INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Research Article

Formulation And Evaluation of Novel Drug Delivery System Containing Anti Parkinson's Agent

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ARTICLE INFO

Published: 12 Dec. 2024
Keywords:
Levodopa, Mucoadhesive buccal tablet, Mucoadhesive strength, Drug release kinetics, Bioavailability, Experimental design, Parkinson.
DOI:
10.5281/zenodo.14406680

ABSTRACT

Introduction : This study explores the use of buccal administration as a potential route for delivering Levodopa (LD) in the treatment of Parkinson's disease (PD). Parkinson's disease is a neurodegenerative disease that affects dopaminergic neurons, leading to a deficiency of dopamine. The current treatment of choice is levodopa, but it has low oral bioavailability and poor brain uptake. The methodology involves the formulation of buccal mucoadhesive tablets that attach to the buccal mucosa. The study highlights the advantages of the formulation by increasing bioavailability and bypassing of gastrointestinal metabolism. The highly vascularized buccal mucosa allows for direct access to the bloodstream, resulting in high plasma drug concentration and rapid onset of action. The findings suggest that buccal tablet of levodopa will help to relieve Parkinson's disease symptoms. Aim and Objectives : Formulation and evaluation of novel drug delivery system containing anti-parkinson's agent. To prepare a formulation that will increase the bioavailability of the drug and bypass the first-pass metabolism of the levodopa. Experimental Work : In the present work, a buccal tablet of levodopa was prepared by direct compression method. Different excipients were used to obtain the suitable buccal tablet that passes the criteria for mucoadhesion, swelling and dissolution were used to formulate the buccal tablet. The tablet was evaluated for pre compression parameters for powder blend and post-compression parameters like Hardness, Friability, Mucoadhesive strength, Residence Time, In-vitro dissolution study, and Ex-vivo permeation study. Results : This research has implications for improved bioavailability of drugs and bypasses the gastrointestinal tract. Thus, the prepared Buccal tablets have promising applications for the treatment of Parkinson's Disease. ThePrepared formulation effective for the treatment and the perioperative management of Parkinson's disease patients.

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

INTRODUCTION

Parkinson's disease is pathologically defined by dopaminergic neuron degeneration in the substantia nigra of the midbrain, which leads to pathophysiologic abnormalities in the neural networks of the downstream basal ganglia. A frequent neurological condition affecting a large number of people, especially those over 60, is Parkinson's disease. Bradykinesia, or slowness of movement, together with one or more additional motor characteristics like rigidity or rest tremor, are characteristics of the condition. In addition, non-motor symptoms are common in Parkinson's disease patients. Parkinson's disease was the first neurodegenerative disease to have highly effective treatments available. In Parkinson's disease, 70-80% of dopamine-producing cells degrade or disappear over time. The loss of dopamine-producing neurons causes low levels of dopamine in the brain, which regulates movement and balance. As a result of neurons being unable to transmit information effectively, regular movements become uncontrollable, and Parkinson's symptoms emerge. The loss of dopaminergic cells in the brain results in motor defects, with about 60-70% of neuronal cell loss occurring at the time of diagnosis.

Mucoadhesive drug delivery is regarded as a novel approach to oral administration, especially for drugs that undergo hepatic first-pass metabolism.Delivery of these medications via the buccal route may overcome issues related to the oral route, such as the substantial hepatic first pass effect and drug breakdown in the gastrointestinal tract (GIT)[1]. Many advantages come with this buccal delivery method, including convenience of administration, direct entry into the systemic circulation following absorption, avoidance of the hepatic first-pass impact, no enzymatic degradation, and the ability to terminate the delivery whenever necessary[2].Various mucoadhesive dosage forms, such as tablets[3], films[4], ointments[5], gels[6], patches[7], disks[8], and strips[9], have been developed through numerous tries. Systems for delivering drugs buccally that have an excellent mucoadhesive would be desirable. To have the intended therapeutic effect, the medicine should also be released in a controlled and predictable manner[10]. The dosage form and buccal mucosa must establish a strong mucoadhesive contact in order to accomplish this. Therefore, choosing an adhesive polymer system is the first step in the creation of buccal drug delivery systems. Numerous bioadhesive polymers have been evaluated for use in the development of buccal delivery systems, either individually or in combination.

