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Design and Development of Solid Dispersed Selegiline Sublingual Tablets

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ABSTRACT:Sublingual tablets of selegiline were prepared to improve its bioavailability and avoid first pass metabolism.Sublingual tablets prepared by direct compression method with usig CCS as a superdisintegrant,Additionally sublingual tablets prepare by using solid dispersion, solid dispersions of drug were prepared using solvent evaporation method. Preformulation studies were conducted, and infrared spectral analysis confirmed that there were no chemical interactions between the drug and the excipients, indicating compatibility.Tablet weight variation,hardness, friability disintegration and dissolution time evaluatea 32-factorial design was employed to assess the effects of CCS and Avicel 102 on disintegration and wetting times. Batch T9 from the factorial design emerged as the optimized formulation, exhibiting a low wetting time of 7 seconds and a disintegration time of 8 seconds. Batch T9 also released 99.9% of the drug in 6 minutes. Stability studies showed that batch T9 remained stable after one month. Therefore, batch T9 was identified as the optimized formulation..

KEYWORDS: Sublingual tablets, Selegiline.

I. INTRODUCTION

Oral mucosal drug delivery presents an alternative approach to systemic drug administration, offering distinct benefits compared to injectable and enteral methods. The oral mucosa has a rich blood supply, allowing drugs absorbed through it to enter systemic circulation directly, bypassing the gastrointestinal tract and hepatic first-pass metabolism. This mechanism can lead to a faster onset of action and provides a more comfortable and convenient option than intravenous administration. However, not all drugs are suitable for this route, as their effectiveness depends on the characteristics of the oral mucosa and the physicochemical properties of the drug. The primary regions within the oral cavity targeted for drug delivery include the buccal, sublingual, periodontal areas, tongue, and gums. Additionally, structures adjacent to the oral cavity, such as the pharynx, larynx, adenoids, and tonsils, can serve as potential drug absorption sites. Within the oral cavity, drug administration through the mucosal membranes is generally classified into three categories:

Sublingual delivery: This method facilitates systemic drug absorption through the mucosal lining on the floor of the mouth, allowing direct entry into systemic circulation.Buccal Delivery: This method involves administering drugs through the mucosal membranes inside the cheeks and the region between the gums and both upper and lower lips, allowing the drug to enter systemic circulation.

Local Delivery: This approach is used to deliver drugs directly to specific areas within the oral cavity, such as the periodontal and gingival regions. It is primarily utilized for the localized treatment of conditions like ulcers, bacterial and fungal infections, and periodontal diseases. The sublingual route of drug administration typically leads to a quicker onset of action compared to oral ingestion of tablets. When a drug is absorbed through the sublingual blood vessels, it bypasses the hepatic first-pass metabolism. The primary absorption mechanism involves passive diffusion through the lipophilic membrane. The drug absorption rate via the sublingual route is significantly higher—approximately 3 to 10 times greater—than that of oral administration, with only hypodermic injection offering a faster alternative. In these formulations, even a small amount of saliva is sufficient to facilitate tablet disintegration in the oral cavity. While sublingual absorption acts rapidly, its effects are generally short-lived.

Sublingual drug formulations are used to manage various conditions, including migraines, where a fast onset of action is crucial, as well as mental health disorders such as depression and schizophrenia, where maintaining consistent patient adherence to medication is essential for treatment effectiveness.

TECHNIQUES USED IN PREPARATION OF SUBLINGUAL TABLET1

1. Direct Compression Technology

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2. Fast Melting Technology
3. Sublimation
4. Lyophilization

II. MATERIALS AND METHODS

Materials

Selegiline was obtained from Piramal Pharma, India. Cross Carmellose Sodium, Crospovidon e and Sodium starch glycolate were obtained from Astron Chemical, Ahmedabad. Avicel Ph 101 and Soluplush was obtained from JRS Pharma. Arosil, Talc and Aspartame were obtain from Astron Chemical, Ahmedabad. All the polymers acquired were of pharmaceutical grade, and the remaining materials used were of analytical grade.

Drug Identificartion and Drug Interaction Study

The Fourier Transform Infrared (FTIR) spectroscopy (FTIR 8400 S,himadzu, Kroyoto, Japan) analysis was conducted on a moisture-free powdered drug sample and its physical mixture with excipients. The spectra were recorded using an IR spectrophotometer through the potassium bromide (KBr) pellet method. The spectral range observed was between 600 and 4000 cm^{-1}, with characteristic peaks corresponding to various functional groups being documented.

Table No.2:Trial batches

Sr. No	Ingredients (mg)	F1	F2	F3	F4	F 5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
1.	Selegiline solid dispesion(1:4)	25	25	25	25	25	25	25	25	25	25	25	25	**25**	25	25
2.	Starlac	53	48	43	38	33	53	48	43	38	33	53	48	**43**	38	33
3.	SSG	5	10	15	20	25	-	-	-	-	-	-	-	-	-	-
4.	Crospovidone	-	-	-	-	-	5	10	15	20	25	-	-	-	-	-
5.	Croscarmello se sodium	-	-	-	-	-	-	-	-	-	-	5	10	**15**	20	25
6.	Avicel PH104	14	14	14	14	14	14	14	14	14	14	14	14	**14**	14	14
7.	Apartame	2	2	2	2	2	2	2	2	2	2	2	2	**2**	2	2
8.	Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	**0.5**	0.5	0.5
9.	Talc	1	1	1	1	1	1	1	1	1	1	1	1	**1**	1	1
10.	Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	**2**	2	2
Total weight of tablet		**100mg**														

Preparation of Solid Diseprsion: Solvent Evaporation Method

The drug was first dissolved in an adequate amount of methanol as a solvent. A measured quantity of polymer was then added to this solution, followed by thorough stirring. The solvent was evaporated using a water bath, and the resulting solid dispersion was further dried in a vacuum oven. The final product was stored in an airtight container and kept in a desiccator to maintain stability. To determine the most suitable polymer for solid dispersion formulation, Soluplus was used in the preparation process.

