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Design and Characterization of Selegiline Bio-Nanoparticles as novel drug carriers for Parkinson's therapy

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ABSTRACT: Background: Selegiline is a monoamine oxidase inhibitor used for the treatment of Parkinson's disease. **Aim:** The present study was aimed to formulate Selegiline polymeric nanoparticles by using various polymers, PLGA (poly (lactic-co-glycolic acid) copolymer, TPGS (D-α-tocopherol-polyethylene glycol-1000 succinate) by Solvent dispersion (Nanoprecipitation) method. **Methods:** Absorption maximum of Selegiline was determined and analytical method was developed. The polymeric nanoparticulate formulations were subjected for Particle size, Zeta Potential, Drug Loading and Entrapment Efficiency studies. *In vitro* diffusion studies were conducted and release data was subjected to kinetic analysis. **Results:** The preformulation studies indicated that absorption maximum of Selegiline was corroborated with literature value. Calibration curve showed a high degree of linearity which represents the sensitivity and accuracy of developed analytical methods. The compatibility studies exhibited no interactions indicating drug polymer compatibility. Zeta potential of all polymeric nanoparticles indicates their stability. Formulations exhibited particle size in nano range with good drug entrapment and uniform drug content. Selegiline *In vitro* release studies showed sustained and prolonged release of drug indicates better absorption with patient compliance. Among all F6 formulations, it exhibited maximum drug release and was considered as optimized formulation with respect to its ideal drug entrapment and *in vitro* drug release. Release kinetics analysis of optimized formulation revealed that the F6 formulation followed zero order kinetics of drug release. **Conclusion:** Results obtained from the above studies conclude that Selegiline polymeric nanoparticles could be formulated for targeted drug delivery with better absorption and improved drug action for Parkinson's therapy.

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INTRODUCTION:

Nanotechnology (NT) uses materials that are the devices of nanometric size range (1 to 100 nm) to treat neurodegenerative disorders. Current drug delivery nanosystems have been tailored to deliver drugs and contrast agents to the brain by crossing the blood brain barrier or through sustained local release. Currently, much attention is focused on research aimed at the development of biocompatible nanocarriers for drugs as indicated in Fig 1. Nanoparticles (NPs) are one of the

preferred nanostructures due to their small size, vast surface and surface-volume ratios. NPs have potential applications in high-technology fields, such as drug delivery, separation technology, nanoelectronics, and catalysis.

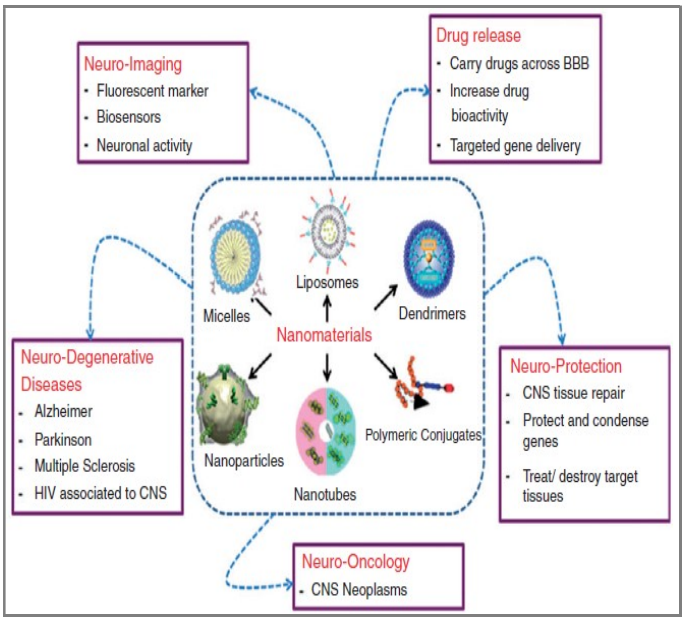


Fig 1. Polymeric Nano materials varying in shape and their applications.

NPs can be generated from a wide range of polymers such as poly(lactide-co glycolide), poly(lactic acid), poly(e-caprolactone), chitosan, and poly(alkyl cyanoacrylates). The drug may be attached to a nanoparticle matrix, or dissolved, encapsulated and entrapped, giving rise to different terminologies as nanoparticles, nanospheres or nanocapsules. Nanotechnology approaches for Parkinson's disease therapy were indicated in Fig 2 [1-4]. Parkinson disease (PD) is a chronic, progressive neurodegenerative disorder. Over 2 % of the population aged over 65 years and 5 to 20/100,000 individuals per year are affected by the disease. The chief clinical manifestations of PD include resting tremor, bradykinesia, impaired postural reflexes, muscle rigidity, and varying degrees of autonomic dysfunction.

