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Design and in vivo evaluation of selegiline mouth dissolving films

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ABSTRACT

The main objective of the present investigation was aimed at formulation and evaluation of Selegiline fast dissolving oral thin films to enhance the patient convenience and compliance in the effective treatment of Parkinson's disease. Oral thin films of Selegiline were prepared by solvent casting method with using different film forming agents like HPMC5LV, HPMC 15LV, HPMC50LV and HPMC K4M. Propylene glycol, Sucrose, Vanillin is used as a plasticizer, sweetening agent, flavouring agent respectively and citric acid as saliva stimulating agent. FDOFs were evaluated for physical characteristics, Surface pH, weight variation, thickness, folding endurance, percent drug content, percentage elongation, disintegration time, in vitro dissolution studies. Based on all the evaluation studies F18 is selected as optimized formulation and in vitro disintegration time and amount of drug release from the film was 9secs and 99.68% within 7min respectively. A further *in vivo* study proved that the fast dissolving films of Selegiline produced a faster onset of action and improved bioavailability as compared to the conventional tablets.

Keywords: Selegiline, HPMC, Fast dissolving oral films, Solvent casting method, Parkinson's disease, Bioavailability studies.

INTRODUCTION

Flash release of Mouth dissolving film consists of solid dosage forms that are postage stamp-sized thin polymeric films, which when placed onto the tongue disintegrate or dissolve rapidly i.e., within seconds in the oral cavity without administration of water. Mouth dissolving films are a suitable alternative to conventional delivery as found in formulations by various formulators [1].

The delivery system consists of a very thin oral strip, which is simply placed on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medication for oro-mucosal absorption or with formula modifications, will maintain the quick dissolving aspects allow for gastrointestinal absorption to be achieved when swallowed [2]. The film is prepared using the hydrophilic polymers (e.g., Hydroxypropyl

methylcellulose) which dissolves on the tongue or buccal cavity in a no while. And upon contacting with liquid, the drug is delivered to the systemic circulation through dissolution [3]. Hydroxypropyl methylcellulose (HPMC) polymer is non-toxic, non-irritant and void of leachable impurities. It should have good wetting and spread ability characteristic. HPMC shows enough peel, shear and tensile strengths. Moreover, it is readily accessible and cheap. Accordingly, film strips should be tough adequately so that there would not be any damage while handling or transportation [4]. Selegiline's used in the treatment of Parkinson's disease are not fully understood, the selective, irreversible inhibition of monoamine oxidase type B (MAO-B) is thought to be of primary importance. MAO-B is involved in the oxidative deamination of dopamine in the brain. Selegiline binds to MAO-B within the nigrostriatal pathways in the central nervous system, thus blocking microsomal metabolism of dopamine and enhancing the dopaminergic activity in the substantial nigra. Selegiline may also increase dopaminergic activity through mechanisms other than inhibition of MAO-B. At higher doses, selegiline can also inhibit monoamine oxidase type A (MAO-A), allowing it to be used for the treatment of depression. The present work was aimed at developing a fast dissolving oral film of Selegiline to enhance therapeutic efficacy in the effective management of Parkinson's disease [5].

MATERIALS AND METHODS

Materials

Selegiline API was procured from Hetero drugs Ltd, Hyderabad. HPMC 5LV, 15LV, 50LV and HPMC K4M procured from Granules India Ltd, Hyderabad. Crospovidone, Propylene glycol, Sucrose, Citric acid, Menthol, Vanillin procured from S. D. Fine Ltd, Mumbai.

Methods

Preparation of Selegiline oral films

It was aimed to prepare fast dissolving oral films of Selegiline with the dose of 5 mg per 4 cm^2 film. Film forming polymers Hypromellose different grades were weighed accurately, added to a small amount of water in a small beaker, covered with an aluminium foil and soaked for 24 hours to ensure complete hydration. Then, PG was added and stirring was continued for 30 minutes at 50rpm. Selegiline, sucrose, citric acid and vanillin were dissolved in sufficient quantity of water and added to the polymer mixture. This film forming solution was then stirred well to obtain a homogenous solution. Dry and clean Petridish was selected and the solution was poured into it. Drying was carried out at 45°C in a hot air oven for 6 hours. The Petridish was then removed and left aside to cool down to room temperature. The film was then peeled carefully using surgical scalpel by making a small incision in the film on one side of the Petridish. Small films of 4 cm^2 were cut from one big film and packed primarily in aluminium foil and secondarily in a self- sealing polythene bag to ensure least moisture penetration and the resulting films were evaluated. The composition of Selegiline fast dissolving oral films with different HPMC grades are shown in **Table 1, 2, 3.**

Evaluation of selegiline fast dissolving oral films

Physical characterization of FDOFs

Physical characterization of FDOFs can be carried out by visual inspection for characteristics such as colour, thickness, brittleness, peeling ability, transparency, surface smoothness, tack property and film forming capacity.