This procedure was followed to prepare in different ratios like 1:1,1:2,1:3, 1:4 and 1:5.

TABLE 1:

Ratio	%Practicle Yiled	Drug content(%)	Solubility (µg/ml)
1:1	78.3 ± 2.8	97.2 ± 2.9	3.9 ±1.8
1:2	79.8 ± 1.9	99.4 ± 1.1	5.6 ±2.0
1:3	81.4 ± 1.5	97.4 ± 2.7	8.2 ±1.7
1:4	83.5 ± 4.2	98.3 ± 1.4	25.0 ±2.9
1:5	85.4 ± 3.8	99.7 ±0.8	25.1 ±3.1

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Preparation of Sublingual tablets Direct compression method

a. Weigh all materials as per formula given in table no. 2
b. Sift all the materials from 40 # sieve.
c. First mix solid dispersed Selegiline and Diluent
d. Add Superdisintegrant to the step (c) material and mix well.
e. Then add Aspartame, Aerosil, Talc and Magnesium Stearate in to step(d) material and mix well in polybag manually for 5 minutes.
f. Finally, the blend was subjected for compression using Rotary tablet punching machine.

Drug Excipients Compatibility Study

Fourier transform infrared spectroscopy (FTIR) used to study about physical and chemical interaction between drug and excipients was recorded on FTIR by potassium bromide (KBr)pellet method.The drug exhibited peaks due to N-H,O-H,C-O stretching.There is no significant chemical incompatibility observed between the drug and excipients.

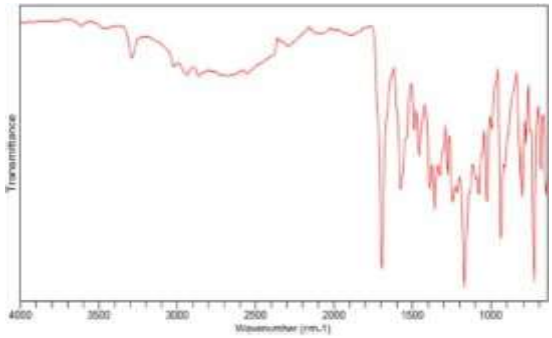

Figure 1.1: FTIR Spectra of Drug

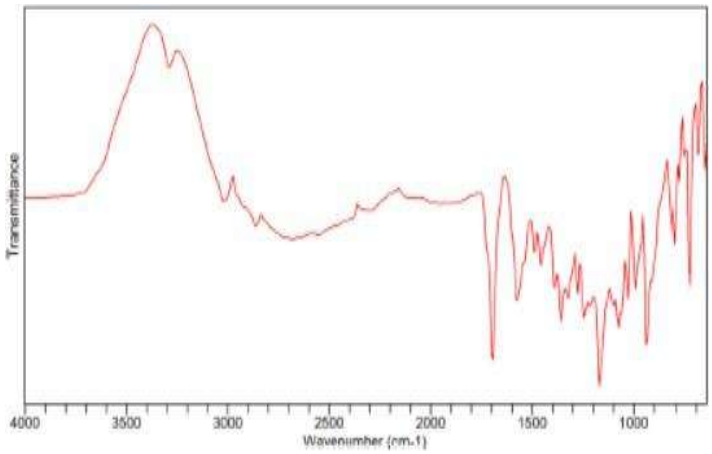

Figure 1.2: FTIR Spectra of Drug + Excipients

Differential Scanning Calorimetry (DSC):

n the DSC thermogram, selegiline typically exhibits a sharp endothermic peak (142°C) corresponding to its melting point. This peak represents the transition from solid to liquid and is indicative of the purity of the drug. A well-defined peak suggests the absence of impurities or amorphous forms that could affect the formulation's stability and release behavior. The same sharp endothermic peak was observed in the formulation. Please refer below DSC thermogram.

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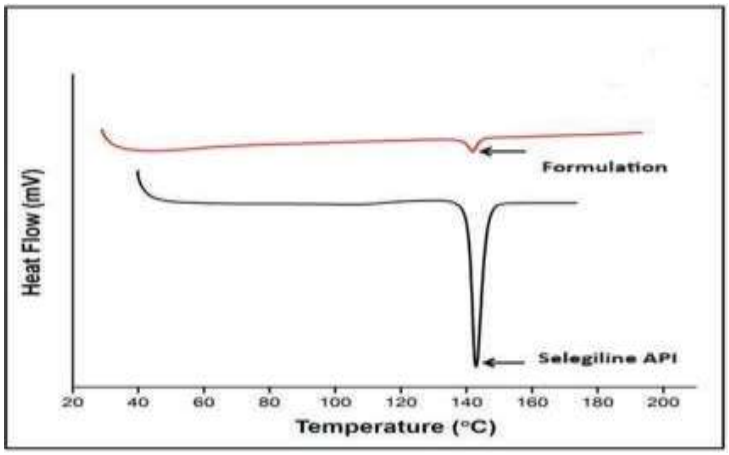

Figure 1:3 DSC of Formulation and API XRD STUDY

The XRD analysis of selegiline and formulations provides valuable information about the physical state of the drug, its crystallinity, and potential drug- excipient interactions. A shift from crystalline to amorphous forms, or the absence of distinct crystalline peaks, suggests improved solubility and dissolution characteristics, which are beneficial for formulation.