Selegiline hydrochloride is l-deprenyl, is an acetylenic derivative of phenethylamine. It acts as an irreversible inhibitor of monoamine oxidase (MAO), an intracellular enzyme associated with the outer membrane of mitochondria. Studies have shown that selegiline can also slow the progression of Alzheimer's disease [5-8].

MATERIALS AND METHODS:

Selegiline was a gift sample from Scion Pharma, Taiwan. The PLGA polymer was obtained from Lactel, Durect Corporation Birmingham Division. TPGS procured from Eastman Company, UK. Acetone was procured from SD fine chemicals, Mumbai, India. All other chemicals used were of analytical grade. Homogenizer, Kinematica AG (Poly tron PT2100), HPLC Shimadzu, Lyophiliser, Lyophilisation systems, India, Particle size analyzer Malvern.

Determination of absorption maxima:

Standard stock solution of drug with 10 µg/ml concentration was prepared in 0.1N HCl. The solution was scanned for absorption maxima in double beam UV/VIS spectrophotometer between 200 to 400 nm [9-11].

Preparation of calibration curve:

About 10 mg of pure Selegiline drug was taken in a 10 ml standard flask and dissolved in distilled water. The volume of the stock solution was made up to 10 ml with pH 6.8 phosphate buffer. From the above stock solution, 1 ml was transferred into a 10 ml volumetric flask and volume was adjusted to 10 ml that corresponded to 100 µg/ml drug in solution. From that solution different aliquots of 0.2, 0.4, 0.6, 0.8, 1.0 and 1.2 ml were transferred to 10 ml volumetric flask and volume was adjusted to 10 ml with pH 6.8 phosphate buffer, which gave a concentration of 2, 4, 6, 8, 10 and 12 µg/ml respectively of final standard [9-11].

FTIR spectral studies:

The drug polymer compatibility was ascertained by subjecting the drug, homogenates of drug and polymer to Infrared spectrophotometric (FTIR) studies [11,12].

Preparation of selegiline nanoparticles by Solvent dispersion (Nano precipitation):

The nanoparticles are prepared according to formulations F1 to F8 (Table 1). First by dissolving the drug in an organic phase along with the polymer (PLGA) and adding it to the aqueous solution containing TPGS which acts as an emulsifier. The solution of organic phase was added in drop wise into aqueous phase under homogenization at 11,000 rpm. The dispersion was kept under magnetic stirring for 4 h at room temperature. The solution is kept under reduced pressure for about 2 to 3 min resulting in generation of nanoparticles loaded with drugs [13,14].

Evaluation of selegiline loaded nanoparticles:

Particle size and zeta potential of formulated selegiline loaded nanoparticles was determined by using Malvern instrument UK. Specifications: Instrument: Master sizer 2000 from Malvern Instruments. Laser specification:

	Drug	Nanocarrier	Model	Via	
Parkinson's disease (PD)					
Dopamine delivery	L-DOPA	PLGA	Rats	s.c.	Reduces dyskinesia in dyskinetic rats
	Dopamine hydrochloride	Liposomes	Rats	i.c.	Levels remained 25 days post administration and partial behavioral recovery
	L-DOPA	Liposomes with cholorotoxin	Mice	i.p.	Increased the distribution of dopamine
	Dopamine	CAP	Rats	i.c.	Allows site-specific delivery
Drugs for PD	Ropirole	Nanoemulsion gel	Rats	t.d.	Better pharmacokinetic than the oral dosing
	Bromocriptine	Tristeatin/tricaprin	Rats	i.p.	Prolongs half-life of bromocriptine than free drug
	Bromocriptine	Chitosan	Mice	i.n	Development of a noninvasive brain drug delivery

i.v.: intravenous; v.o: via oral; i.c.: intracerebral, t.d.: transdermal; i.n.: intranasal.

Fig 2. Nanotechnology approaches for Parkinson's disease therapy.

Table 1. Formulation table for selegiline nanoparticles.

Ingredients	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
PLGA (50:50) (mg)	1300	1300	1300	2500	5000	7500	10000	12500
TPGS (mg/ml)	3	4	5	6	7	8	9	10
Selegiline (mg)	250	250	250	250	250	250	250	250
Acetone (ml)	30	30	30	30	30	30	30	30
Water (ml)	100	100	100	100	100	100	100	100

PLGA: poly(lactic-co-glycolic acid); TPGS: D -α-Tocopherol polyethylene glycol 1000 succinate.