The prepared films were subjected for in vitro evaluation tests like Surface pH [6], weight variation [7] and Thickness [8], Folding Endurance [9], Morphological properties, Moisture content, % Drug content and content uniformity [10], Percent elongation [11], Tensile strength [12], In vitro Disintegration time and In vitro Dissolution studies.

In vitro disintegration studies

Disintegration time was performed using disintegration test apparatus. Film (4 cm^2 of each) was placedin the basket, raised and lowered it in such a manner that the up and down movement was done at a rate equivalent to thirty times a minute. Time required by the film, when no traces of film remain above the gauze was noted [13].

In vitro dissolution studies

The in-vitro dissolution studies were conducted using phosphate buffer pH 6.8 (300 mL). The dissolution studies were carried out using USP dissolution apparatus XXIV (Electrolab, Mumbai,

India) at 37 ± 0.5 °C and at 50 rpm using specified dissolution media. Each film with dimension (4 cm^2 of each) was placed on a stainless-steel wire mesh with sieve opening 700µm. The film sample placed on the sieve was submerged into dissolution media. Samples were withdrawn at regular time intervals and filtered through 0.45µm Whatman filter paper and were analyzed spectrophotometrically at 220nm. To maintain the volume, an equal volume of fresh dissolution medium maintained at same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment. The dissolution testing studies were performed in triplicate for all the batches [14].

Moisture Content

The patches were weighed and kept in a desiccators containing calcium chloride at 40^{o}C for 24 hr. The final weight was noted when there was no further change in the weight of patch. The percentage of moisture content was calculated as a difference between initial and final weight with respect to initial weight [15].

Drug excipient compatibility studies

The drug excipient compatibility studies were carried out by Fourier Transmission Infrared Spectroscopy (FTIR) method [16].

SEM studies

The surface characteristics of film 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 optimized fast-dissolving films was carried out under different conditions according to ICH guidelines. The film was packed in the aluminium foil and stored in a stability chamber for stability studies. Accelerated Stability studies were carried out at 40 ^{0}C / 75 % RH for the best formulations for 6 months. The patches were characterized for the drug content and other parameters during the stability study period.

In Vivo bioavailability studies

Animal Preparation

Twelve New Zealand white rabbits of either sex rabbits were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature 25^{0}C, RH 45% and 12h alternate light and dark cycle with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee.

In vivo Study design [17]

Rabbits were randomly divided into two groups each group contains six animals. The group A rabbits were anaesthetized with intravenous injection of pentobarbital in a dose of 25mg/kg then positioned on table with the lower jaw supported in a horizontal position and the Optimized FDF F18 contains selegiline was carefully placed on the rabbit tongue. The marketed drug was administered orally to group B with equivalent to animal body weight.

Blood samples for pharmacokinetic analysis were obtained at different time intervals 0, 0.25, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00 & 24.00h after dosing. Blood samples were collected in heparinised tubes and were centrifuged for 10min at 3,000 rpm at room temperature.

Preparation of Plasma Samples for HPLC Analysis

Rabbit plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5 ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1 ml of acetonitrile by vortexing for 1 min. After centrifugation (5000 – 6000 rpm for 10 min), the acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature. Samples were reconstituted in 200 µ1 of 70 % of acetonitrile and 30% water was injected for HPLC analysis.

HPLC method

For HPLC C8 column with 5µm particle size and the Mobile phase was composed of phosphate buffer 0.1 M (pH 6.5)-acetonitrile (70:30 v/v) with a flow rate of 1 ml/min. The eluted peaks were detected by a UV detector was set at wavelength of 205 nm. Internal standard Lornoxicam was used. The retention time of selegiline and Lornoxicam was 4.96 min and 5.5 respectively [18].

Pharmacokinetic Analysis

The pharmacokinetic parameters, peak plasma concentrations (C_{max}) and time to reach peak concentration (t_{max}) were directly obtained from concentration time data. In the present study, AUC_{0-t} refers to the AUC from 0 to 24 hrs, which was determined by linear trapezoidal rule and $AUC_{0-\alpha}$ refers to the AUC from time at zero hours to infinity.

The $AUC_{0-\alpha}$ was calculated using the formula AUC_{0-t} + [C_{last}/K] where C_{last} is the concentration in µg/ml at the last time point and K is the elimination rate constant.

The pharmacokinetic parameters were performed by a non compartmental analysis using Win Nonlin 3.3® pharmacokinetic software (Pharsight Mountain View, CA USA). All values are expressed as the mean ±SD. Statistical analysis was performed with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Preparation of Selegiline oral films

It was aimed to prepare fast dissolving oral films of Selegiline with the dose of 5 mg per 4 cm^2 film. Total 18 formulations were prepared using different polymers, HPMC 5LV, HPMC 15LV, HPMC 50LV, HPMC K4M the resulting films were shown in Figure 1.

Physical Characterization of films

Physical characterization of FDOFs was carried out by visual inspection and the following results were observed.

