Physical evaluation of rasagiline mesylate trilayered tablets

F.NO	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm^2)	#Friability (%)	# Content uniformity (%)	Swelling index (%)
AF17	301.65±1.2	3.0±0.12	5.0±0.12	0.52±0.01	95.23±0.63	183±0.76
BF17	298.69±0.8	3.1±0.06	5.1±0.06	0.55±0.02	97.04±0.06	183±0.72
CF17	299.04±0.5	3.1±0.06	5.1±0.06	0.63±0.03	95.56±0.14	182±0.64
DF17	301.05±0.0	3.2±0.12	5.6±0.12	0.72±0.01	95.11±1.01	188±0.81
EF17	300.54±0.4	3.0±0.10	5.0±0.00	0.62±0.02	96.23±0.8	173±1.03
FF17	302.78±0.4	3.3±0.10	53±0.06	0.66±0.01	95.45±0.31	182±0.84
GF17	299.65±0.3	3.1±0.10	5.1±0.10	0.58±0.02	97.11±0.49	180±0.72
HF17	**300.57±0.2**	**3.3±0.25**	**5.7±0.40**	**0.69±0.01**	**99.23±0.51**	**204±0.79**

*Values are expressed in mean± SD :(n=20)
#Values are expressed in mean± SD :(n=3)

The rasagiline mesylate trilayer matrix tablets are shown in **Figure7**. The hardness of the trilayer matrix tablets was found to be 5.0 to 5.7 kg/cm^2. The friability of the formulations was found to be less than 1% and hence the tablets with lower friability may not break during handling on machines and or shipping. All the batches of the tablets complied with the weight variation limits as per the IP. The drug content in different formulation was highly uniform and the results are depicted in **Table 4**. Formulation HF17 showed highest degree of swelling index **204±0.79**%, where as in EF17 showed leased swelling with a swelling index of 173±1.03%.

In vitro Drug Release Profile for prepared extended release trilayered tablet of rasagiline mesylate

The release of Rasagiline Mesylate from different formulations was carried out in phosphate buffer pH 6.8. The trilayer tablets extended the drug release upto 24 hrs. The highest drug release was found in the formulation HF17 i.e 98.21% within 24 h. HF17 was found to be optimized formulation based on the dissolution and other evaluation parameters. The results are shown in **Figure 7**. The comparison of marketed product Rasagiline Mesylate conventional tablet and optimized formulation HF17 was shown in **Figure 8**. The drug release from marketed product was 98.21% within 120 min.

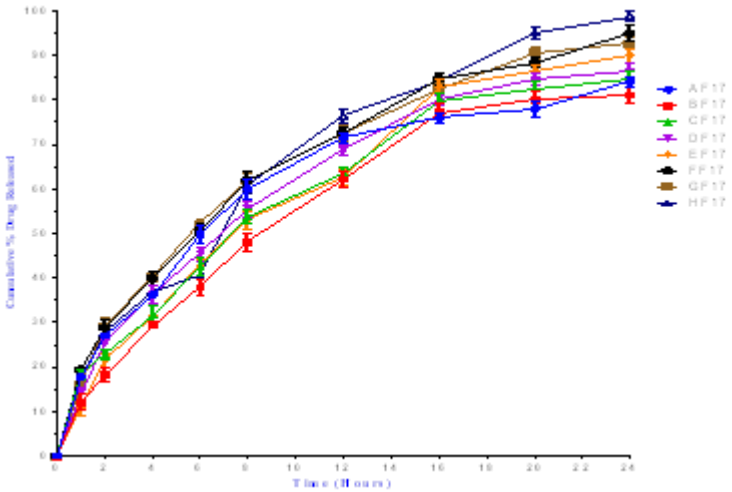

Fig 7: *In vitro* Drug Release Profile for Prepared Extended release trilayered Tablet of Rasagiline mesylate (AF17-HF17)

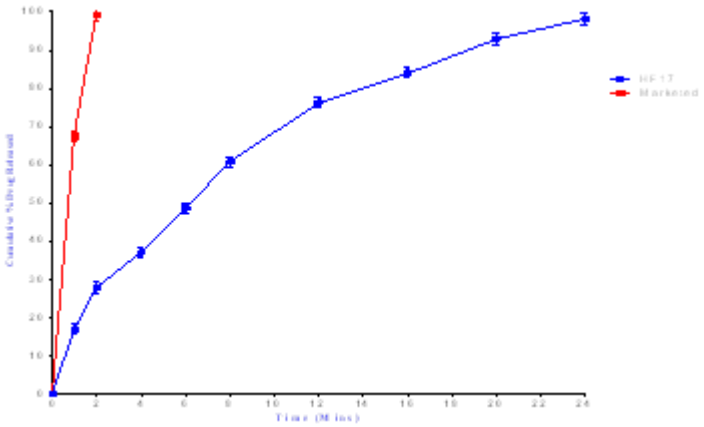

Fig 8: Comparative *In vitro* study plot of optimized formulation (HF17) and conventional marketed tablet

Table 5: Drug release kinetics of optimized HF17 and marketed product.