Red light: CDRH and CE compliant. Type: HeNe gas laser. Max. Output power: 4 mW. Beam diameter: 0.63 mm (1/e²). Beam divergence: 1.5 mrad. Beam wavelength: 633 nm. Blue Light: Mastersizer 2000 and Mastersizer 2000LF is: Beam wavelength: 466 nm. Type: LED [15,16].

***Particle size and Zeta potential determination*:**

Each type of sample material has its own ideal range of sample concentration for optimal measurements. If the sample concentration is too low, there may not be enough light scattered to make a measurement. If the sample is too concentrated, then light scattered by one particle will itself be scattered by another. The upper limit of the concentration is also governed by the point at which the concentration no longer allows the sample to freely diffuse, due to particle interactions. An important factor in determining the maximum concentration the sample can be measured at, is the size of the particles. Each complete measurement is divided into a number of measurement runs. All the individual measurement runs are accumulated together and then summed to give a final zeta potential result [15, 16].

Lyophilization:

The obtained centrifuged samples were lyophilized and stored at 2 to 8 °C. The samples are lyophilized to attain stability. The obtained lyophilized powder is utilized for

determination of entrapment efficiency and *in-vitro* drug release parameters [17].

Drug encapsulation efficiency:

Lyophilized nanoparticles of 3 mg were dissolved in 1 ml of diluents and the drug amount was determined by HPLC analysis. The encapsulation efficiency was determined as the mass ratio of entrapped Selegiline in nanoparticles to the theoretical amount of the drug used in the preparation. The entrapment of the Selegiline PLGA nanoparticles was given in equation 1 [18].

EE (%) = (AE/ TDL) × 100 ….(1)

Where, EE is entrapment efficiency, AE is amount entrapped and TDL is total drug loaded.

***HPLC Method*:**

Mode: Reverse phase. Method: Isocratic, Mobile phase: Acetonitrile: water: Methanol: 42:32:26, Column: Zorbax-SB-C18, 250 × 4.6 mm, 5µ- particle size, Flow rate: 1.0 ml/min, Detection: 230 nm, Column temperature: Ambient, Injection volume: 10 µl, Linear Regression coefficient in the range of 0.25 to 0.75 mg/ml 0.9998 (n=3) [9-11].

***In vitro* selegiline release studies:**

Drugs equivalent to 10 mg freeze dried Selegiline loaded nanoparticles were dispersed in 3 ml pH 7.4 phosphate buffer which is transferred in a dialysis bag and suspended in 100 ml of isotonic pH 7.4 Phosphate buffer solution (PBS). The bag was placed under magnetic stirring in a water bath maintained at 37 ± 0.5 °C. At fixed time intervals 5 ml of samples were taken out and fresh buffer was replaced. The obtained solution was analyzed by HPLC to determine the drug content [19].

***In vitro* drug release kinetics:**

Mathematical modelling of the release kinetics of specific classes of controlled-release systems may be used to predict solute release rates from and solute diffusion behaviour through polymers and to elucidate mechanism of solute transport by simply comparing the release data to mathematical models. The mechanism of drug release from the formulations during the diffusion in pH 7.4 phosphate buffer was determined using the Zero order, First order, Higuchi equation and Korsmeyer Peppa's plot [20-22].

Stability studies:

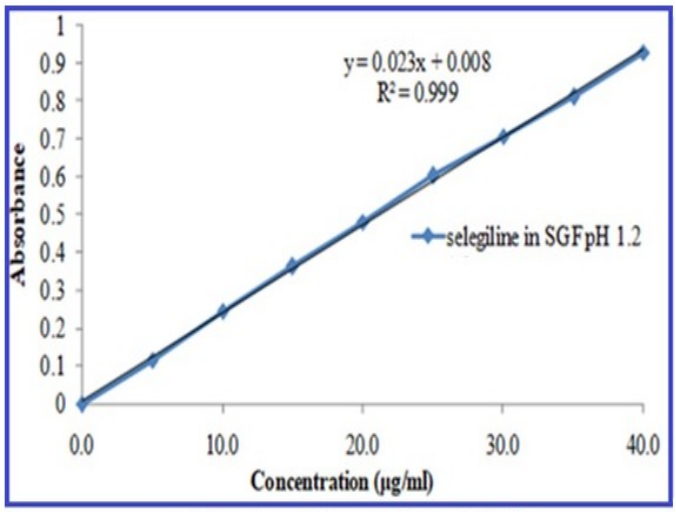
Stability studies were carried out for optimized formulation F6 for 2 months at 25 °C/ 60 % RH; 30 °C/ 75 % RH; 40 °C/ 75 % RH and analysed for Percent drug release and assay [23,24].