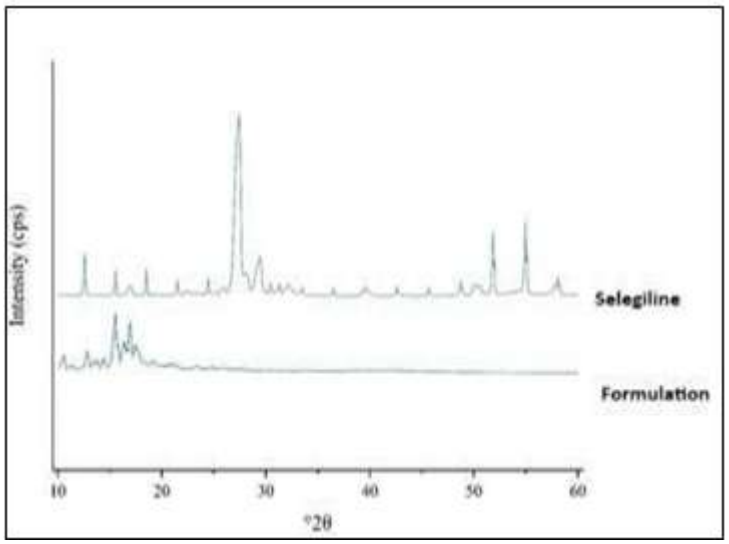

Figure 1:4 XRD of Selegiline and Formulaion

EVALUATION

Pre Compression Parameters

Pre compression of trial batches evaluated for their flow and compressibility.Flow properties of powder were determined by angle of repose and compressibility index of powder determined by Carr's index and Hauser ratio.

Table No.3: Pre Compression Parameters

Formulation	Bulk Density (gm/ml) (n=3)	Tapped Density (gm/ml) (n=3)	% Carr's index	Hausner's ratio	Angle of Repose (θ)
F1	0.56 ± 0.03	0.63 ± 0.02	11.11 ± 0.05	1.13 ± 0.05	26°56'
F2	0.42 ± 0.02	0.49 ± 0.04	12.24 ± 0.04	1.14 ± 0.04	27°72'
F3	0.45 ± 0.04	0.51 ± 0.05	15.09 ± 0.06	1.18 ± 0.07	25°60'

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F4	0.43 ± 0.05	0.53 ± 0.03	15.69 ± 0.02	1.19 ± 0.08	28°10’
F5	0.48 ± 0.02	0.56 ± 0.03	14.29 ± 0.04	1.17 ± 0.05	29°38’
F6	0.48 ± 0.03	0.55 ± 0.05	12.73 ± 0.05	1.15 ± 0.06	27°48’
F7	0.48 ± 0.05	0.54 ± 0.04	11.11 ± 0.08	1.13 ± 0.04	25°89’
F8	0.46 ± 0.04	0.50 ± 0.06	08.00 ± 0.07	1.09 ± 0.08	26°32’
F9	0.43 ± 0.06	0.49 ± 0.04	12.24 ± 0.05	1.14 ± 0.02	30°12’
F10	0.46 ± 0.05	0.52 ± 0.04	17.31 ± 0.04	1.21 ± 0.06	24°75’
F11	0.42 ± 0.05	0.53 ± 0.03	20.75 ± 0.02	1.26 ± 0.08	22°45’
F12	0.43 ± 0.05	0.53 ± 0.03	18.87 ± 0.02	1.23 ± 0.08	21°48’
F13	**0.48 ± 0.03**	**0.55 ± 0.05**	**12.73 ± 0.05**	**1.15 ± 0.06**	**25°11’**
F14	0.48 ± 0.02	0.55 ± 0.04	12.73 ± 0.08	1.15 ± 0.04	22°69’
F15	0.43 ± 0.05	0.53 ± 0.03	18.87 ± 0.02	1.23 ± 0.08	23°28’

Post compression parameter

Post compression parameter of formulation evaluated.weightvariation,Thickness,Hardness,Friability

Weight variation test

The 10 tablets were selected randomly from every formulation and weight independently to check weight variation.

Thicknesss

Thickness of the formulation was measured by vernier calliper.

Harness test

Three tablets were randomly picked from each formulation and hardness of the tablets was determined using Monsanto Hardness tester.

Friability test

6,5 gram weight equivalents tablets were initially weighed and transferred into friabilator and friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again and percentage friability was calculated.

Drug content

Five tablets were randomly selected, accurately weighed and average weight per tablet calculated. The tablets were ground individually to fine powder. Accurately weighed tablet powder transferred to 100 ml volumetric flask. Add 6.8 phosphate buffer up to the spot. After few minutes the solution was filtered; rejecting first few ml of the filtrate analysed spectrophotometrically at 282 nm.

Wetting time

The tablet was placed at the centre of 2 layers of absorbent paper fitted into a Petri dish. After the paper was thoroughly wetted with distilled water, excess water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch.

Table No.4:Post Compression Parameter

Formulation Code	Weight Variation (mg) (n=3)	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	Friability %
F1	100.6±2.36	3.07±0.02	3.40±0.36	0.50
F2	100.4±2.36	3.04±0.03	3.76±0.32	0.40
F3	100.5±2.05	3.04±0.02	3.86±0.25	0.35
F4	100.2±2.78	3.20±0.06	3.67±0.14	0.50
F5	100.0±2.72	3.06±0.08	3.96±0.12	0.60
F6	100.3±2.46	3.06±0.03	3.84±0.20	0.20
F7	100.7±2.30	3.04±0.03	3.77±0.35	0.40
F8	100.2±2.10	3.07±0.01	3.54±0.30	0.55
F9	100.8±2.01	3.02±0.05	3.88±0.22	0.45
F10	100.1±2.56	3.43±0.03	3.53±0.37	0.35

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F11	100.7±2.20	3.51±0.02	3.90±0.10	0.40
F12	100.1±2.31	3.52±0.03	3.79±0.43	0.30
F13	100.6±2.42	3.45±0.02	3.39±0.29	0.40
F14	100.0±2.52	3.46±0.02	3.46±0.31	0.30
F15	100.4±2.32	3.43±0.01	3.81±0.25	0.40

In vitro disintegration time

In- vitro Disintegration times for sublingual tablets were determined using USP tablet disintegration apparatus with phosphate buffer of pH 6.8 as medium. The volume of medium was 900 ml and temp was 37±2°C. The time in seconds taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus measured.