S.No	Formulation	Zero order	First order	Higuchi model	Korsmeyer-Peppas model	n
1	**HF17**	0.994	0.847	0.956	0.988	0.817
2	**Marketed**	0.923	0.967	0.925	0.945	0.823

The *in vitro* drug release profiles were fitted to several kinetic models and release data followed by their R^2 and n values shown in the **Table 5**. The optimized formulation was best fitted in Zero Order and Korsmeyer-Peppas. The optimized formulation n value was 0.817 indicating non Fickian (anomalous) transport thus it projected that delivered its active ingredient by coupled diffusion and erosion. The marketed conventional formulation followed the first order kinetics indicating drug release is directly proportional to the concentration of drug.

DRUG-EXCIPIENT COMPATABILITY STUDIES
FT-IR STUDIES

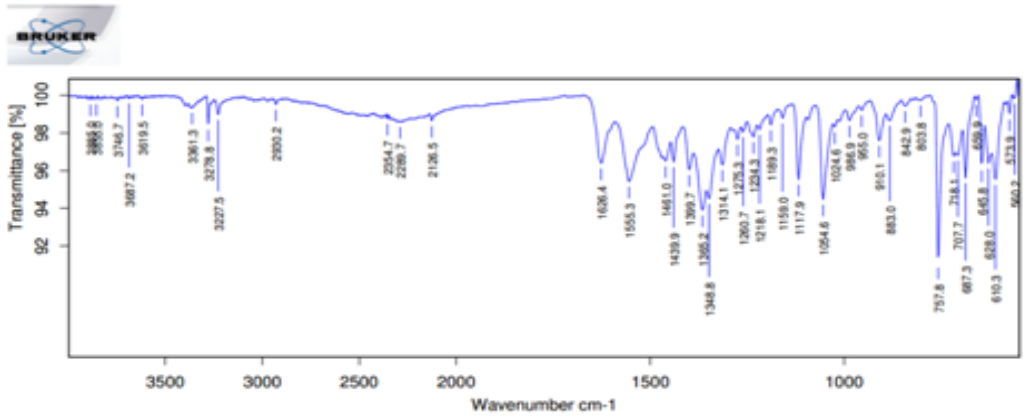

Fig 9: FT-IR spectrum of pure drug Rasagiline mesylate

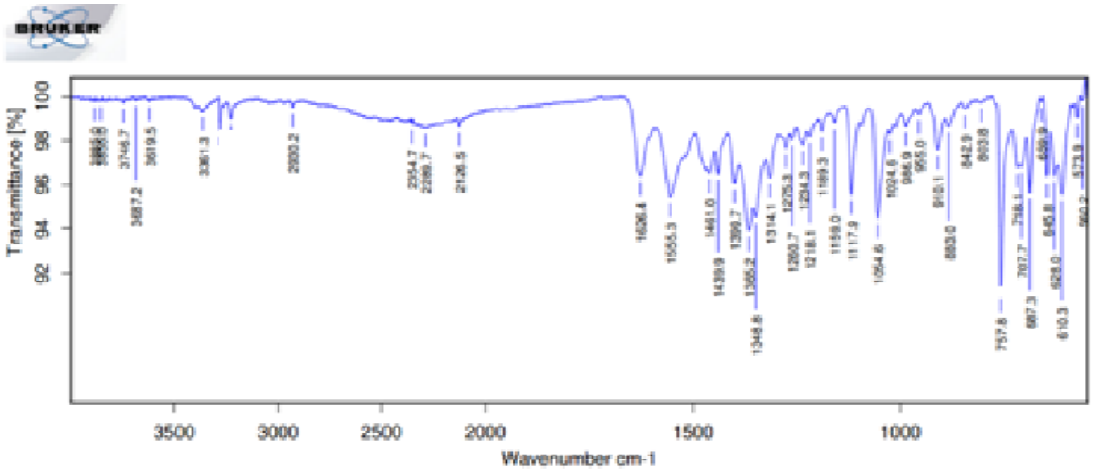

Fig 10: FT-IR spectrum of optimized formulation HF17

The pure Rasagiline mesylate characteristic spectra were shown, a band of 2934 cm-^{1}and 2849 cm- ^{1}owing to Aromatic C-H stretching and Aliphatic C-H stretching groups. The other bands Peaks at 3219 cm-1 (Secondary amine N-H) and 1192 cm-1 FTIR spectra of Rasagiline mesylate, A characteristic broadband at 1157 cm-^{1} associated with the stretching of C-O. The band at 2920 cm-1 is attributed to the Aromatic C-H stretching. Overall there was no alteration in peaks of Rasagiline mesylate pure drug (Fig 9) and optimized formulation (Fig 10), suggesting that there was no interaction between drug & excipients. There is no significant changes in peak of optimized formulation were observed when

compared to pure drug indicating absence of any interaction.

