DESIGN AND EVALUATION OF EXTENDED RELEASE TRILAYERED MATRIX TABLETS OF SELEGILINE HCL

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Abstract:
The present investigation was aimed for the formulation and evaluation of trilayer matrix tablets of Selegiline HCl used in the treatment of depression and in the therapy of Parkinson disease. 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 natural polymers like Locust Bean Gum, Karaya, HPMC K 15M. The barrier layers was formulated employing hydrophobic swellable polymer natural wax i.e carnauba wax the swelling erosion modeling fillers which include water soluble Sodium CMC and EC. The procedure adopted to make the compacts was via direct compressions. The tablets were also evaluated for physicochemical characteristics and release kinetics. The physicochemical characteristics of the prepared tablets were satisfactory. The developed drug delivery systems showed prolonged drug release rates over a period of 24 h. The release profile of the optimized formulation (CF26) was described by the Zero-order and Higuchi model. These results also demonstrated the suitability of three-layered tablet formulation of Selegiline HCl to provide controlled release for prolonged period of time and improved linearity for Selegiline HCl in comparison to marketed product with conventional drug release profile in the management of Parkinson's disease.
Keywords: *Selegiline HCl, Parkinson's disease, Locust bean gum, Geomatrix.*

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INTRODUCTION:

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 tableting [1].

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].

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. Selegiline is an inhibitor of monamine oxidase used in the treatment of depression and as adjunctive therapy in combination with levodopa and carbidopa in the therapy of Parkinson disease. The short half life of Selegiline

HCl 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 Selegiline HCl with different hydrophobic and hydrophilic polymers. The results indicate that the optimized trilayered Selegiline HCl tablet can be successfully used for treatment of Parkinson's disease [3,4].

MATERIALS AND METHODS:

Selegiline HCl was obtained from JB Chemical Co. (Ankleshwar, Gujarat, India). Locust Bean Gum, Karaya Gum, HPMC K 15M was obtained from Girijana society, Hyderabad. Carnauba wax Sodium CMC and EC was obtained from Loba Chemical Pvt. Ltd. (Mumbai, India). All other chemicals used were of analytical grade.

Methods:

Preparation of selegiline HCl 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 HPMC K15M, Locust bean gum, Karaya gums. 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 extended release matrix tablets (middle layer) of selegiline Hcl.

F.No	Selegiline Hcl	Locust Bean Gum	Karaya Gum	HPMC K 15 M	PVP K-30	DCP	Mg Stearate	Total
F1	5	20	30	45	8	38	4	**150**
F2	5	30	30	45	8	28	4	**150**
F3	5	20	40	40	8	33	4	**150**
F4	5	25	30	45	8	33	4	**150**
F5	5	20	30	45	8	38	4	**150**
F6	5	30	30	40	8	33	4	**150**
F7	5	20	40	40	8	33	4	**150**
F8	**5**	20	40	45	8	28	4	**150**
F9	5	20	40	40	8	33	4	**150**
F10	5	30	35	45	8	23	4	**150**
F11	5	25	30	35	8	43	4	**150**
F12	5	25	40	35	8	33	4	**150**
F13	5	25	35	45	8	28	4	**150**
F14	5	25	35	40	8	33	4	**150**
F15	5	25	35	35	8	38	4	**150**
F16	5	25	30	35	8	43	4	**150**
F17	5	30	40	40	8	23	4	**150**
F18	5	25	40	40	8	28	4	**150**
F19	5	30	30	40	8	43	4	**150**
F20	5	25	40	45	8	23	4	**150**
F21	5	30	35	45	8	23	4	**150**
F22	5	30	35	35	8	33	4	**150**
F23	5	30	40	35	8	28	4	**150**
F24	5	20	35	35	8	43	4	**150**
F25	5	30	35	35	8	33	4	**150**
F26	**5**	**30**	**40**	**45**	**8**	**18**	**4**	**150**
F27	5	25	35	40	8	33	4	**150**

Preparation of upper and lower layers of Selegiline HCl trilayered tablets:

The barrier layers were formulated employing hydrophobic swellable polymer Carnauba wax the swelling erosion modeling fillers which include water soluble DCP, EC and Sodium CMC. The procedure adopted to make the compacts was via direct compressions. For the first procedure the Carnauba wax, Sodium CMC and the filler was mixed in mortar and lubricated with magnesium stearate. Formulation of upper and lower layers was depicted in Table 2.