RESULTS AND DISCUSSION:

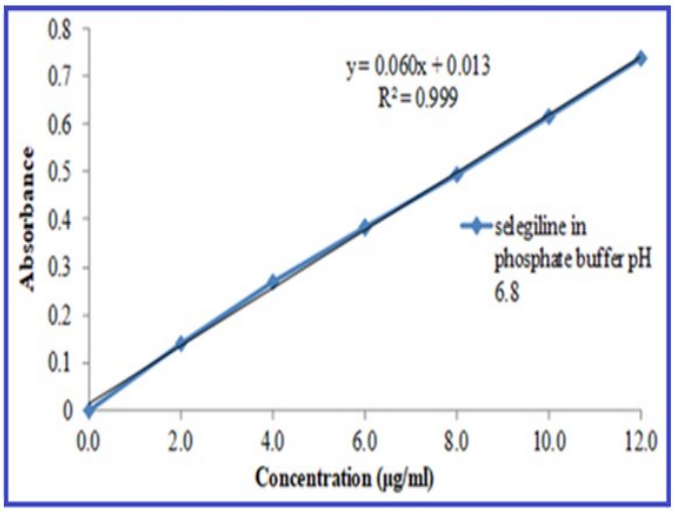
The pre formulation studies indicated that the absorption maximum of selegiline drug was 298 nm which corroborated with literature value.

Analytical Method:

Calibration curve of Selegiline was constructed in Simulated Gastric fluid (pH 1.2) and in a pH 6.8 phosphate buffer at 298 nm. The calibration curve showed a high degree of linearity indicated by the regression value 0.999 which in turn represents the sensitivity and accuracy of the developed analytical method [9]. The developed analytical method is used for the drug estimation during *in vitro* drug release studies (Fig 3).



a) Simulated Gastric fluid (pH 1.2)



b) Phosphate buffer pH 6.8

Fig 3. Standard graph of a) Selegiline in simulated gastric fluid pH 1.2 and b) Phosphate buffer pH 6.8.

FTIR Drug - Excipient compatibility studies:

The compatibility studies of pure drug polymers exhibited no interaction peaks in corresponding IR spectras. The FTIR spectral studies of the Selegiline, polymer mixtures were represented in Fig 4. The IR spectra of Selegiline exhibited distinctive peaks at 2900 cm^{-1} due to NH stretching of the secondary amine, 1572.66 cm^{-1} owing to –C=O stretching of the carboxyl ion and at 745.35 cm^{-1} because of C-Cl stretching. The FTIR spectra of polymer mix displayed characteristic peaks at 2981.41 due to CH aliphatic stretching and at 1724.05 due to –C=O stretching. In the IR spectra of the polymer mix the peak due to the drug carboxyl group was shifted to 1577.49 cm^{-1} whereas the signal resulting from the polymer carboxyl appeared at 1734.66 cm^{-1}.