The films were evenly colored and no migration of color was observed. The increased thickness of film is attributed to the increase in the amount of HPMC 5LV, HPMC 15LV, HPMC 50LV, HPMC K4M and blend of polymers. All formulations were found to be excellent in film forming property, non-tacky, thin, flexible and easy to peel. The films obtained from all the formulations had smooth surface on either side.

Evaluation of fast dissolving oral films of Selegiline

Thickness & Weight variation

Thickness of all mouth dissolving films was measured with Digital Vernier calliper (Mitutoyo) (Table 4). The optimized film has thickness of 0.246±0.05mm. A result of thickness measurement showed that as the concentration of polymer increases, thickness of mouth dissolving film also increases. A result showed that as the concentration of polymer increases weight of film also increases. The weight variation of the optimised formulation was in the range of 22±0.58mm, which was acceptable.

In vitro disintegration studies

The disintegrating time of all the formulations was ranges from 8 to 19sec. The disintegration time of optimized formulation (F18) was found to be 8 sec, which was very less and desirable for quick onset of action (Table 4).

Folding endurance

Folding endurance gives an indication of brittleness of the film. It was shown that as the concentration of polymer and plasticizer increases, folding Endurance of mouth dissolving film increases (Table 5). The optimized film (F18) has folding endurance value of 121±4, which was desirable.

Surface pH

Surface pH of all mouth dissolving films prepared by using different polymers was found to be in the range of 6.42 to 6.98pH (Table 5), which was close to the neutral pH, which indicated that films may have less potential to irritate the sublingual mucosa, and hence, more acceptable by the patients.

% Drug content

All the fast dissolving oral films were found to contain an almost uniform quantity of the drug, as per content uniformity studies indicating reproducibility of the technique. Drug content in the films was evaluated and the values were found to be between 88.64 to 99.64% (Table 5) for three different cuts from each film, formulation F18 shown best drug content. As per the USP requirements, the films found to meet the criteria for content uniformity. No significant difference in the drug content among the films indicated good content uniformity.

Tensile strength and Percent Elongation

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters, tensile strength and elongation at break. Results revealed thatoptimized formulation (F18) showed better tensile strength (11.6 g/cm^2) and moderate % elongation (9.7) (Table 6).

In vitro drug dissolution study of formulation batches F1 to F18

The cumulative % drug release for the formulations F1 to F18 are presented Figure 3-5. The optimized formulation (F18) shows highest Percent of drug release 99.68±5.38 within short time of 7 min when compared with other formulations.

Drug excipient compatibility studies by FTIR spectroscopy

Overall there was no alteration in peaks of Selegiline HCl pure drug **(**Figure 6**)** and optimized formulation **(**Figure 7**)**, 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.

Scanning electron microscopy

SEM of Selegiline mouth dissolving film shows the rough and uneven surface with circular pits with the absence of particles suggesting the presence of the drug in dissolved state in the polymer HPMC. They further ensure the loss of crystallinity when formulated as a film comprising amorphous HPMC (Figure 8).

Stability Studies for optimized formulation

Optimized formulation was selected for stability studies on the basis of high cumulative % drug release. Disintegrating time, drug content and In vitro drug release studies were performed for 6 months according to ICH guidelines. From these results it was concluded that, optimized formulation F18 is stable and retained their original properties with minor differences.

Pharmacokinetic studies

The mean Selegiline plasma concentrations - time profiles for the prepared Selegiline film and Marketed Product are shown in **Figure 9**. The bioavailability parameters for the both test film and reference standard are summarized in **Table 7**. Mean time to reach peak drug concentration (T_{max}) was 0.50±0.5h and 1.5±0.1h for the optimized and commercial formulations, respectively, while mean maximum drug concentration (C_{max}) was 54.58±0.1ng/ml and 43.44±0.2ng/ml, respectively. C_{max} was significantly increased when compared with marketed product. AUC is an important parameter in evaluating bioavailability of drug from dosage form, as it represents the total integrated area under the blood concentration time profile and represents the total amount of drug reaching the systemic circulation after oral administration. $AUC_{0-\infty}$ infinity for film formulation was higher (220.46±4.14ng. h/ml) than the marketed Product 157.11±2.12ng. h/ml. Statistically, AUC_{0-t} of the Film formulation was significantly higher ($p<0.05$) as compared to marketed formulation. Higher amount of drug concentration in blood indicated better systemic absorption of Selegiline from Film formulation as compared to the Marketed Product.