Table 2: Composition of Selegiline Hcl trilayered matrix tablet

INGREDIENTS	AF26	BF26	CF26	DF26	EF26	FF26	GF26	HF26
MIDDILE ACTIVE LAYAER (F26) (150 mg)								
Selegiline HCl	5	5	5	5	5	5	5	5
Locust Bean Gum	30	30	30	30	30	30	30	30
Karaya Gum	40	40	40	40	40	40	40	40
HPMC K 15 M	45	45	45	45	45	45	45	45
PVP K30	08	08	08	08	08	08	08	08
Di Calcium Phosphate	18	18	18	18	18	18	18	18
Magnesium stearate	04	04	04	04	04	04	04	04
UPPER AND LOWER LAYER (100 mg)								
Carnauba wax		10	15	20	30	35	40	45
Sodium CMC		45	40	35	25	20	15	10
Ethyl cellulose		12	12	12	12	12	12	12
Di Calcium Phosphate		29	29	29	29	29	29	29
Magnesium stearate		2	2	2	2	2	2	2
Talc		2	2	2	2	2	2	2

Formulation of extended release tryilayered matrix tablets of selegiline HCl:

The powder mixtures required for active and barrier layers were weighed accurately and thoroughly mixed using mortor and pestle for about 20 minutes. Initially, the volume of die cavity; (12 mm, round) was adjusted equivalence to the weight of trilayered matrix tablets (350 mg). Then the pre weighed amount of powder equivalent to bottom layer (100 mg) was taken and placed in the die cavity and slightly compressed for uniform spreading. The upper punch was lifted up and the granules equivalent to 150 mg of the drug was placed over the bottom layer in the die cavity and again slightly compressed. The remaining volume of the die cavity was filled with pre weighed (100 mg) amount of powder equivalent to top layer and compressed with the full force of compression on rotary tablets press to obtain tri-layered tablets. Tri-layered matrix tablets of each composition were compressed and tested for their friability, Hardness, drug content and drug release characteristics with a suitable number of tablets for each test [6].

Post Compression Evaluation Tests:

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 220nm.

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 0C / 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 K15M) on other two factors (Locust Bean Gum, Karaya Gum) is explained.