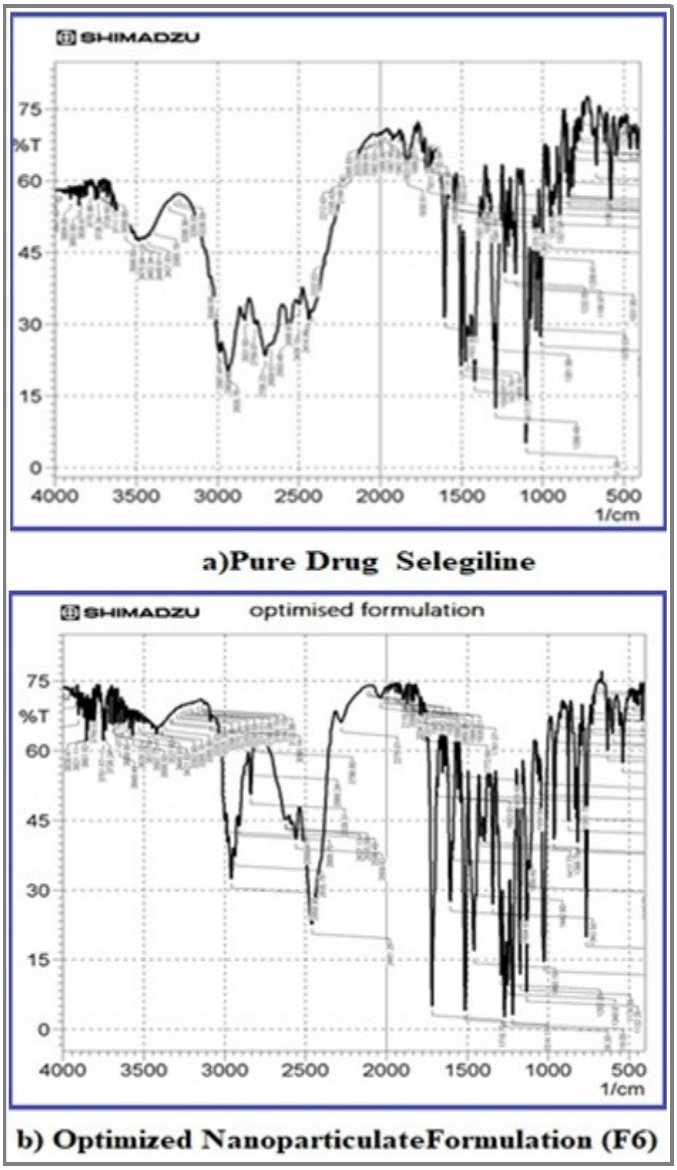


Fig 4. FTIR Compatibility studies of pure drug and optimized formulation (F6).

The FTIR studies revealed minimum drug polymer interaction and drug polymer compatibility in the formulations respectively. Compatibility studies indicated the suitability of PLGA and TPGS for Selegiline nanoparticulate formulations [12].

Selegiline nanoparticles evaluation studies:

Selegiline nanoparticles were formulated by Solvent dispersion (Nano precipitation) method. Evaluation parameters like zeta potential indicated minimal surface charge of all the developed formulations showed their stability properties. All formulations exhibited particle size in the nanoscale range with optimal drug loading respectively, drug encapsulation efficiency as high as 97 % has been achieved. Evaluation Studies of Selegiline Nanoparticles depicted in Table 2 exhibited good drug entrapment efficiency for all nanoparticulate preparations of Selegiline. The particle size and size distribution depends on the amount of TPGS added in the formulation. TPGS could be an efficient polymer for fabrication of polymeric nanoparticles, which can achieve excellent effects in drug encapsulation efficiency, size and size distribution [15]. Drug content studies revealed that all formulations showed uniform drug content in the range of 95 to 99 %.

***In vitro* drug release studies:**

The *in vitro* diffusion studies results were indicated in Table 3 and 4 for F1 to F8 formulations respectively. Studies were performed in pH 6.8 buffer using dialysis membrane for 18 h. Initially the release of drugs was found to be about 25 to 35 % in 3 h. This was due to the release of adsorbed drugs from the surface of Nanoparticles. Later on a constant and slow drug release was observed for 18 h which showed prolonged drug action suitable for better absorption and patient compliance. The drug release from F1, F2, F3, F4, F5, F6, F7 and F8 formulations as indicated in Fig 5 was found to be 95.39, 92.25, 91.17, 95.42, 91.47, 97.96, 95.39 and 93.35 % respectively [9]. Therefore the F6 formulation with 1:30 drug polymer ratio showed 97.96 % release was selected as optimized formulation and subjected for further drug release kinetic studies.

***In vitro* release kinetics studies:**

In vitro drug release kinetics of optimized selegiline F6 Formulation showed in Table 5 and Fig 6. The drug release from the Nanoparticles was found to follow zero order release based on the r value obtained for first order 0.989 of F6 formulation.

Table. 2. Evaluation Studies of Selegiline Nanoparticles.

Batch No	Particle size (nm)	Zeta potential (mV)	Drug Loaded (mg)	EE (%)
F1	152.3±0.234	-25.34	124.2±1.24	49.88±1.48
F2	164.21±0.241	-24.16	153.4±1.16	61.36±1.24
F3	174.25±0.351	-23.41	189.54±2.15	75.816±1.34
F4	253.1±0.235	-22.18	193.48±2.67	77.39±1.31
F5	100.3±0.142	-21.34	202.14±2.98	80.856±1.38
F6	124.8±0.125	-12.14	222.1±2.62	88.84±1.67
F7	121.5±0.421	-6.47	236.47±2.37	94.58±1.11
F8	152.4±0.321	-16.48	241.1±2.69	96.44±1.75

All data are presented as Mean ± Standard deviation (n=3). EE – Entrapment Efficiency.

Table 3. *In vitro* drug release profile of F1 to F4 selegiline nanoparticles formulations.