Table 1: Formulation Trails Using HPMC 5LV and HPMC 15 LV

INGREDIENTS	F1	F2	F3	F4	F5	F6
Selegiline (mg)	79.47	79.47	79.47	79.47	79.47	79.47
HPMC 5LV	80	80	80	100	100	100
HPMC 15LV	100	110	120	130	140	150
Crospovidone	1	2	3	4	5	6
Propylene glycol	100	100	100	110	110	110
Sucrose	10	10	10	10	10	10
Citric acid	50	50	50	50	50	50
Menthol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Vanillin	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 2: Formulation Trails Using HPMC 15LV and HPMC 50 LV

INGREDIENTS	F7	F8	F9	F10	F11	F12
Selegiline (mg)	79.47	79.47	79.47	79.47	79.47	79.47
HPMC 15 LV	80	80	80	100	100	100
HPMC 50 LV	120	140	160	180	200	220
Crospovidone	7	8	9	10	11	12
PG	120	120	120	130	130	130
Citric acid	50	50	50	50	50	50
Sucrose	10	10	10	10	10	10
Menthol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Vanillin	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 3: Formulation Trails Using HPMC 15LV and HPMC K4M

INGREDIENTS	F13	F14	F15	F16	F17	F18
Selegiline (mg)	79.47	79.47	79.47	79.47	79.47	79.47
HPMC 15 LV	80	80	80	100	100	100
HPMCK4M	240	260	280	300	320	340
Crospovidone	13	14	15	16	17	18
PG	140	140	140	150	150	150
Citric acid	50	50	50	50	50	50
Sucrose	10	10	10	10	10	10
Menthol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Vanillin	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S

Table 4: Evaluation parameters of Selegiline mouth dissolving films

Formulation Code	Weight (mg)	Transparency	Thickness (mm)	Disintegration time (sec)
F1	24±0.59	Clear	0.259±0.09	16±0.35
F2	24±0.60	Clear	0.268±0.07	12±0.23
F3	25±0.80	Clear	0.262±0.02	14±0.24
F4	24±0.79	Clear	0.261±0.02	18±0.36
F5	25±0.72	Clear	0.258±0.07	19±0.40

F6	26±0.68	Clear	0.254±0.05	15±0.36
F7	24±0.60	Clear	0.253±0.05	13±0.24
F8	25±0.62	Clear	0.251±0.02	11±0.21
F9	23±0.59	Clear	0.248±0.07	14±0.24
F10	26±0.80	Clear	0.249±0.09	13±0.24
F11	27±0.72	Clear	0.255±0.05	18±0.36
F12	28±0.79	Clear	0.269±0.09	12±0.23
F13	26±0.68	Clear	0.262±0.02	17±0.36
F14	23±0.59	Clear	0.260±0.02	15±0.36
F15	25±0.79	Clear	0.254±0.05	14±0.24
F16	26±0.68	Clear	0.258±0.09	12±0.22
F17	24±0.60	Clear	0.250±0.02	10±0.20
F18	25±0.58	Clear	0.246±0.05	9±0.19

Values are expressed in mean± SD (n=3)

Table 5: Evaluation parameters of Selegiline mouth dissolving films

Formulation Code	Drug Content (%)	Moisture content (%)	Folding Endurance (count)	Surface pH
F1	90.21±0.45	3.41±0.30	115±2	6.85±0.5
F2	89.76±0.42	3.66±0.45	114±1	6.81±0.1
F3	88.64±0.40	3.80±0.50	119±1	6.70±0.1
F4	94.58±0.56	3.37±0.29	108±3	6.54±0.3
F5	96.74±0.60	3.25±0.18	105±2	6.66±0.5
F6	91.79±0.49	3.15±0.09	104±1	6.79±0.7
F7	90.12±0.45	3.03±0.04	101±2	6.90±0.1
F8	92.34±0.50	4.29±0.20	97±1	6.85±0.5
F9	97.46±0.62	4.34±0.23	98±2	6.82±0.2
F10	91.61±0.49	4.69±0.35	101±1	6.71±0.1
F11	89.62±0.42	3.59±0.34	119±2	6.66±0.5
F12	90.92±0.45	3.64±0.45	111±2	6.42±0.2
F13	92.61±0.50	3.85±0.54	108±2	6.54±0.3
F14	93.79±0.52	3.90±0.58	102±3	6.67±0.6
F15	94.44±0.56	3.95±0.60	104±1	6.72±0.2
F16	91.67±0.49	3.98±0.62	98±2	6.74±0.3
F17	93.12±0.52	4.32±0.23	110±4	6.89±0.8
F18	99.64±0.69	4.12±0.18	121±4	6.98±0.7

Values are expressed in mean± SD (n=3)

Table 6: Tensile Strength and Percent Elongation

Formulation code	Tensile strength (g /cm^2)	Percent elongation (%)
F18	11.6	9.7

Table 7: Comparison of pharmacokinetic parameters of Selegiline between the film and marketed product in Rabbits (mean ± SD, n = 6).