In the graph the effect of HPMC K15 M on % cumulative drug release is examined and it clearly indicates that there is a very significant effect of HPMC K15 M on % cumulative drug release. The formulations with all 3 factors shown % cumulative drug release in between 70.39-99.86 but when Guar Gum is removed from the formulations the maximum % CDR is near 70.39.This is the effect of factor (HPMC K15 M) on response (Figure 1)
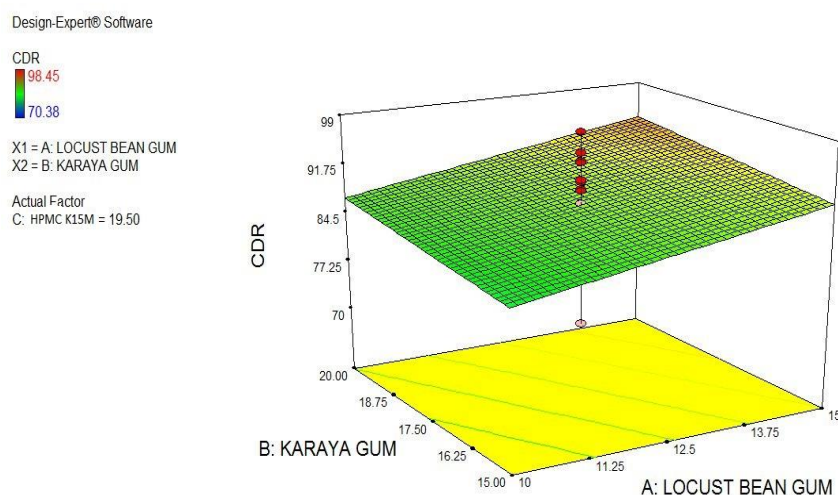
Fig 1: Response surface plot showing the influence of amount of polymer on the release profile of selegiline Hcl for cumulative % drug released.
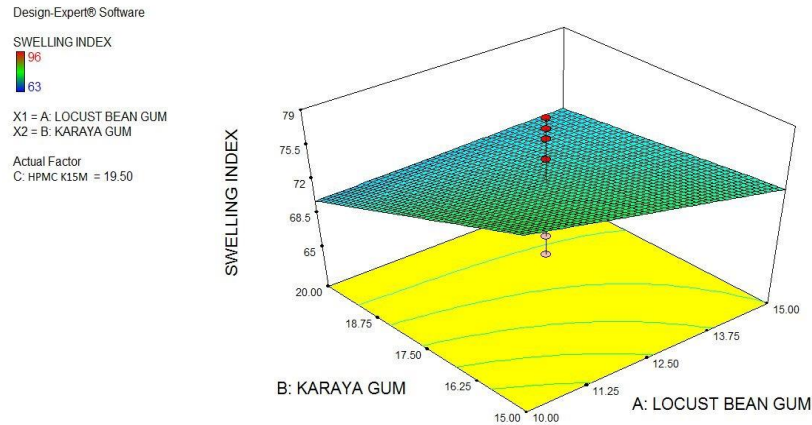
Fig 2: Response surface plot showing the Influence of amount of polymer on swelling index of selegiline Hcl

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 K15 M (Figure 2 & Table 3)