Time (h)	Cumulative percent selegiline release			
	F1	F2	F3	F4
0	0.00±0.000	0.00±0.000	0.00±0.000	0.00±0.000
1	19.24±0.291	15.61±0.276	17.08±0.206	19.53±0.121
2	27.67±0.387	25.96±0.187	27.25±0.303	27.65±0.185
3	37.14±0.162	32.80±0.104	33.99±0.255	37.49±0.427
4	44.17±0.106	39.94±0.395	41.82±0.214	44.47±0.208
5	54.79±0.340	51.51±0.301	47.48±0.323	54.81±0.185
6	60.05±0.188	57.13±0.135	53.69±0.330	60.54±0.344
7	61.99±0.155	59.12±0.239	59.15±0.162	62.71±0.384
8	64.73±0.349	61.62±0.272	64.59±0.405	64.74±0.196
10	72.21±0.248	68.93±0.239	69.01±0.466	72.30±0.110
12	81.49±0.327	75.73±0.300	75.67±0.363	81.53±0.186
14	83.87±0.111	78.09±0.185	79.36±0.365	84.00±0.128
16	89.90±0.478	86.67±0.326	85.96±0.338	89.81±0.276
18	95.39±0.197	92.25±0.245	91.17±0.214	95.42±0.183

All data are presented as Mean ± Standard deviation (n=3).

Table: 4. *In vitro* drug release profile of F5 to F8 selegiline nanoparticles formulations

Time (h)	Cumulative percent selegiline release			
	F5	F6	F7	F8
0	0.00±0.000	0.00±0.000	0.00±0.000	0.00±0.000
1	17.39±0.202	21.89±0.462	19.43±0.179	19.29±0.416
2	27.66±0.104	29.75±0.677	28.80±0.294	28.57±0.546
3	34.50±0.307	39.80±0.507	35.62±0.633	37.39±0.266
4	41.92±0.167	46.94±0.502	44.15±0.507	44.49±0.376
5	47.58±0.551	55.85±0.524	54.57±0.323	54.99±0.278
6	53.74±0.398	59.59±0.468	60.08±0.202	59.92±0.552
7	59.49±0.225	63.80±0.413	61.99±0.127	62.17±0.261
8	64.62±0.292	66.51±0.375	64.46±0.110	65.89±0.235
10	69.21±0.115	73.84±0.557	71.63±0.427	72.20±0.247
12	75.69±0.321	83.09±0.513	80.77±0.302	81.46±0.262
14	79.46±0.260	86.41±0.425	83.28±0.424	84.27±0.554
16	86.24±0.497	91.44±0.531	89.36±0.271	89.87±0.242
18	91.47±0.219	97.96±0.587	95.39±0.294	93.35±0.389

All data are presented as Mean ± Standard deviation (n=3).

Table 5. ***In vitro*** **drug release kinetics of optimized selegiline nanoparticulate Formulation F6.**

Time (h)	Root (t)	Cum. (%) release q	Log (t)	Log (%) release	log (%) remain	release rate (cum. % release / t)	1/cum% release	Peppa's log q/100
0	0	0.00	0.000	0.000	2.000	0.000	0.0000	0.000
1	1.000	21.89	0.000	1.335	1.894	21.620	0.0463	-0.665
2	1.414	29.75	0.301	1.475	1.846	14.930	0.0335	-0.525
3	1.732	39.80	0.477	1.595	1.783	13.117	0.0254	-0.405
4	2.000	46.94	0.602	1.667	1.729	11.613	0.0215	-0.333
5	2.236	55.85	0.699	1.754	1.635	11.360	0.0176	-0.246
6	2.449	59.59	0.778	1.794	1.577	10.375	0.0161	-0.206
7	2.646	63.80	0.845	1.808	1.553	9.177	0.0156	-0.192
8	2.828	66.51	0.903	1.824	1.522	8.341	0.0150	-0.176
10	3.162	73.84	1.000	1.871	1.409	7.434	0.0135	-0.129
12	3.464	83.09	1.079	1.922	1.217	6.960	0.0120	-0.078
14	3.742	86.41	1.146	1.935	1.141	6.155	0.0116	-0.065
16	4.000	91.44	1.204	1.963	0.916	5.734	0.0109	-0.037
18	4.243	97.96	1.255	1.990	0.375	5.424	0.0102	-0.010