Pharmacokinetic Parameters	Optimized formulation (F18)	Marketed Product
C_{max} (ng/ml)	54.58±0.1	43.44±0.2
AUC_{0-t} (ng. h/ml)	146.88±3.74	113.47±5.16
$AUC_{0-\infty}$ (ng. h/ml)	220.46±4.14	157.11±2.12
T_{max} (h)	0.50±0.5	1.5±0.1
$t_{1/2}$ (h)	1.453 ± 0.519	3.04 ± 0.11

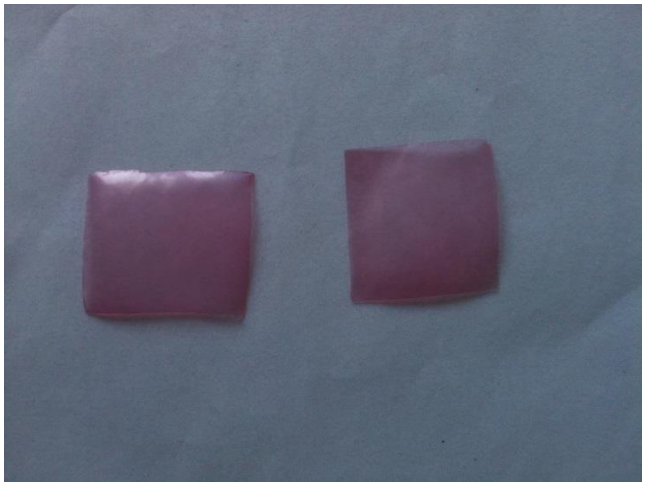

Figure 1: Preparation of Selegiline mouth dissolving films

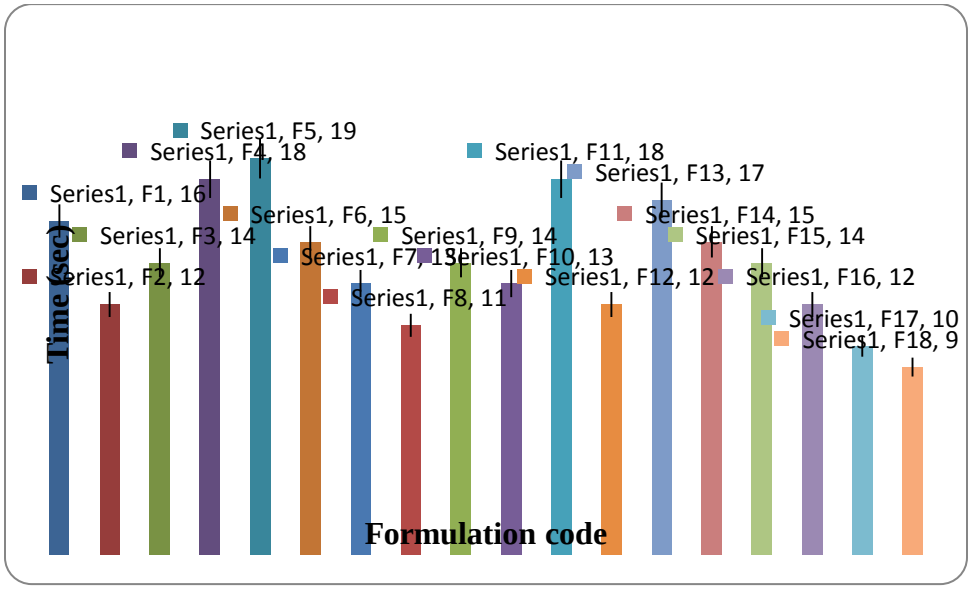