In vitro **Drug Release Profile for Prepared middle**

active layer of Selegiline HCl
Among all the formulations the formulation F26 was decided as optimized formulation for active layer based on the highest drug release i.e. 98.68±1.52 within 12 hrs when compared with other preparations (**Figure 3,4,5&6**). Formulation F26 was chosen as active layer for further studies.
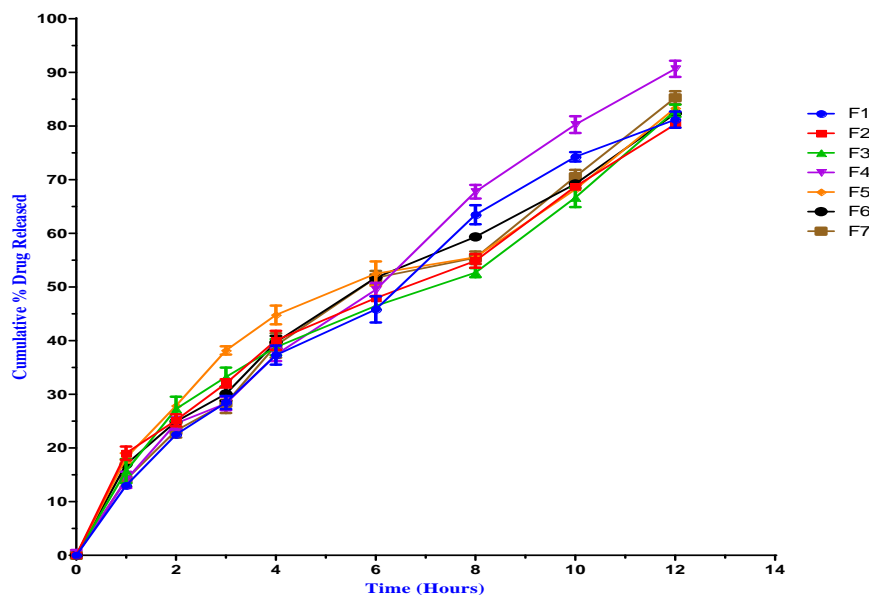
Fig 3: *In vitro* **Drug Release Profile for Prepared middle active layer of selegiline HCl tablets F1-F7**
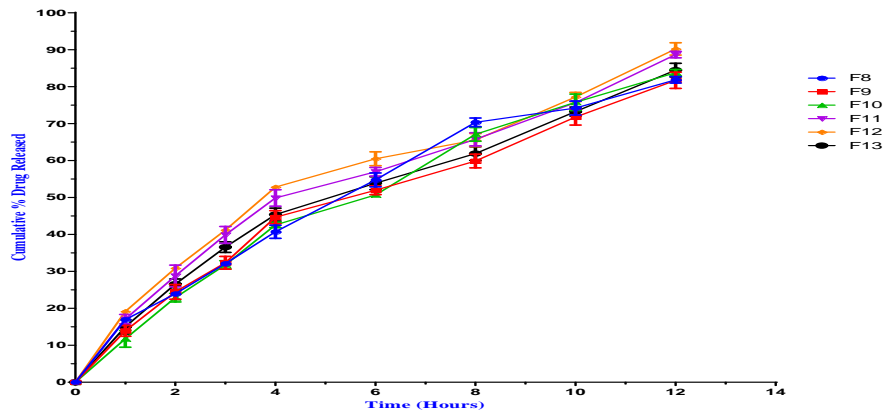
Fig 4: *In vitro* **Drug Release Profile for Prepared middle active layer of selegiline HCl tablets F8-F13**
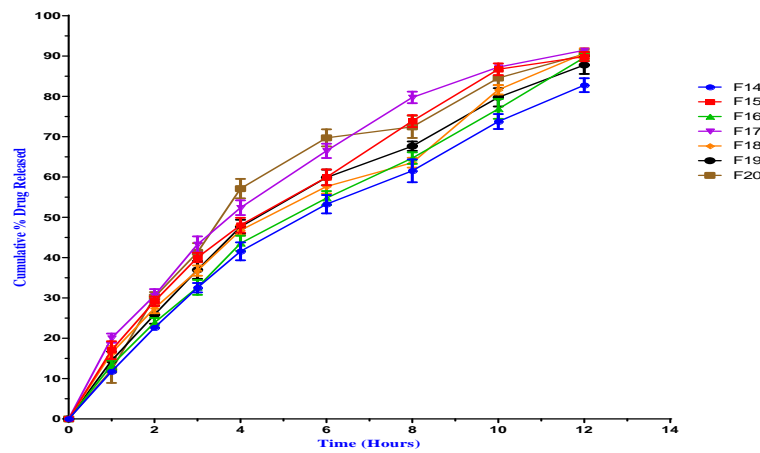

Fig 5: *In vitro* **Drug Release Profile for Prepared middle active layer of selegiline HCl tablets F14-F21**
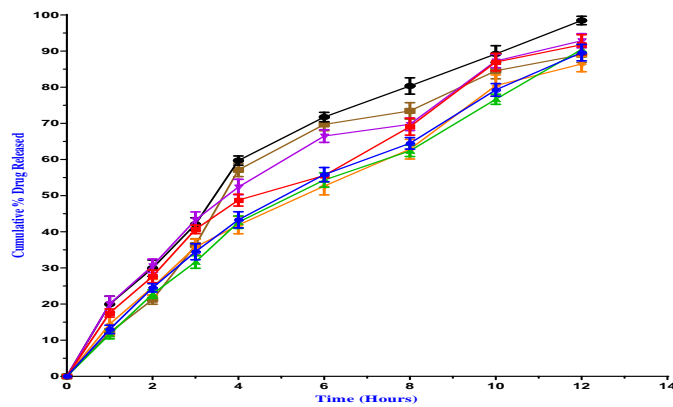

Fig 6: *In vitro* **Drug Release Profile for Prepared middle active layer of selegiline HCl tablets F21-F27**

Table 3: Physical evaluation of middle active layer of Selegiline HCl tablets (F1-F27)