The Hydroxypropyl Methylcellulose (HPMC) is the most hydrophilic and bioadhesive polymer due to its higher hydration and swellability. The overall performance depends upon the design of the system. The difference in the chain length and substitutions in the different HPMC grades imparts the different degrees of mucoadhesivity and release properties.Combining several HPMC grades can be advantageous since they function as a mucoadhesive system and expand in water to create a transparent to opalescent, viscous, colloidal dispersion. In order to determine the impact of the various HPMC grades on mucoadhesion characteristics and the rate of drug release from the formulations, different proportional combinations of HPMC have been explored in this study.

Levodopa (LD) belongs to the non selective dopamine receptor agonist category. Levodopa is a dopamine replacement agent that is most commonly used to treat Parkinson's disease. It can cause nausea and vomiting[11]. It is available in different oral dosage forms in the market like tablets, capsules. Such oral formulations are convenient to use but produce fluctuating drug

blood levels resulting in non-reliable and inconsistent response. Also, it has been reported that, upon oral administration it gets rapidly absorbed, but subjected to the first pass effect. This leads to poor systemic bioavailability of (30%) due to extensive pre systemic hepatic metabolism[12, 13]. This oral bioavailability sometimes gets worsened for the patients who are vomiting or suffering from impaired gastric emptying. Thus, the therapeutic success of levodopa has been limited by its invariable, incomplete absorption and presystemic metabolism. All these reasons make levodopa a suitable drug candidate for buccal delivery. Thus, a mucoadhesive buccal tablet with the use of adhesive polymers seems to be an appropriate dosage form for the delivery of levodopa with improved mucoadhesion, residence time and absorption.

Full factorial design is a widely practiced statistical optimization tool in the development and optimization of drug delivery systems[14]. The statistical optimization involves the use of various types of experimental designs, creation of polynomial equations, and measuring of the response over the experimental domains to determine the optimum formulation. The procedure is less time-consuming and experimental than the traditional approaches for creating dosage forms, making it more practical and economical.

Thus, the overall selection of suitable polymeric combinations and optimization of their concentrations remain an important goal and challenge for formulation development of buccal dosage form from adhesion and controlled drug release point of view.

Hence, the present research work attempted to develop buccal mucoadhesive tablet as a potential, cost-effective and patient-compliant delivery system for levodopa using the 3^2 full factorial design as the statistical optimization tool[15, 16].

MATERIALS AND METHODS

Materials :

Levodopa was purchased from Molychem pvt. Ltd, Mumbai. All other excipients were received as a gift sample from various companies like Hydroxypropyl Methylcellulose (HPMC K 15M and HPMC K 100M) from Colorcon Asia Pvt Ltd, Mumbai. Microcrystalline cellulose (MCC), Magnesium Stearate from Alpha Chemicals Pvt Ltd, Mumbai. Aerosil 200 from Evonik India pvt Ltd, Mumbai.

Methods :

Preformulation Study :

In this study, preliminary batches were prepared with an aim to find the best suitable combination of different grades of HPMC. These studies help in the selection of appropriate excipients for the formulation of a stable and effective dosage form. Prepared various batches with different combinations of excipients and evaluated the results.

Melting Point :

The capillary tube method was used to evaluate the melting point of levodopa to ensure the compound's purity. The capillary tube was filled with a small quantity of drugs, connected to the thermometer, and then partially submerged in Thiele's tube filled with liquid paraffin. The capillary's compound melted when Thiele's tube was heated. the temperature at which the drug totally melted[16].

Solubility Study :

According to the I.P.2018, a solubility study was conducted. In this case, the maximum solvent volume needed to dissolve the solute was found. The solubility of the drug was checked in various solvent like water, ethanol, methanol, simulated salivary fluid (SSF), and phosphate buffer pH 6.8[16].