In vitro dispersion time

In- vitro dispersion time was measured by dropping a tablet in a 10 ml petridish containing 6 ml of buffer solution simulating saliva fluid (pH 6.8).

In vitro dissolution studies

Dissolution study was conducted for all the formulations using USP dissolution rate test apparatus type-II. A total volume of 300 ml of 6.8 phosphate buffer was taken in dissolution apparatus, which was maintain at 37°C ± 0.5°C at 100 rpm. Ten milliliters of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. Samples were collected at 2 min intervals and filtered by whatman filter paper. Samples were analyzed spectrophotometrically at 282 nm.

In vitro permeation study

The buccal mucosa is very similar to the sublingual mucosa, so in this study, goat buccal mucosa was used to check the permeation of drug through the mucosa using a Franz diffusion cell at 37 ± 0.5°C. Fresh goat buccal mucosa was mounted between the donor and receptor compartments. The sublingual tablet was placed with the core facing the mucosa, and the compartments were clamped together. The donor compartment was filled with 1 ml of phosphate buffer (pH 6.8). The receptor compartment (45 ml capacity) was filled with phosphate buffer (pH 6.8) and the hydrodynamics in the compartment was maintained by stirring with a magnetic bead at uniform slow speed. Five-milliliter samples were withdrawn at pre-determined time intervals (2 min) and analyzed for drug content using an ultraviolet (UV) spectrophotometer at 28

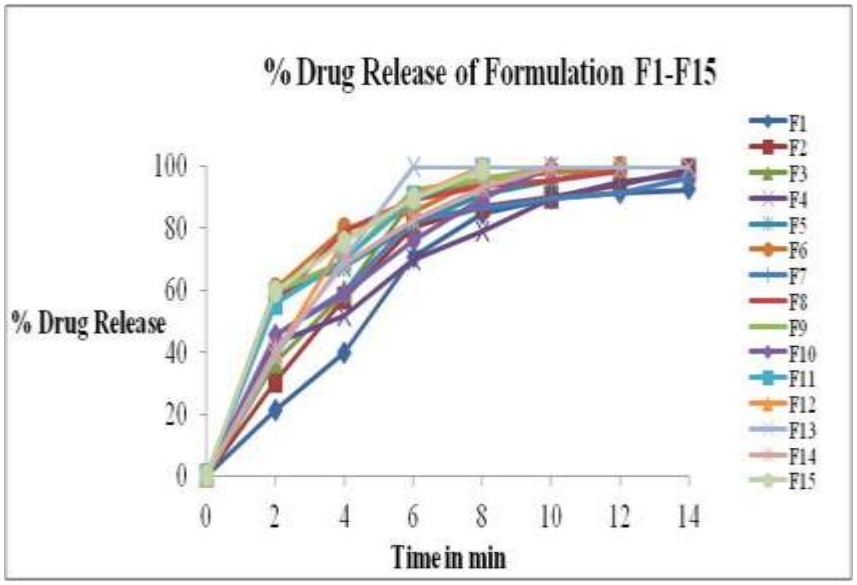

Figure No 1.5:Drug Release

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Table No:5 Post compression parameters

Formulation code	Wetting Time (Seconds) (n=3)	In vitro Dispersion Time (Seconds) (n=3)	Invitro Disintegration time (Seconds) (n=3)	% Drug Content (n=3)
F1	420 ± 20	388 ± 15	378 ± 18	98.5 ± 0.5
F2	303 ±15	249 ± 13	311 ± 21	97.9 ± 0.2
F3	142 ± 2	109 ± 10	239 ± 17	99.7 ± 0.3
F4	86 ± 5	64 ± 6	99 ± 8	96.6 ± 0.2
F5	47 ± 2	37 ± 6	89 ± 8	97.2 ± 0.4
F6	45 ± 6	42 ± 8	80 ± 10	101. ± 0.3
F7	51 ± 10	38 ± 5	108 ± 13	99.5 ± 0.4
F8	59 ± 6	48 ± 12	52 ± 16	99.9 ± 0.6
F9	75 ± 2	59 ± 4	65 ± 8	99.5 ± 0.2
F10	17 ± 1	14 ± 2	19 ± 7	98.9 ± 0.6
F11	18 ± 2	12 ± 1	12 ± 3	93.5 ± 0.3
F12	14 ± 4	7 ± 1	13 ± 4	101.5 ± 0.5
F13	**12 ± 2**	**7 ± 2**	**9 ± 2**	**96.6 ± 0.9**
F14	12 ± 3	7 ± 1	17 ± 7	98.3 ± 0.6
F15	**8 ± 1**	**10 ± 3**	**19 ± 4**	**97.7 ± 0.5**