F.NO	Swelling index (%)
F1	85±0.37
F2	89±0.49
F3	85±0.6467
F4	86±0.38
F5	89±1.23
F6	87±0.64
F7	85±0.73
F8	83±0.31
F9	82±0.48
F10	87±0.93
F11	84±0.24
F12	81±0.71
F13	86±1.13
F14	83±0.94
F15	87±0.38
F16	83±0.59
F17	87±0.74
F18	83±0.92
F19	84±0.54
F20	89±0.31
F21	86±1.23
F22	87±0.74
F23	830.60
F24	91±0.89
F25	86±0.67
F26	**96±0.38**
F27	84±0.17

In phosphate buffer pH 6.8, HPMC polymers showed good swelling property. In middle layer of selegiline HCl, among all the formulations F26 showed highest degree of swelling index 96.0%, where as in F12 showed leased swelling with a swelling index of 81.0%.

Evaluation of trilayer matrix tablets of Selegiline HCl:

Fig 7: Selegiline HCl trilayer matrix tablet

Table 4: Physico-chemical evaluation properties of selegiline Hcl trilayered tablets

F.NO	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm^2)	#Friability (%)	# Content uniformity (%)	Swelling Index (%)
AF26	352±1.2	4.5±0.12	5.7±0.12	0.57±0.01	97.23±0.63	188±0.41
BF26	349±0.8	3.6±0.06	5.6±0.06	0.59±0.02	96.04±0.06	187±0.28
CF26	**350±0.2**	**4.0±0.06**	**6.0±0.06**	**0.54±0.03**	**99.56±0.14**	**199±0.31**
DF26	349±0.0	4.4±0.12	5.2±0.12	0.57±0.01	97.71±1.01	194±0.56
EF26	351±0.4	4.5±0.00	5.8±0.00	0.61±0.02	96.23±0.8	180±1.09
FF26	353±0.4	4.3±0.10	5.9±0.06	0.65±0.01	97.45±0.31	185±0.67
GF26	351±0.3	3.7±0.10	5.1±0.10	0.60±0.02	96.11±0.49	187±0.83
HF26	248±0.2	4.5±0.25	5.7±0.40	0.56±0.01	95.23±0.51	186±0.59

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

Sustained release tablets generally have hardness in the range of 5-7 kg/cm^2. In case of trilayer tablets the hardness of the tablets was found to be 5.1 to 6.0 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 3**.

Swelling studies:
In phosphate buffer pH 6.8, HPMC showed good swelling property. In trilayer tablets of selegiline, CF26 showed highest degree of swelling index 199.0%, where as in GF26 showed leased swelling with a swelling index of 180.0%.

***In vitro* Drug Release Profile for Prepared Extended release trilayered Tablet of selegiline HCl**
The release of Selegiline HCl from different formulations was carried out in phosphate buffer pH 6.8 and the results are depicted in Table. The trilayer tablets extended the drug release upto 24 hrs. The highest drug release was found in the formulation CF26 i.e 99.12% within 24 h. CF26 was found to be optimized formulation based on the dissolution and other evaluation parameters. The results are shown in Figure 8. The comparison of marketed product Selegiline Hcl conventional tablet and optimized formulation CF26 was shown in Figure 9. The drug release from marketed product was 98.78% within 120 min.
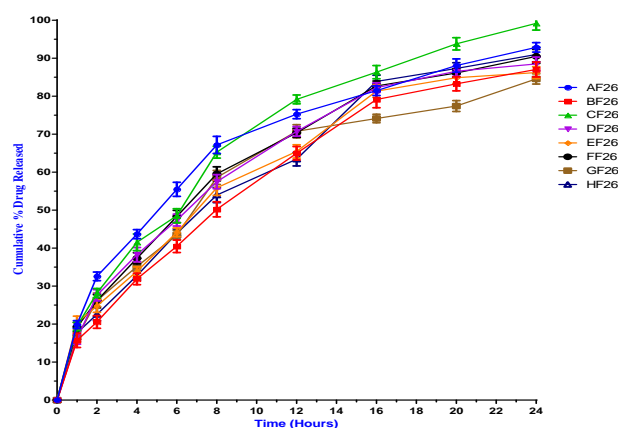
Fig 8: *In Vitro* Drug Release profile for prepared extended release trilayered tablet of selegiline Hcl (AF26-HF26)
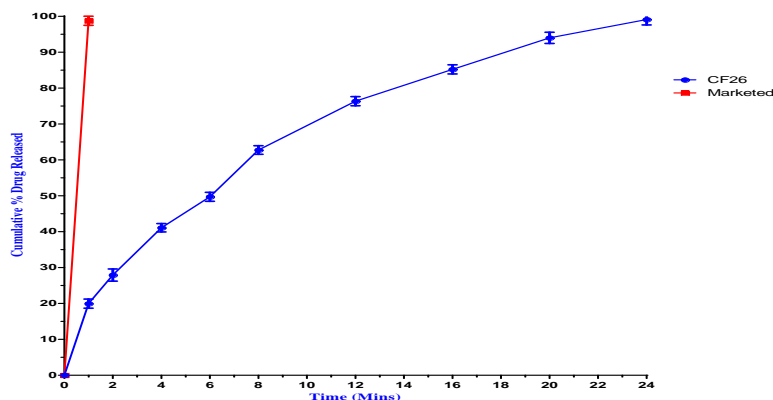
Fig 9: Comparative *In Vitro* study plot of optimized formulation (CF26) and conventional marketed tablet