UV Spectroscopy :

Standard stock solution (100 µg/mL) was prepared by dissolving 10 mg of levodopa in 100 ml

phosphate buffer pH 6.8 and SSF pH 6.8. The solution was then scanned in the range of 200–400 nm using a Shimadzu UV visible spectrophotometer with 10 mm quartz cuvettes used for determination of wavelength of maximum absorption (λ_{max}). Dilutions of 20–100 µg/mL were obtained from the stock solution. The absorbance of each standard dilution was determined at wavelength of maximum absorption (λ_{max}) spectrophotometrically. The calibration curve was plotted using absorbance and concentration data[17].

Drug-Excipients Compatibility Studies :

Compatibility study was carried out for pure levodopa, individual polymers, physical mixture and optimized formulation to check any possible drug– polymer interaction.

FTIR spectrum was obtained by appropriately diluting levodopa with polymers used in the formulation (Levodopa : HPMC K15M), (Levodopa : HPMC K 100M). The FTIR spectrum of the Levodopa was compared with that of the physical mixture and optimized formulation.

DSC analysis was also utilized to check the stability of Levodopa in the presence of polymers used in the formulation (Levodopa : HPMC K15M), (Levodopa : HPMC K 100M). DSC spectra were obtained using Mettler-Toledo DSC-1 Star^e over a temperature range of 37 - 350^{o}C. The obtained DSC spectrum of the Levodopa was compared with that of physical mixture and statistically optimized formulation to check any possible physicochemical drug–polymer interaction[17, 18].

Method of Preparation Of Levodopa Buccal Mucoadhesive Tablets :

Buccal tablets containing Levodopa were prepared by using a direct compression method. All the ingredients were screened through a 0.150 mm sieve (No.60) before mixing to ensure uniform particle size distribution. Required amount of drug, polymer and MCC were blended in a sealable polythene bag for 20 min. Magnesium stearate (1%) and AerosilVR 200 (1%) was added as the lubricant and glidant, respectively, to the powder mixture and blended for an additional 2 min. Compression of the buccal tablets were processed using a ten station Rimek Minipress 1 Multistage tablet punching machine equipped with a 9 mm round flat punch set. Thickness of tablets was around 3 mm and each tablet was kept constant at 150 mg total weight[19].

Optimization of Buccoadhesive Tablet by Using 3^2 Factorial Design :

Statistical optimization technique i.e. Factorial design was employed to obtain an optimized formula for levodopa buccal mucoadhesive tablet. A 3^2 full factorial experimental design approach was adopted, where two factors at three levels of each (3^2) were identified as experimental design. The amounts of bioadhesive polymers HPMC K 15M (X1) and HPMC K 100M (X2) were selected as the independent variables in the study. The three levels (-1, 0, +1) of these independent variables were identified from the results obtained in the study of preliminary batches. All other variables, including formulation components and environmental conditions, were kept constant throughout the study. Key mucoadhesive properties such as bioadhesive strength, swelling index, and percentage drug release were evaluated as response variables to determine the optimal formulation. This systematic approach enhances the understanding of how polymer ratios affect tablet performance, ultimately aiming to improve therapeutic outcomes for patients[19-22] .

Evaluation of 3^2 Factorial Design Batches[23, 24]

Pre Compression Study` :

Determination of Bulk density :

A large funnel can be used to pour conserved bulk powder into a graduated measuring cylinder, and the powder's weight and volume can be measured to ascertain the apparent bulk density. The

following formula can be used to determine bulk density.

Bulk Density = Weight / Bulk Volume (Vo)

Where,

Vo = Bulk Volume

Determination of Tapped density :

By filling a graduated measuring cylinder with preserved powder through a big funnel, tapping a wooden board 100 times, and then weighing and measuring the powder, one can determine the taped density. The following formula can be used to get the tapped density.