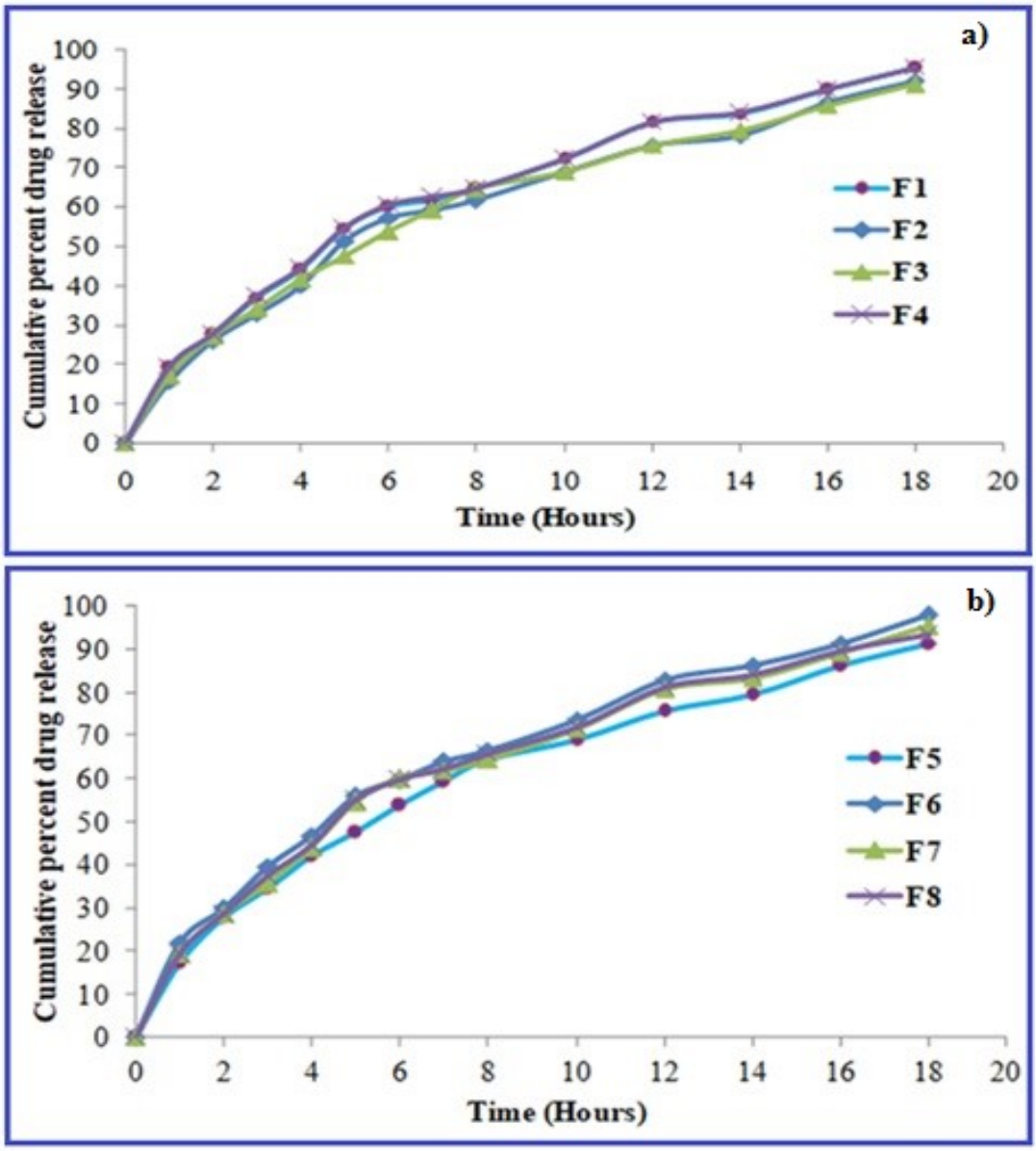


Fig 5. ***In vitro*** **release of a) F1 to F4 and b) F5 to F8 selegiline nanoparticles formulations.**