Table No.5:% Drug Release

% Drug Release in mins							
Formulation code	2	4	6	8	10	12	14
F1	21.3±0.26	39.8±0.10	70.6±0.32	84.5±0.11	89.4±0.25	91.5±0.10	92.4±0.30
F2	30.4±0.30	57.7±0.15	80.4±0.05	86.6±0.30	90.2±0.15	94.3±0.23	98.4±0.15
F3	36.5±0.20	59.6±0.30	89.4±0.15	95.6±0.15	97.5±0.30	99.4±0.20	-
F4	42.3±0.40	51.7±0.10	69.6±0.26	79.3±0.20	89.5±0.20	94.4±0.32	97.4±0.20
F5	58.6±0.26	67.4±0.11	81.4±0.15	90.6±0.20	95.4±0.40	99.5±0.28	-
F6	60.5±0.10	79.7±0.20	85.5±0.15	96.5±0.20	98.4±0.20	99.5±0.20	-
F7	45.3±0.32	59.8±0.10	82.5±0.10	86.3±0.15	89.5±0.32	91.4±0.21	96.5±0.26
F8	55.8±0.10	78.8±0.26	89.5±0.28	93.4±0.11	95.5±0.20	98.3±0.10	-
F9	59.4±0.25	69.6±0.20	92.5±0.05	95.6±0.20	99.6±0.26	-	-
F10	45.6±0.23	57.8±0.98	75.5±0.32	89.5±0.20	99.5±0.20	-	-
F11	55.7±0.15	69.6±0.20	89.6±0.25	98.5±0.25	-	-	-
F12	39.3±0.32	75.8±0.10	90.4±0.20	99.5±0.15	-	-	-
F13	**38.5±0.10**	**70.5±0.15**	**99.6±0.15**	-	-	-	-
F14	40.8±0.20	68.7±0.15	82.5±0.20	93.4±0.25	99.6±0.11	-	-
F15	59.7±0.15	75.6±0.23	89.7±0.20	98.6±0.15	-	-	-

The data obtained in the in vitro release for formulations prepared by direct compression technique are tabulated in the table no.5. The plot of % CPR of drug shown in Figure no. 1.5.

All the formulations showed rapid % drug release. But the rapid drug dissolution was noticed in F10 to F15 formulations compared to other formulations which release more than 95 % drug in 6-8 min because of croscarmellose sodium used as disintegrates in F11-F15 formulation. Because of fast disintegration and so rapid absorption gives high drug release.

Formulation F13 shows extreme faster dissolution than other formulation. It releases 99.6 % of Drug in 6 min.

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From the above data it concluded that croscarmellose sodium as disintegrating agent in formulation help to drug release faster than the other agent used in formulation.length of the air gap.

Table No.6 In vitro Permeability

% Drug Permeability in min							
Formulation code	**2**	**4**	**6**	**8**	**10**	**12**	**14**
F1	25.5±0.15	49.4±0.25	72.5±0.26	81.6±0.30	88.5±0.25	92.4±0.20	93.6±0.25
F2	32.2±0.25	56.6±0.30	82.5±0.32	89.3±0.15	92.4±0.28	94.4±0.30	99.5±0.20
F3	39.4±0.20	60.6±0.26	90.6±0.26	94.4±0.25	96.4±0.26	99.5±0.32	-
F4	49.3±0.15	52.6±0.26	70.5±0.30	82.6±0.26	92.4±0.32	93.5±0.30	98.4±0.26
F5	54.7±0.26	69.3±0.15	82.4±0.15	92.5±0.30	94.5±0.35	99.5±0.25	-
F6	61.5±0.17	80.6±0.25	86.3±0.25	97.3±0.25	98.3±0.20	99.5±0.30	-
F7	49.4±0.20	60.6±0.32	81.3±0.17	87.5±0.20	90.4±0.25	92.6±0.26	97.4±0.32
F8	54.5±0.32	80.4±0.41	90.4±0.20	92.7±0.26	94.4±0.35	99.3±0.15	-
F9	60.5±0.20	70.5±0.15	93.6±0.32	96.4±0.25	99.5±0.36	-	-
F10	49.5±0.26	59.5±0.20	78.7±0.28	90.5±0.25	99.6±0.30	-	-
F11	55.8±0.15	71.6±0.30	90.3±0.15	99.4±0.35	-	-	-
F12	41.5±0.25	78.4±0.11	91.4±0.37	99.4±0.30	-	-	-
F13	**42.3±0.30**	**71.5±0.25**	**99.5±0.30**	-	-	-	-
F14	41.5±0.49	72.6±0.26	86.5±0.32	92.4±0.26	99.4±0.43	-	-
F15	62.4±0.11	78.3±0.35	92.6±0.30	99.3±0.20	-	-	-

In vitro Permeability Study

The data obtained in the in vitro permeability study release for formulations prepared by direct compression technique are tabulated in the table no.

7. The plot of % permeability of drug shown in Figure no. 1.6.

All the formulations showed good permeability as drug release. But the rapid drug permeability was noticed in F10 to F15 formulations compared to other formulations which release more than 95 % drug in 6-8 min because of croscarmellose sodium used as disintegrates in F11-F15 formulation. Because of fast disintegration and so rapid absorption gives high drug release.

Formulation F13 shows extreme faster permeability than other formulation. It releases99.6 % of drug in 6 min.

From the above data it concluded that croscarmellose sodium as disintegrating agent in formulation help to drug permeable faster than the other agent used in formulation.

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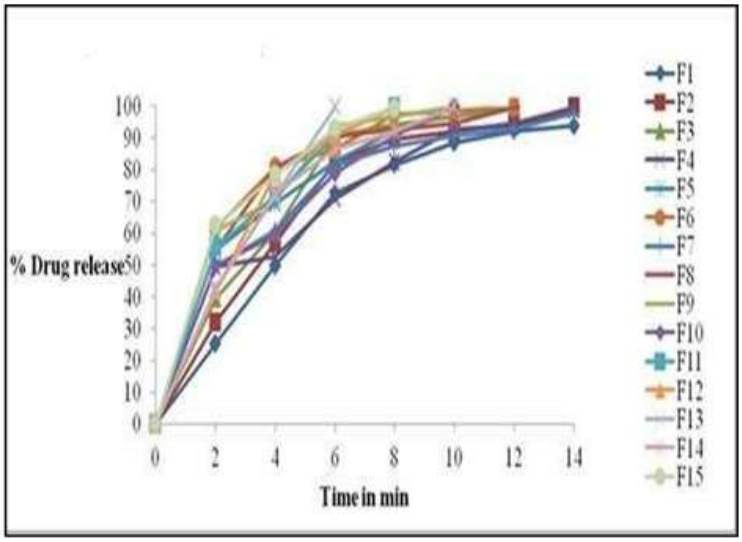

Figure No.1.6: In vitro Permeability Study

EXPERIMENTAL DESIGN

It is alluring to extend a palatable pharmaceutical detailing in straight plausible time utilizing littlest sum approach. The technique is tedious in nature and requires figure of worker hours and crude materials. Customarily pharmaceutical definitions are produced by transforming one variable at any given moment a considerable measure of creative endeavors. Additionally, it might be hard to build up a perfect definition utilizing this traditional system since the impacts of free factors are not considered. It is hence exceptionally fundamental to comprehend tmany- sided quality of pharmaceutical details by utilizing built up factual instruments, for example, factorial plan. Notwithstanding the specialty of definition, the system of factorial plan is a viable strategy for showing the relative criticalness of various factors and their connections.