Tapped Density = Weight / Tapped Volume (Vt)

Where,

Vt = Tapped Volume

Carr's Index :

Carr developed an indirect method of estimating powder flow using bulk densities. A powder's % compressibility provided a precise indication of its possible strength and stability as an arch or bridge. The equation below was used to calculate each formulation's Carr's index.

Carr's Index (%) = TD - BD *100 / TD

Where,

TD = Tapped density

BD = bulk density

Hausner's Ratio :

By calculating the ratio of bulk density to tapped density, Hausner's ratio can be used to determine the powder's flow characteristics. It is the tapped density divided by the bulk density. Hausner discovered that this ratio could be used to predict the parameters of powder flow because it was associated with interparticle friction. Good flow qualities are generally indicated by a value smaller than 1.25, or 20% of Carr's index.

Hausner's Ratio = Tapped Density / Bulk Density

Angle of Repose :

The largest angle that the powder plane forms with the horizontal surface while it rotates is known as the angle of repose. The angle of repose is useful for evaluating the flow characteristics of particles, which may be further connected to the mechanical configurations and packing densities of the particles. The method of using a fixed funnel and a free-standing cone helped establish the granules' angle of repose. The finely measured grains were placed in a funnel. The funnel was raised to the point where its tip was barely touching the top of the granule pile after its height was adjusted. Granules were let to freely pour onto the surfaces through the funnel. The powder cone's diameter and angle of repose were also measured and by using the following equation angle of repose is calculated.

$\tan \theta = h / r$

Where,

h = height of the powder heap

r = radius of the powder heap

θ = is the angle of repose

Post Compression Study :

The physicochemical properties of the suggested compression tablets were studied for, such as weight variation, hardness, thickness, friability, and drug content.

Weight Variation :

Weigh 20 tablets individually .Calculate average weight. Compare individual weight with average weight. The tablet meets the IP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Hardness :

The amount of force needed to shatter a tablet has been referred to as tablet hardness. It is also termed as tablets crushing strength. Devices used to test tablet hardness was Monsanto hardness tester (Kg/cm^2)

Thickness :

The thickness and diameter of individual tablets were measured using a micrometer or a standard caliper scale i.e. vernier caliper.

Friability :

A removable transparent plastic drum that rotates at 25 rpm and drops the tablets six inches with each rotation is used by Roche Friabilator to submit a lot of tablets to the combined effects of shock and abrasion. Six tablets in total were taken. The friabilator was filled with a preweighed tablet sample and ran for 100 revolutions (4 minutes). After that, the tablets are reweighed and dedusted. Friability should be less than 1%.

Friability (%) = W1 – W2/ W1 X 100

Where,

W1 = Weight of Tablets (Before friability) &

W2 = Weight of Tablets (After friability)

Uniformity of Drug Content :

Tablets were randomly taken from each prepared formula. They were crushed to obtain fine powder. Powder equivalent to 50 mg of levodopa were accurately weighed and dissolved in a 50 ml SSF pH 6.8 taken into a 100 ml volumetric flask. 1 ml of sample is removed and diluted to 10 ml with SSF pH 6.8. The solution was analyzed spectrophotometrically at 280 nm to determine the drug content[25].

Swelling Index :

The swelling index of buccal mucoadhesive tablets was evaluated by calculating the proportion of swelling. First, the buccal mucoadhesive tablet of levodopa from each formulation (denoted as M1) was weighed. Each of these tablets was put in a petri plate with a SSF pH 6.8. At predetermined intervals (0.5, 1, 2, 4, 5 hours), these tablets were taken off of the petri plates. Filter paper was used to gently remove any excess water from the surface. We reweighed these swollen tablets (denoted as M2)[25, 26]. The following equations were used to determine the swelling index:

Swelling index = M2 - M1 / M1

Where,

M1: Initial weight of tablet.

M2: Weight of tablet after 5 h.

Surface pH :

The buccal mucosa may get irritated and experience adverse effects from significant pH variations. Therefore, it's crucial to investigate surface pH in order to see this type of interaction. The tablets were kept in SSF pH 6.8 enclosed in a beaker at room temperature for approximately two hours. By maintaining a glass electrode of pH meter in contact with swollen tablets for one minute, the surface pH was measured. The experiment was repeated in triplicate[27].