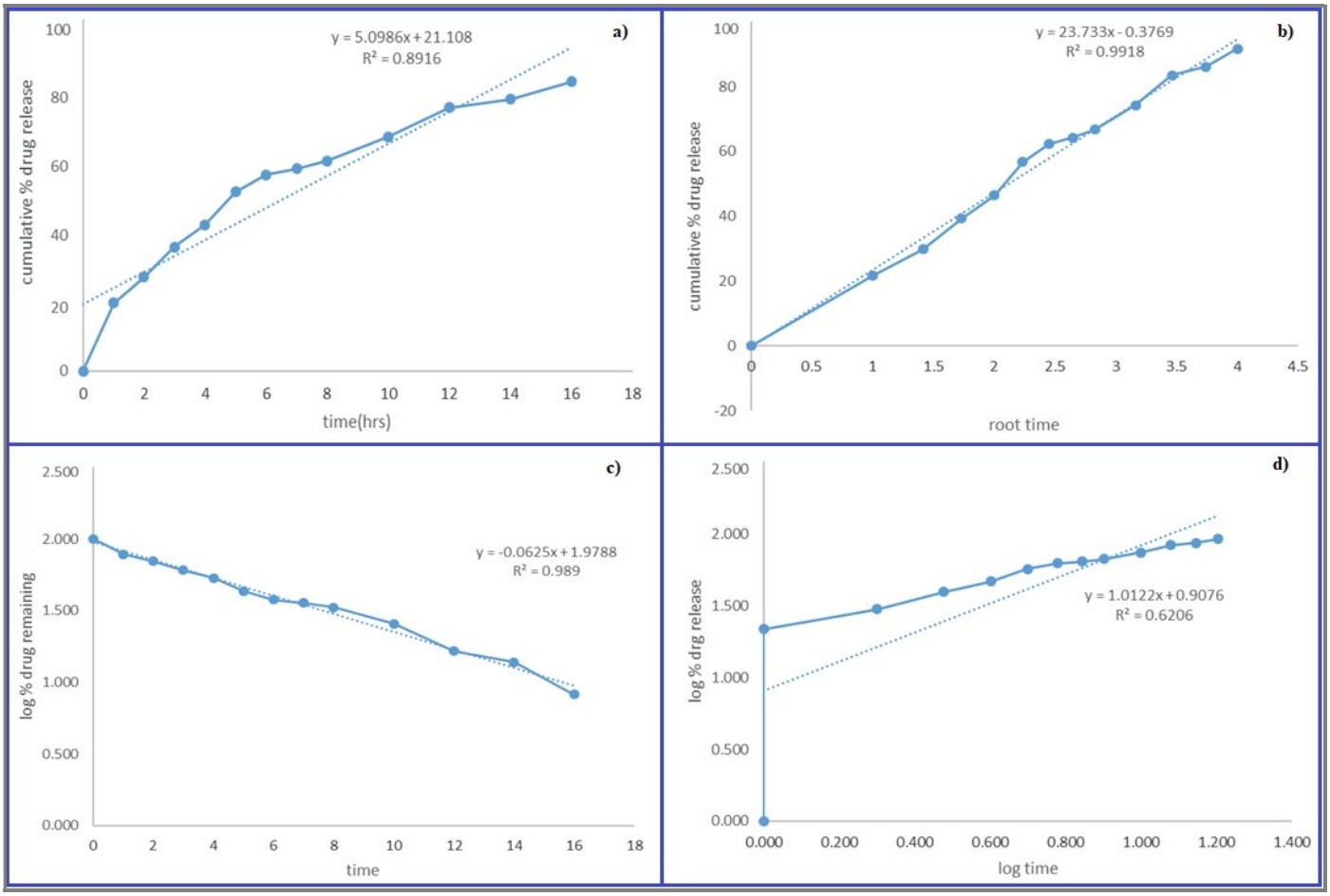


Fig 6. Release kinetics of optimized formulation F6 a) Zero order, b) First order, c) Higuchi, D) Peppa's plots.

Table 6. Stability studies of optimised F6 nanoparticulate formulation.

Formulation	Parameters	Initial	1st Month	2nd Month	Limits
F6	25°C/60%RH % Release	97.62±0.87	96.85±0.34	96.14±0.34	Not less than 85 %
F6	30°C/75%RH % Release	97.54±0.34	97.14±0.24	96.91±0.14	Not less than 85 %
F6	40°C/75%RH % Release	96.92±0.24	96.12±0.42	95.17±0.85	Not less than 85 %
F6	25°C/60%RH Assay value	98.15±0.75	98.02±0.15	97.99±0.15	Not less than 90 % Not more than 110 %
F6	30°C/75%RH Assay value	98.12±0.16	98.10±0.74	98.05±0.41	Not less than 90 % Not more than 110 %
F6	40°C/75%RH Assay value	97.95±1.25	96.54±0.46	96.34±0.32	Not less than 90 % Not more than 110 %

Also, the drug release was found to be diffusion based on the r value of 0.991 obtained for Higuchi's plot. The drug release mechanism was found to be an anomalous diffusion mechanism based on the n value of 0.907 obtained for Peppa's equation [22].

Stability Studies:

Stability studies of optimised F6 nanoparticulate formulation indicated in Table 6 showed that there were no significant changes in physical and chemical properties of drug in optimized nanoparticulate formulation F6 after 2 months [23].

CONCLUSION:

From the current work it was evident that Selegiline nanoparticles were formulated and evaluated for their properties. The developed nanoparticles exhibited characteristics which are in accordance with the official

limits. All the formulations exhibited ideal and good particle size, Zeta Potential, drug loading and entrapment efficiency. Among all the formulations, F6 produced maximum drug release compared to other formulations hence it was considered as the optimized formulation. The F6 formulation release data was subjected to kinetic analysis; from the release kinetics it was evident that the formulation showed anomalous diffusion type of drug release. Hence Selegiline polymeric nanoparticles could be formulated for sustained release, targeted drug delivery for better absorption and improved drug action for Parkinson's therapy.

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