The quantity of examinations required for these investigations is subject to the quantity of autonomous factors chose. The reaction (Yi) is estimated for every trial

$$Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X12 + b22X22$$

Where Y is the needy variable, b0 is the number- crunching mean reaction of the nine runs and bi is the assessed coefficient for the factor Xi. The fundamental impacts (X1 and X2) speak to the normal aftereffect of transforming one factor at any given moment from its low to high esteem. The communication terms (X1X2) demonstrate how the reaction changes when two components are at the same time changed.

All 9 batches were evaluated for the Disintegrating time and Wetting time to find out effect of the both parameters (X1, X2) on the tablets.

Independent variables

X1-Amount of CCS

X2-Amount of Avicel pH 102 Dependent variables

Y1- % Drug Release at 6 min Y2- Disintegration time

Table No. 7 3^2 Full Factorial Designs

Batch No.	X1 Amount of CCS	X2 Amount of Avicel pH 102
T1	-1	-1
T2	-1	0
T3	-1	1
T4	0	-1
T5	0	0
T6	0	1
T7	+1	-1

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T8	+1	0
T9	+1	1

Translation of coded level in actual limit			
Independent variables	**Real Value**		
	Low(-1)	**Medium(0)**	**High(+1)**
Amount of CCS(X_1) mg	10	12	14
Amount of Avicel pH102(X_2) mg	12	14	16

Layout of 3^2 Full Factorial Designs Table

TableNo.8: 3^2 Full Factorial Design

Batch code	**Independent variable**		**Dependent Variables**	
	X1	**X2**	**Y1**	**Y2**
T1	-1	-1	88.5	45
T2	-1	0	92.8	30
T3	-1	1	90.4	34
T4	0	-1	86.0	32
T5	0	0	95.6	22
T6	0	1	96.7	17
T7	+1	-1	90.9	19
T8	+1	0	97.8	16
T9	**+1**	**1**	**99.9**	**8**

Translation of coded level in actual unit			
Independent variables	**Real Value**		
	Low(-1)	**Medium (0)**	**High(+1)**
Amount of CCS (X1) mg	10	12	14
Amount of Avicel pH 102 (X2) mg	12	14	16

Evaluation of Factorial Batches

Table No.9 Evaluation of factorial Batches

Formulation	**Weight Variati on (mg) (n=3)**	**Thicknes s (mm) (n=3)**	**Hardness (kg/cm^2) (n=3)**	**Friability %**
T1	100.2±2.2	3.10±0.06	3.67±0.11	0.30
T2	100.0±2.1	3.06±0.08	3.96±0.11	0.30
T3	100.3±2.3	3.16±0.03	3.84±0.17	0.60
T4	100.7±2.0	3.04±0.03	3.77±0.20	0.35

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T5	100.2±2.4	3.17±0.01	3.54±0.31	0.50
T6	100.8±2.3	3.02±0.05	3.88±0.23	0.20
T7	100.1±2.1	3.23±0.03	3.53±0.34	0.30
T8	100.7±2.4	3.21±0.02	3.90±0.12	0.40
T9	**100.1±2.3**	**3.12±0.03**	**3.79±0.25**	**0.30**

- Factorial batches T1-T9 pass the weight variation test. No any major deviation found.
- Also thickness found within a range of 3.0 to 3.3 mm.
- Hardness of T1-T9 was found good and between the range of 3.4 to 3.9 g/cm^2.
- Because of good hardness, friability found below 1 %.

Table No.10: Evaluation of Factorial Batches

Formulation	Wetting Time (Second) (n=3)	In vitro Disintegration time (Seconds) (n=3)	Drug Content (%) Nebivolol HCl (n=3)	Q6 min % release of Nebivolol HCl (n=3)
T1	19 ± 2	45 ± 3	99.1± 0.5	88.5 ± 0.3
T2	26 ± 4	30 ± 5	98.7 ± 0.6	92.8 ± 0.9
T3	21 ± 3	34 ± 2	98.9 ± 0.4	90.4 ± 0.3
T4	34 ± 6	32 ± 5	99.8 ± 0.6	86.0 ± 0.5
T5	17 ± 2	22 ± 9	99.5 ± 0.7	95.6 ± 0.7
T6	29 ± 4	17 ± 6	99.4 ± 0.8	96.7 ± 0.6
T7	19 ± 3	19 ± 5	97.9 ± 0.4	90.9 ± 0.7
T8	22 ± 1	16 ± 3	99.8 ± 0.3	97.8 ± 0.8
T9	**7 ± 4**	**8 ± 4**	**99.4 ± 0.5**	**99.9 ± 0.3**

- Wetting time checked for factorial batches T1-T9 and found that T9 batch have lowest time 7 sec for wetting.
- In vitro disintegartion time observed below 45 sec for all batches. T9 batch have 8 sec time for disintegration.
- % Drug content of drug found within acceptable range.
- % Drug release in 6 min of T1-T6 results shows that the T9 batch which contains 14 mg of CCS and 16 mg of Avicel gives 99 % drug release among all batchs.