Ex Vivo Mucoadhesive Strength :

Bio adhesive strength is determined by the force necessary to separate two mucosal surfaces from each other. Using a modified physical two-arm balance, the ex vivo bioadhesive force of the tablet was measured. The goat buccal mucosa was chosen as a biological model because of its similarities to the human buccal mucosa. It was utilized two hours after being collected from a neighboring slaughterhouse. Following that, the buccal tissue separated from the underlying tissues. It was cleaned with distilled water and kept at 40 degrees Celsius in a SSF with a pH of 6.8. A piece of mucosa was then cut and attached to a flat surface of an object such as a beaker. The second buccal mucosal piece was secured with an additional flat surface item, like beaker . This second item had its mucosal surface facing downward and was fastened to one of the balance's arms. Each composition's buccal mucoadhesive tablets are placed on the mucosal surface of a stationary item, such as a beaker. The second object's height was then decreased to allow for close contact between the two mucosal surfaces. The time it took for the mucosa and tablet to make intimate contact was about two to three minutes. The weight was added gradually until the tablet separated from the mucosal surface. The weight (grams) needed to separate the tablet was determined to be the mucoadhesion strength[28, 29, 30].

Ex vivo Residence Time :

The ex vivo mucoadhesion time was measured by applying the prepared tablets to the buccal mucosa. Using glue, the sliced buccal mucosa was adhered to the beaker's inner surface. Subsequently, simulated salivary fluid (SSF) at pH 6.8 was added in droplets to wet the prepared tablets. For two minutes, these tablets were kept in contact with the mucosa by applying force with the assistance of a fingertip. After this initial contact period, 25 ml of SSF at pH 6.8 and maintained at 37°C (±1) was gently added into the beaker. The duration required for the tablet to separate from the buccal mucosal membrane was then recorded and used to determine the ex vivo residence time of the formulation[30].

In vitro Drug Release/Dissolution :

In vitro drug release from levodopa mucoadhesive tablets was carried out in the 50 ml beaker placed on a magnetic stirrer. 20 ml of the dissolution medium SSF pH 6.8 was taken in the beaker and the temperature was maintained at 37 ± 0.5°C.To keep the equilibrium at the same temperature, 2 ml of the sample was taken out and filtered through Whatman filter paper at pre-planned sampling intervals of (1, 2, 3, 4, 5, 6, 7 and 8 hrs), and replaced with new aliquot. The UV spectroscopy analysis at 280 nm was used to measure the drug concentrations in the samples. Three tablets were used for the trials, and the total percent drug release was calculated[31, 32].

***Ex-vivo* Permeation Study :**

A diffusion research was conducted utilizing a Franz diffusion cell to assess drug permeability over the goat buccal mucosa. Goat buccal mucosa was sourced from a local slaughterhouse and used within 2 hours following slaughtering. After collection, the tissue was kept in an ice-cold water solution. To conduct permeation tests, surgical scissors were used to remove the epithelium from the underlying connective tissues and clamp it between the donor and receiver chambers of diffusion cells. The receptor compartment held 20 ml of phosphate buffer pH 6.8, whereas the donor compartment held 2 ml of simulated salivary fluid pH 6.8. The tablet was put on the donor compartment's mucosal surface. At a predetermined time interval of (1, 2, 3, 4, 5, 6, 7 and 8 hrs), 2 ml aliquots were withdrawn from the receptor compartment and stirred continuously using a magnetic stirrer. Each aliquot was replaced with a fresh 2 ml of medium. The absorbance was measured at 280 nm using a UV-visible spectrophotometer[31, 32].

Kinetic Data Treatment :

Mathematical models were used to fit the in vitro drug dissolution data from all optimization batches. We found the n and R values for the models of zero order, first order, Higuchi equation, Hixson–Crowell equation, and Korsmeyer–Peppas equation. The research was carried out to ascertain which model best fit the data regarding the drug release from mucoadhesive tablets[33].