Figure 2: In vitro disintegrating time of all Formulations F1-F18

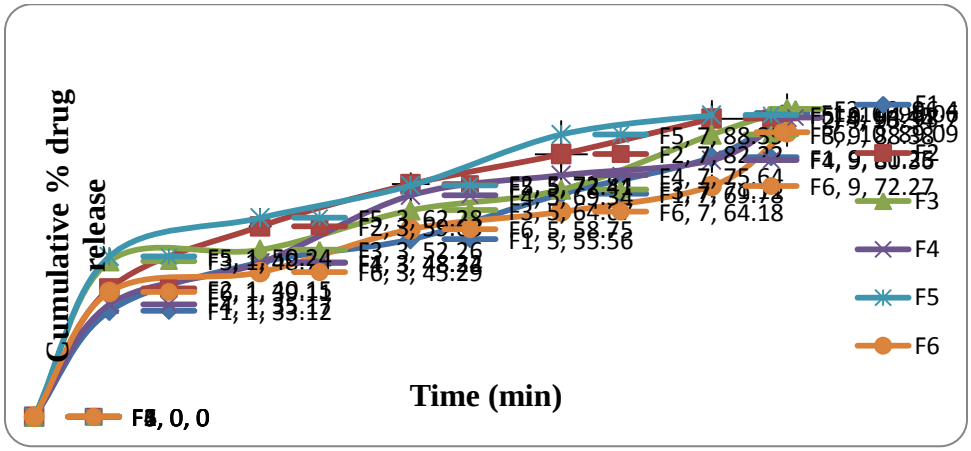

Figure 3: Cumulative % Drug Release for formulation F1-F6

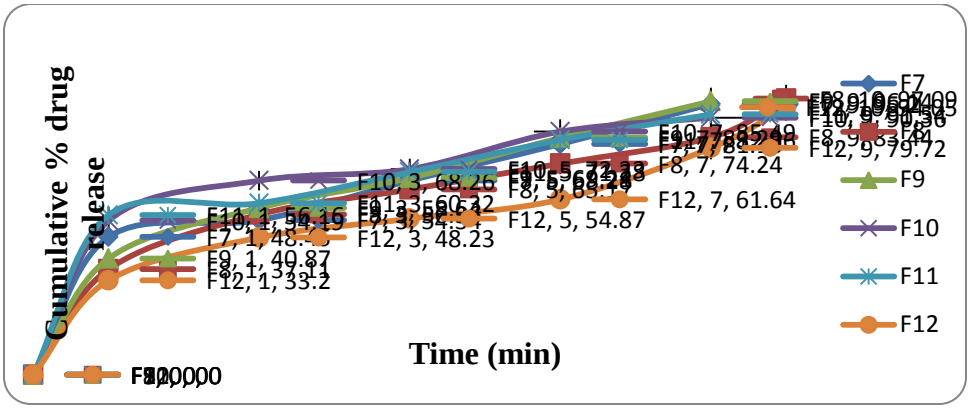

Figure 4 : Cumulative % Drug Release for formulation F7-F12

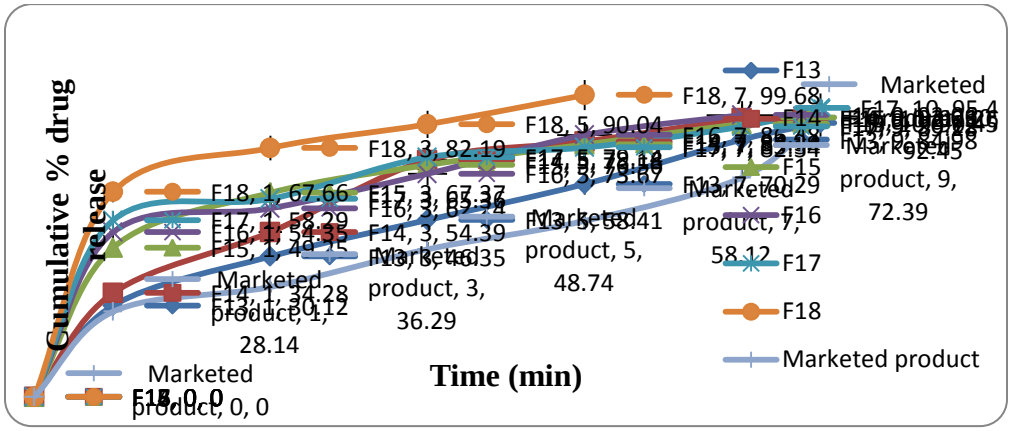

Figure 5: Cumulative % Drug Release for formulation F13-F18

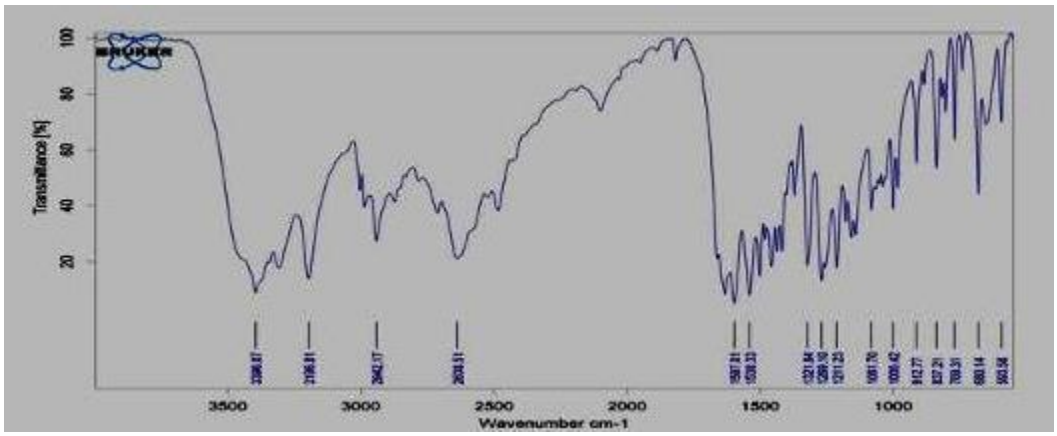