Correlation coefficient values for optimized:

Table 5: Regression coefficient (R^2) Values, n.

S.No	Formulation	Zero order R^2	First order R^2	Higuchi Model R^2	Korsmeyer-Peppas model R^2	n
1	CF26	0.999	0.748	0.937	0.959	0.835
2	Marketed	0.927	0.983	0.943	0.968	0.833

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 6. The optimized formulation was best fitted in Zero Order and Korsmeyer-Peppas. The optimized formulation n value was 0.835 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.

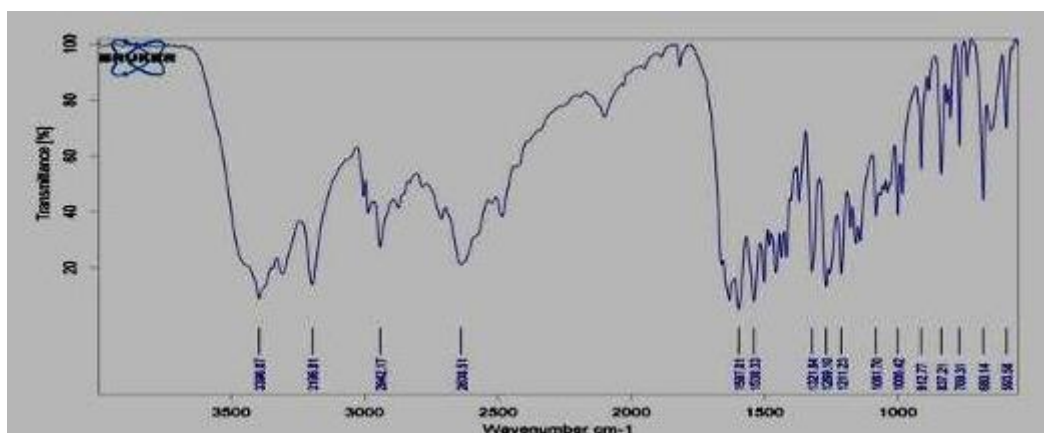**Drug-Excipient Compatability Studies:**
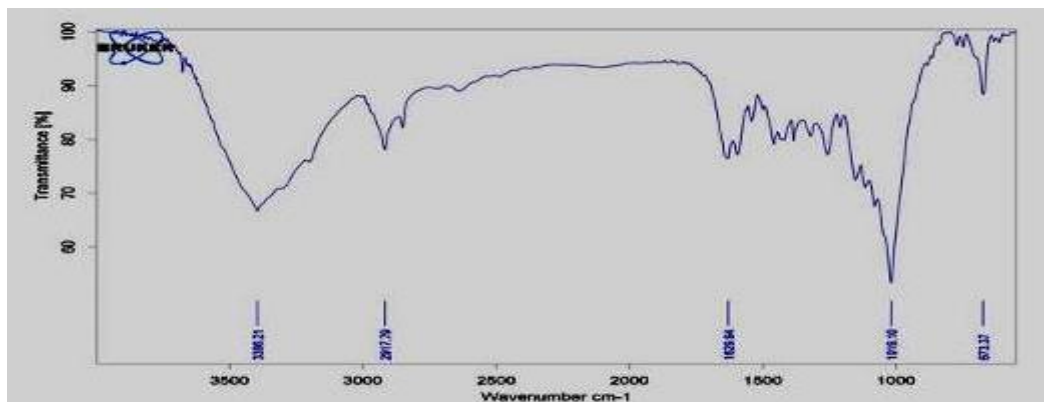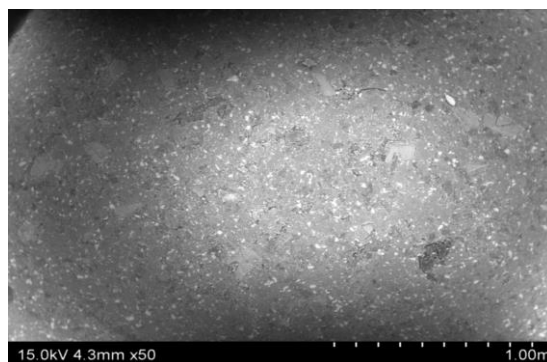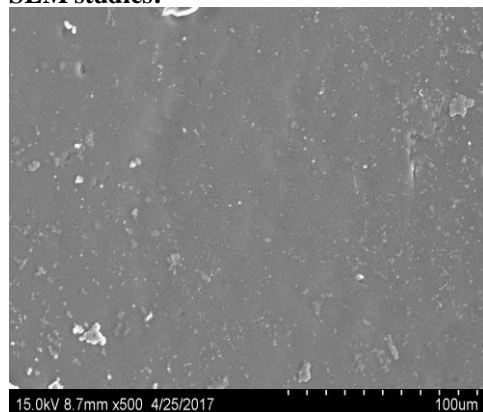**FT-IR STUDIES:**

Fig10:   FT-IR spectrum of pure drug Selegiline HCl

Fig 11:   FT-IR spectrum of Selegiline HCl optimized formulation CF26

Overall there was no alteration in peaks of Selegiline HCl pure drug **(Figure 13)** and optimized formulation **(Figure 14)**, suggesting that there was no interaction between drug & excipients. There is additional peaks appeared or disappeared hence no significant changes in peaks of optimized formulation was observed when compared to pure drug indicating absence of any interaction.

SEM further confirmed both diffusion and erosion mechanisms to be operative during drug release from the optimized formulation (CF26). Initially, tablet matrix showed swelling with pore formation that is clearly visible from SEM image. At the end of 12 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.

SEM studies:

Fig12: SEM photographs of Selegiline optimized trilayer tablets CF26

Stability Study:
There were no physical changes in appearance and flexibility. After subjecting the optimized formulation (CF26) 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 Selegiline HCl. Attempts were made to achieve extended drug release from the dosage form. Prepared twenty seven formulations of Selegiline HCl 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 F26 was finalized as optimized formulation base on the dissolution profile for 12 h. FTIR studies results revealed that there was no incompatibility between drug and excipients. *In vitro* drug release studies were carried out to know the drug release with respective of the time. Maximum drug was released from the formulation CF26 within 24 Hrs. Based on the physico-chemical properties and *in vitro* drug release, the formulation CF26 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 ($75 \pm 5\%$RH) were seen. Hence the developed formulation was found to be stable even after subjecting to accelerated stability conditions. It can be concluded that the extended release trilayered matrix Tablets of Selegiline HCl formulations can be an innovative and promising approach for the delivery of Selegiline HCl in the efficient management of Parkinson's disease.

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