Statistical Analysis of Optimization Data and Validation of Model :

In the current work, DOE (Design of Experiments software, Stat Ease version 13) was used for statistical data analysis, model optimization, and validation. Multiple linear regression analysis produced polynomial equations for each dependent variable in the form of y = f(x). Based on a comparison of several statistical criteria, including adjusted R^2, predicted R^2, and p value, the best model fitting the data was selected. In order to identify the variables that significantly affected the dependent variables, analysis of variance (ANOVA) was also employed. Response surface graphs such as contour plots and 3D surface plots are used to graphically represent the relationship between these independent and dependent variables. These plots can also be used to determine the reaction of dependent variables at the intermediate levels of independent variables, as well as the effect of independent factors at a specific level over the dependent variables. In the

end, the desirability approach was employed to create an optimum formulation with the desired results utilizing these polynomial equations and response graphs. The parentage practical error was calculated by comparing the experimental response values with the projected response values in order to validate this optimized formula and design, ensuring accuracy and reliability in the formulation process. This comprehensive analysis helps confirm that the optimized formulation meets the predefined performance criteria effectively[28].

Short-term Stability Studies :

Short term stability evaluation of the optimized batch was carried out using ICH guidelines at 40°C ± 2°C and 75% ± 5% RH. The samples were packed in a sealable pouch and packed in an amber coloured bottle. Samples were withdrawn at one month intervals and evaluated for their stability by checking tablet properties [34].

RESULT AND DISCUSSION

Melting Point :

The melting point of Levodopa was found to be 276-278°C. This range indicates a relatively high purity of the compound, suggesting that it meets the required specifications for pharmaceutical applications. Such thermal characterization is crucial for determining the suitability of Levodopa in various formulations and ensuring consistent performance in therapeutic settings.

Solubility :

The solubility of the drug was checked and found out that it sparingly soluble in methanol, slightly soluble in ethanol, very slightly soluble in water, soluble in SSF and phosphate buffer pH 6.8, These solubility characteristics indicate that the drug may be effectively formulated for therapeutic administration, as its solubility in biologically relevant media suggests potential for absorption and therapeutic efficacy.

UV Spectroscopy :

UV Spectrum of the drug performed in phosphate buffer pH 6.8 and SSF pH 6.8. The spectrum of levodopa in phosphate buffer pH 6.8 and SSF pH 6.8 is represented in [Figure 1 and 2]. Analysis revealed that Levodopa showed maximum absorbance at 280 nm. This peak is significant for identifying the drug's presence and concentration in formulations, aiding in quality control and pharmacokinetic studies. Understanding the absorption characteristics also facilitates the development of effective analytical methods for routine monitoring of Levodopa in various biological matrices, ensuring therapeutic efficacy and safety.