Figure 6: FT-IR spectrum of pure drug Selegiline HCl

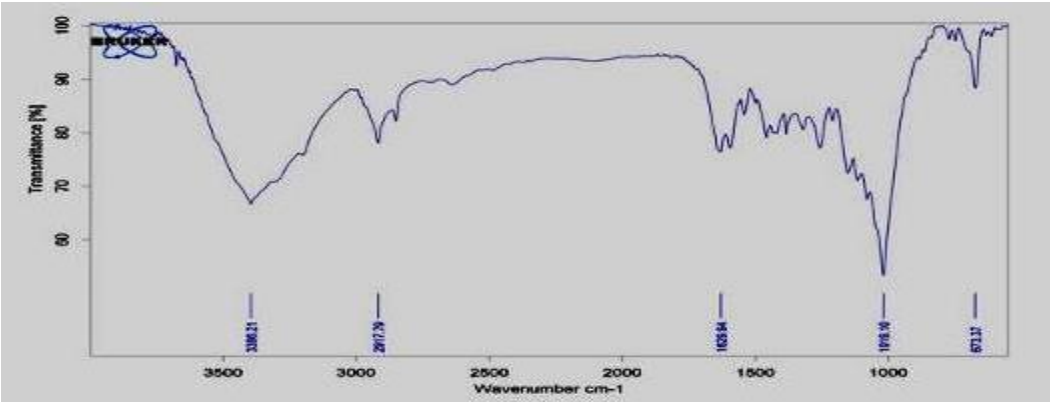

Figure 7 : FT-IR spectrum of Selegiline HCl optimized formulation F18

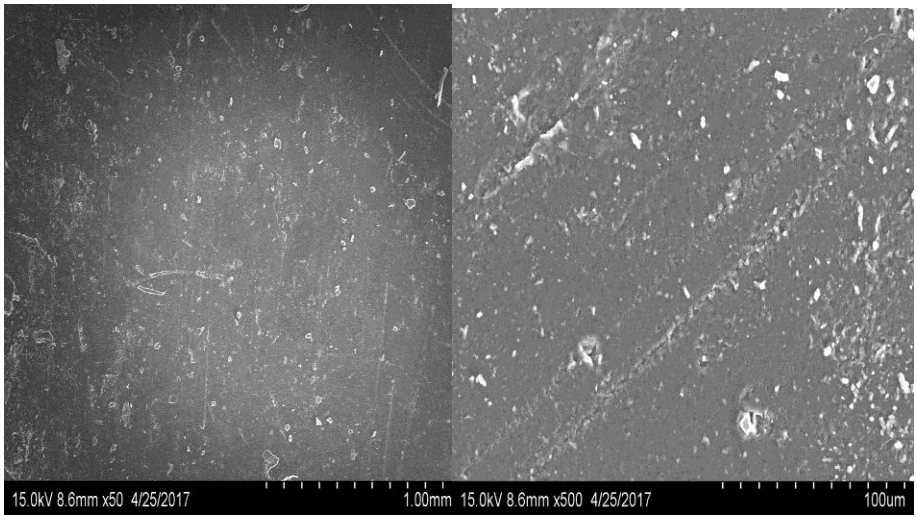

Figure 8: Scanning electron micrograph of Selegiline optimized mouth dissolving films F18

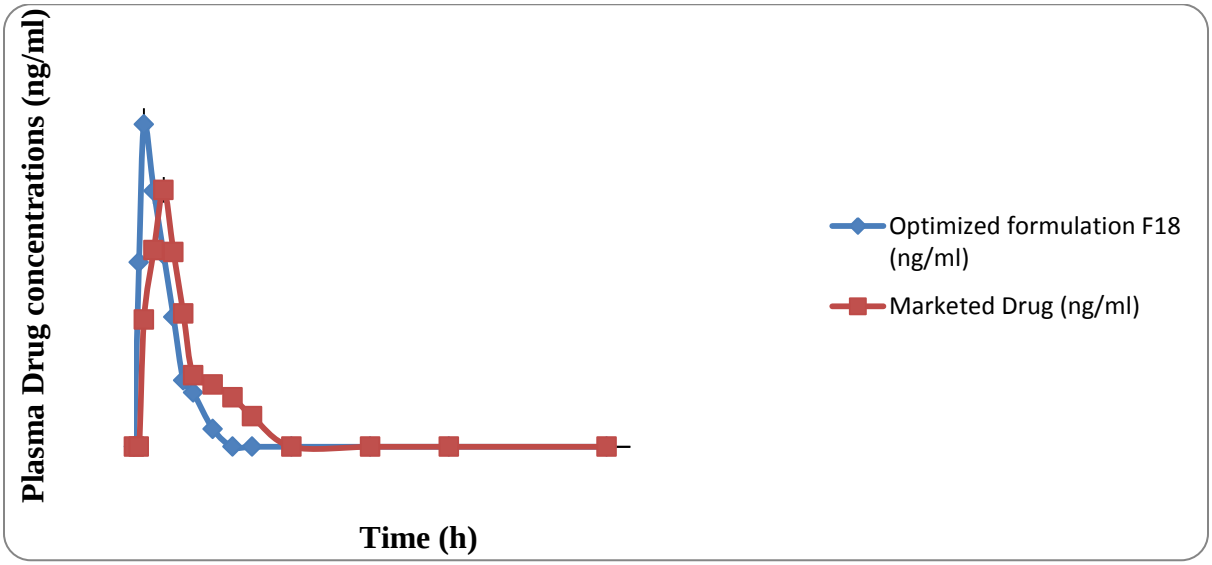

Figure 9: Plasma concentration–time curves for the Selegiline optimized formulation and pure drug suspension