SEM studies

SEM further confirmed both diffusion and erosion mechanisms to be operative during drug release from the optimized formulation (HF17). Initially, tablet matrix showed swelling with pore formation that is clearly visible from SEM image. At the end of 24 h, the matrix was intact and pores had formed through it. SEM images also show the formation of gel structure indicating swelling and pore formation on the tablet surface.

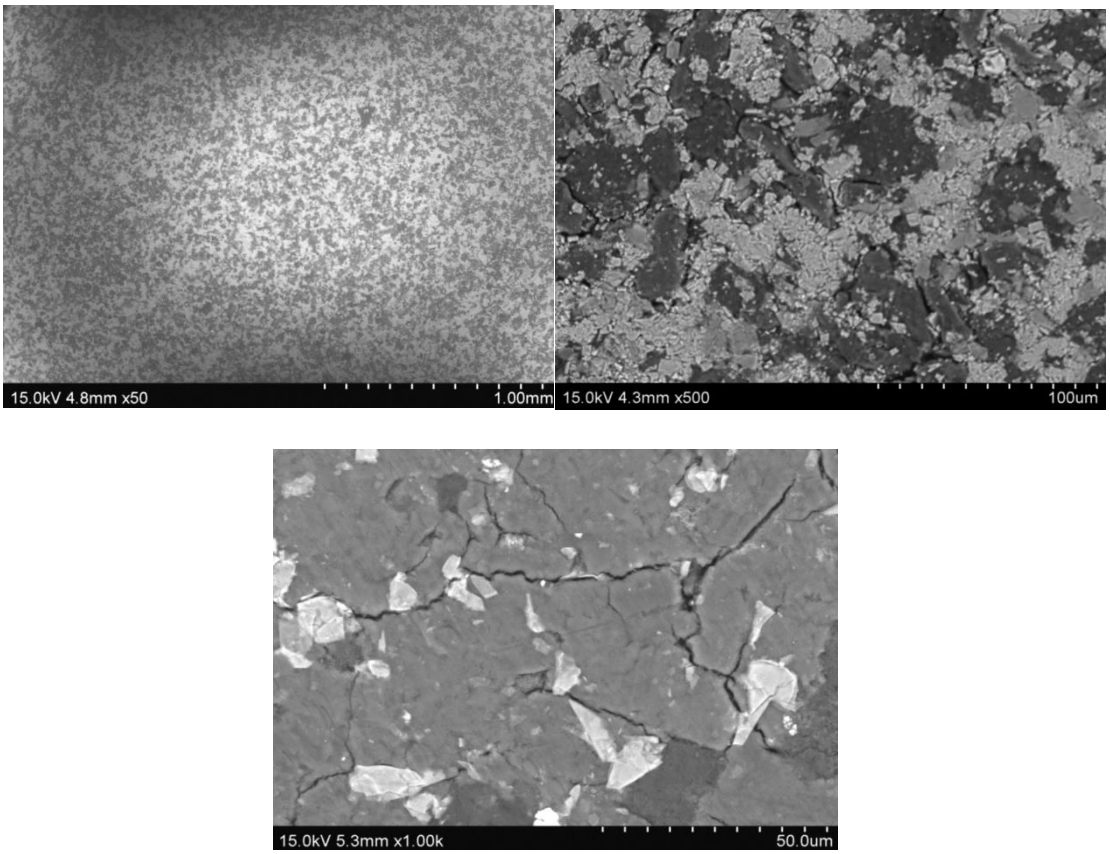

Fig11: SEM photographs of Rasagiline mesylate optimized trilayer tablets

Stability study

There were no physical changes in appearance and flexibility. After subjecting the optimized formulation (HF17) to the Accelerated Stability Studies, the results were shown that there were no major changes in Drug Content, In Vitro Drug Release, Swelling Index and Hardness.

Hence the formulation was found to be stable.

CONCLUSION

In present work attempt was made to formulate and evaluate extended release trilayered matrix tablets of Rasagiline mesylate. Attempts were made to achieve extended drug release from the dosage form. Prepared twenty seven formulations of Rasagiline mesylate middle active layer by direct compression method using 3^3 response surface method (3 variables and 3 levels of polymers) by using design of experiment software with polymers like different HPMC grades and F17 was finalized as optimized formulation base on the dissolution profile for 12 h. FTIR studies revealed that there was no incompatibility between drug and excipients. Prepared trilayer rasagiline matrix tablets, *In vitro* drug release studies were carried out to know the drug release with respective of the time. Maximum drug (98.21%) was released from the formulation HF17 within 24 Hrs. Based on the physico-chemical properties and *in vitro* drug release, the formulation HF17 was concluded as the

best formulation. No prominent changes in physico-chemical properties of formulation after its exposure to accelerated conditions of temperature (40 ± 2^0C) and humidity conditions (75 ± 5%RH) were seen. Hence the developed formulation was found to be stable even after subjecting to accelerated stability conditions. From the above, it can be concluded that the extended release trilayered matrix Tablets of Rasagiline mesylate formulations can be an innovative and promising approach for the delivery of Rasagiline mesylate for the treatment of Parkinson's disease.

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