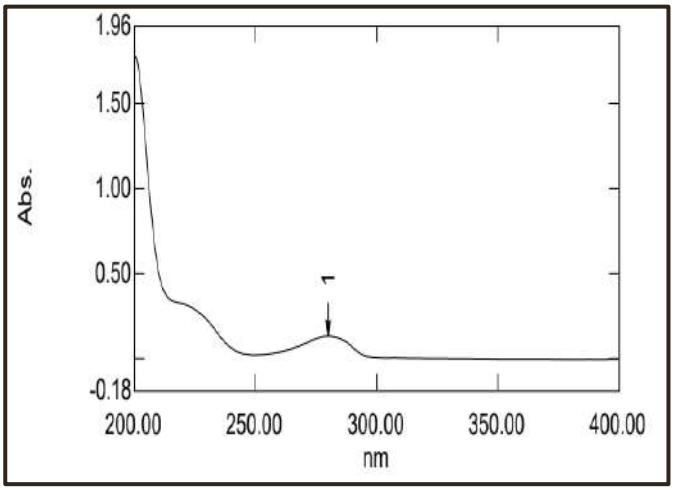

Figure 1: UV spectra of the drug in phosphate buffer pH 6.8

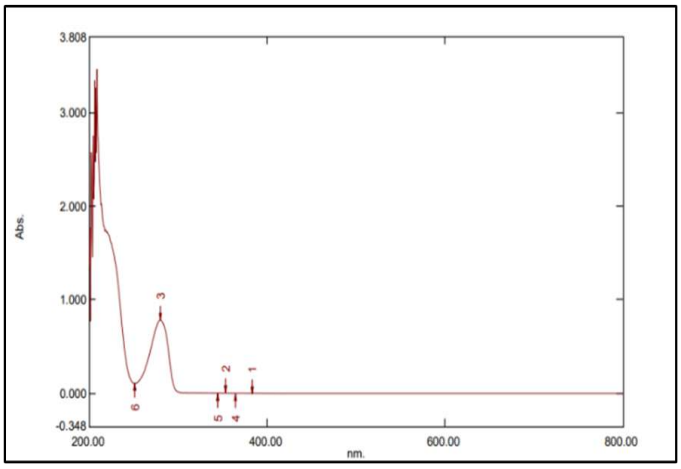

Figure 2: UV spectra of the drug in SSF pH 6.8.

Calibration Curve of Drug in SSF pH 6.8 :

The curve indicated that levodopa follows Beer's law and has a linearity range of 20-100µg/ml. Experimental data (Y = 0.0094x + 0.0328) with a correlation coefficient of 0.9983 were utilized to estimate levodopa concentration in an in-vitro dissolution study. This strong correlation suggests high accuracy and reliability in quantifying Levodopa concentrations, making it suitable for pharmacokinetic assessments and formulation development, ultimately supporting effective therapeutic applications in clinical settings.

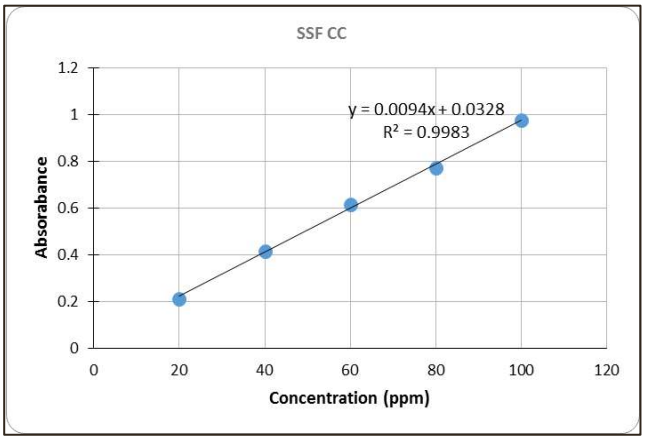

Figure 3: Levodopa Calibration curve in SSF pH 6.8

Calibration Curve of the Drug in Phosphate Buffer pH 6.8 :

The curve indicated that levodopa follows Beer's law and has a linearity range of 20-100µg/ml. Experimental data (Y = 0.0147x + 0.0075) with a correlation coefficient of 0.9906 were utilized to estimate levodopa concentration in an Ex-vivo permeation study. This high correlation coefficient underscores the effectiveness of the analytical method, providing confidence in the accuracy of concentration measurements, which is vital for assessing the drug's permeation profile and its potential for effective therapeutic applications.

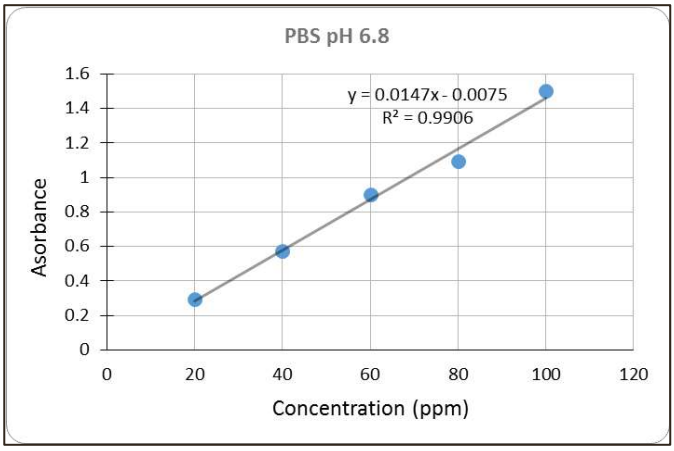

Figure 4: Levodopa Calibration curve in Phosphate buffer pH 6.8

Drug- Excipients Compatibility Studies :