CONCLUSION

Current research work is to formulate and evaluate mouth dissolving films of Selegiline. Fast dissolving films were formulated by varying proportions of polymers by solvent casting method and they were evaluated**.** The physical appearance of the film formulations was transparent in nature. The drug content of the formulations was in the values were showing content uniformity. The thickness uniformity of the film formulations generally assures its dose accuracy per strip. It was observed that as the polymer concentration increased thickness was also increased.Upon increasing addition of super disintegrating agent crospovidone it was noted that for F18 it shows better disintegration property 9 sec. In vitro drug release studies were carried out to select appropriate polymer composition for the formulation having suitable drug dissolution property for the dosage form. Maximum drug was released from the formulation F18 within 7 minutes. Based on the physico-mechanical properties and in-vitro drug release, the formulation F-18 was concluded as the Optimized formulation. A further *in vivo* study proved that the fast dissolving films of Selegiline produced a faster onset of action and improved bioavailability as compared to the conventional tablets. In the present work, it can be concluded that the fast dissolving film formulation can be an innovative and promising approach for the delivery of Selegiline for the treatment of Parkinson's disease.

REFERENCES

[1]. Kokate C K, Tagalpallewar A A, Aragade P S, Bagul U S, Bacchav R K, Nanjwade B K. Formulation Evaluation and Optimization of Asenapine Maleate Fast Mouth Dissolving Film: J. Pharm. Sci. Pharmacol. 3(2), 2015.

[2]. Buchi N, Nalluri B, Sravani K, Maheswari M,Sai Sri Anusha V, Sri Brahmin R. Development and Evaluation Of Mouth Dissolving Films of Salbutamol Sulfate: Journal Of Chemical And Pharmaceutical Research. 5(3), 2013, 53-60.

[3]. Semalty M, Semalty A, Kumar G. Formulation and Characterization of Mucoadhesive Buccal Films of Glipizide: Ind J Pharm Sci. 70(1), 2008, 43.

[4]. Vaishali YL, Kashmira BU. Formulation Development and Evaluation of Fast Dissolving Film of Telmisartan: Indian J Pharm Sci. 74(2), 2012, 122–126.

[5]. Shiva Kumar Yellanki. Design And In Vitro Evaluation of Orally Disintegrating tablets Of Selegiline Original Article: Int J Curr Pharm Res. 7(2), 2000, 37-39.

[6]. Harshal A P, Swati, Ramesh K, J Mol Pharm Org Process Res. 5(1), 2017, 138.

[7]. Mahesh A, Shastry N, Sadanandam M. Development Of Tastes Masked Fast Disintegrating Film Of Levocetirizine Dihydrochloride For Oral Use: Curr Drug Deliv. 1, 21-27.

[8]. Arun A, Chandra A, Sharma V, Pathak K. Fast Dissolving Oral Films An Innovative Drug Delivery System And Dosage Form: International Journal Of Chemtech Research. 2(1), 2010, 576–583.

[9]. Prabhu P, Dubey A, Kamath K. Formulation and Evaluation of Fast-Dissolving Films of Lisinopril: Egypt Pharmaceut J. 14, 2015, 56-64.

[10]. Nafee NA, Boraie MA, Ismail FA, Mortad LM. Design and characterization of mucoadhesive buccal patches containing cetyl pyridinium chloride: Acta Pharm. 53, 2003, 199-212.

[11]. Peh KK, Wong FC. Polymeric films as vehicle for buccal Delivery Swelling, mechanical and bioadhesive properties: J Pharm Sci. 2, 1999, 53-61.

[12]. Agarwal GP, Seth AK, Saini TR. Evaluation of free films: Ind Drugs. 23, 1985, 45-7.

[13]. Mishra R and Amin A. Design And Development Of Rapidly Dissolving Films Using Ion Exchange Resin For Taste Masking: International Journal Of Drug Formulation &Research. 2(2), 2010, 314-43.

[14]. Mishra R, Amin, A. Formulation Development of Taste-Masked Rapidly Dissolving Films of Cetirizine Hydrochloride: Pharma. Techn. 2009, 48-56.

[15]. Tanwar YS, Chauhan CS Sharma A. Development and evaluation of carvedilol transdermal patches: Acta Pharm. 57, 2007, 151-59.

[16]. Dinge A, Nagarsenker M. Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity: AAPS Pharm Sci Tech. 9(2), 2012, 349-56.

[17]. Kishore Kumar S, Maddi Venkata Nagabhushanam , K. R. S. Sambasiva Rao and D. V. R. N. Bhikshapathi, Preparation and in vivo evaluation of oral dissolving films containing sumatriptan succinate, Der Pharmacia Lettre, 5(3), 2013, 27-38

[18]. Hossein Danafar, Simple and sensitive high performance liquid chromatographic (HPLC) method for the determination of the selegiline in human plasma, cogent medicine, 3(1), 2016.