Analysis of Factorial Batches

The statistical analysis of the design batches was performed by multiple linear regression

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analysis using Design Expert 11.0®.The coefficients showing p value >0.05 were removed from the regression to generate reduced model.The refined model may be used for calculations of residuals or for drawing contor plots using design expert.The summary of results of regression analysis of full and refined model(p<0.05) for % Drug release at 6 min and disintegration time are shown in Table No.10.

The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, i.e. positive or negative. Those coefficients were found to be insignificant at p >0.05, their values were omitted from the full model to generate the reduced model. The high values of correlation coefficient for % Drug release @ 6 min and disintegration time (DT) indicates a good fit.

Factorial Equation for % Drug release @ 6 min:
$Y1 = 94.98.98 + 2.8166X1 + 3.6X2 + 1.775X12 + 0.6166X1^2 – 3.3333X2^2$

Factorial Equation for Disintegration Time: $Y2 = 21.5556 – 11X1 – 6.16X2 - 0.14X12 + 1.6667X1^2 – 3.1667X2^2$

Table No.11: Results of Regression Analysis for design batches

Response 1: % Drug Release @ 6 min:

Source	Sum of Squares	df	Mean Square	F-value	p- valu e	
Model	160.95	5	32.19	9.35	0.0476	**significant**
A-Amount of CCS	47.60	1	47.60	13.83	0.0338	
B-Amount of Avicel pH 101	77.76	1	77.76	22.59	0.0177	
AB	12.60	1	12.60	3.66	0.1516	
A^2	0.7606	1	0.7606	0.2209	0.6704	
B^2	22.22	1	22.22	6.45	0.0846	
Residual	10.33	3	3.44			
Cor Total	171.28	8				

Results of Regression Analysis for design batches
Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 9.35 implies the model is significant. There is only a 4.76% chance that an F-value this large could occur due to noise.

Table No.12: Results of ANOVA Response 2: Disintegration Time

Source	Sum of Squares	df	Mean Square	F-value	p-valu e	
Model	979.78	5	195.96	10.93	0.0384	***significant***
A-Amountof CCS	726.00	1 1	726.00	40.50	0.0079	
B-Amountof AvicelpH101	228.17		228.17	12.73	0.0376	
AB	0.0000	1	0.0000	0.0000	1.0000	

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A^2	5.56	1	5.56	0.3099	0.6166	
B^2	20.06	1	20.06	1.12	0.3678	
Residual	53.78	3	17.93			
Cor Total	1033.56	8				

P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model **Results of ANOVA** Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 10.93 implies the model is significant. There is only a 3.84% chance that an F- value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model

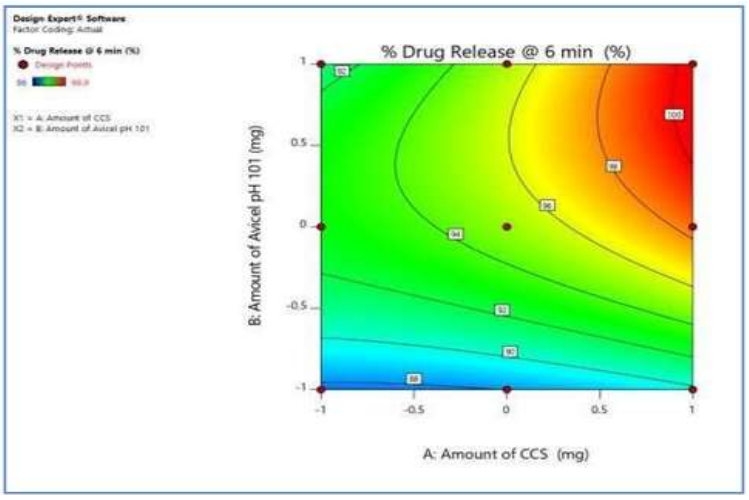

Figure No. 1.7: Surface Plot for % Drug release

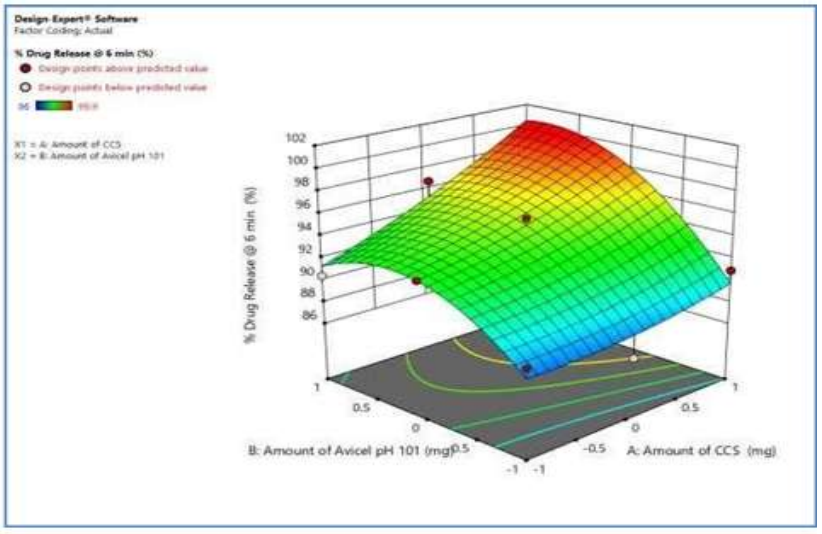

Figure No. 1.8: Response Plot for % Drug release

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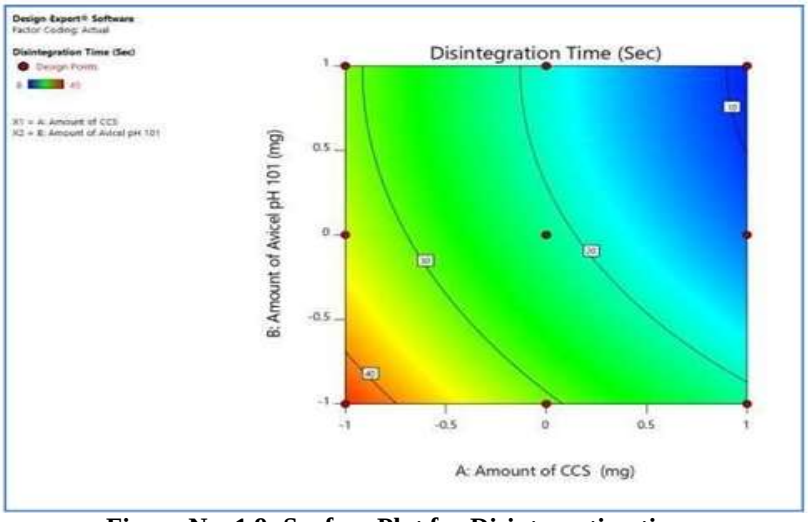

Figure No. 1.9: Surface Plot for Disintegration time

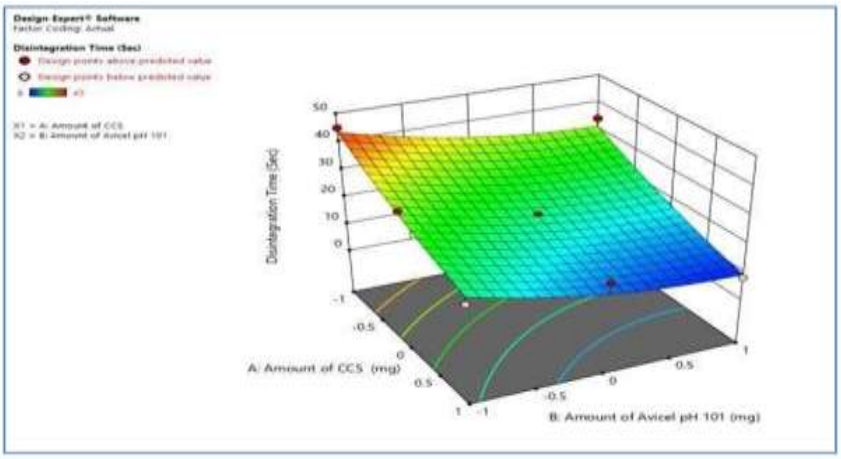

Figure No. 1.10: Response Plot for Disintegration time

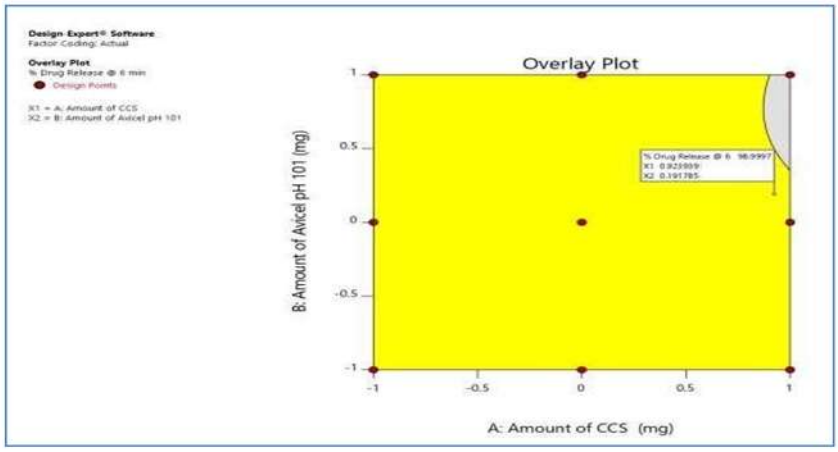

Figure No. 1.11: Overlay Plot

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STABILITY STUDY

Results of stability study of optimized formulation T9 shows that the formulations having no significant change in % drug content. Further it was observed that the disintegrating time of the formulations was not affected. There is no more different observed in wetting time.

Table No. 13 Results of stability study of batch T9

Batch	Time Perio d	% Drug release at 6 min (n=3)	% Drug Content (n=3)	Disintegration time (sec) (n=3)	Wetting time (sec) (n=3)
T9	Initial	99.4 ± 0.8	99.6 ± 0.3	8 ± 2	7 ± 3
	After 10 days	99.2 ± 0.6	98.4 ± 0.5	8 ± 1	10 ± 1
	After 20 days	98.8 ± 0.5	98.5 ± 0.8	9 ± 1	12 ± 4
	After 35 days	99.1 ± 0.7	98.2 ± 0.6	9 ± 2	11 ± 2

III. CONCLUSION

Sublingual tablets of selegiline were successfully formulated using the direct compression method. Preformulation studies were conducted, and infrared spectral analysis confirmed that there were no chemical interactions between the drug and the excipients, indicating compatibility. Evaluation parameters such as hardness and friability demonstrated that the tablets had good mechanical strength across all formulations. The percentage of weight variation and drug content uniformity were within the approved limits for all formulations. In vitro release studies showed more than 90% of the drug was released within 6 minutes, and in vitro permeability studies revealed 90% drug release in under 10 minutes. Among all the formulations prepared by direct compression, F13, which contained 15 mg of CCS as a superdisintegrant, was found to be the best, as it released 99% of the drug in just 6 minutes. Additionally, a 32-factorial design was employed to assess the effects of CCS and Avicel 102 on disintegration and wetting times. Batch T9 from the factorial design emerged as the optimized formulation, exhibiting a low wetting time of 7 seconds and a disintegration time of 8 seconds. Batch T9 also released 99.9% of the drug in 6 minutes. Stability studies showed that batch T9 remained stable after one month. Therefore, batch T9 was identified as the optimized formulation.

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