FTIR and DSC studies were conducted on levodopa, polymers, a levodopa-polymer physical mixture, and an improved formulation to determine potential physicochemical interactions. These analyses provide valuable insights into the compatibility between Levodopa and the excipients, helping to identify any significant interactions that could impact drug stability, release characteristics, and overall formulation performance.

Fourier Transform Infrared (FTIR) Spectroscopy Studies :

The FTIR spectrums for all mixes showed no changes in levodopa peaks and kept the original IR bands of the drug (Figure 5). The study found no physicochemical interactions between the drug and polymers. The FTIR spectrum of levodopa (Figure 5) supports this observation. The FTIR spectra of pure levodopa revealed distinct bands at the following wavelengths.

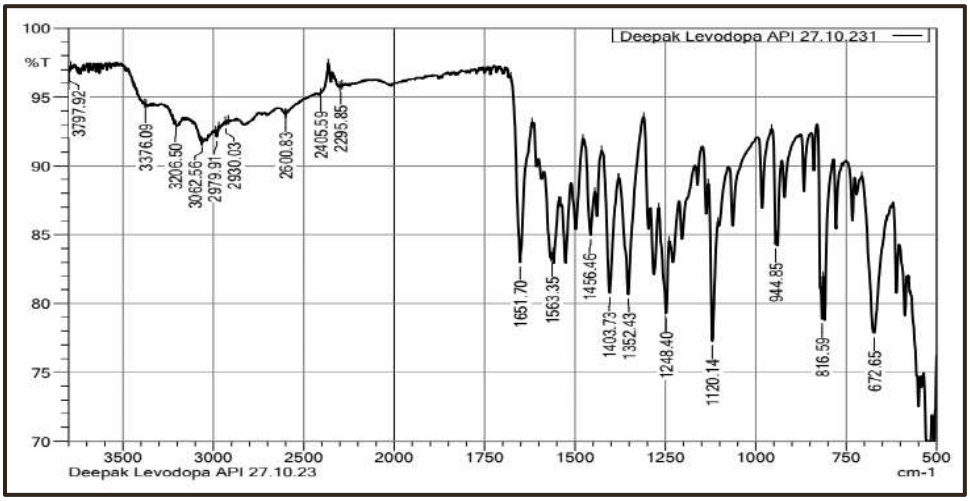

Figure 5: FTIR Spectra of Levodopa

Functional group	Range (cm−1)	Obtained value (cm−1)
Amines	3300-3500	3376.09
Carboxylic acid	2500-3300	3063.99
-C=O	1640-1800	1651.70
C-H aromatic ring	650-1000	816.59

Table 1: Result of FTIR.

Physical mixture of drug and excipient is evaluated in ratio the 1:1 by using FTIR and then compared with FTIR of levodopa for change in range or interaction between them. In the assessment of potential interactions between compounds, spectroscopic techniques serve as a valuable tool. When analyzing spectral data, the absence of significant changes or only minor variations in peak positions typically indicates a lack of interaction between the compounds under investigation. Conversely, a notable shift in peak positions suggests that an interaction may be occurring, which could be indicative of either a chemical interaction or the degradation of the drug. Such interactions can significantly impact the physicochemical properties of the formulation, potentially altering drug solubility, stability, and release profiles, ultimately influencing its therapeutic efficacy. Therefore, a comprehensive analysis is crucial for ensuring that the formulation is optimized for safe and effective use in clinical applications.

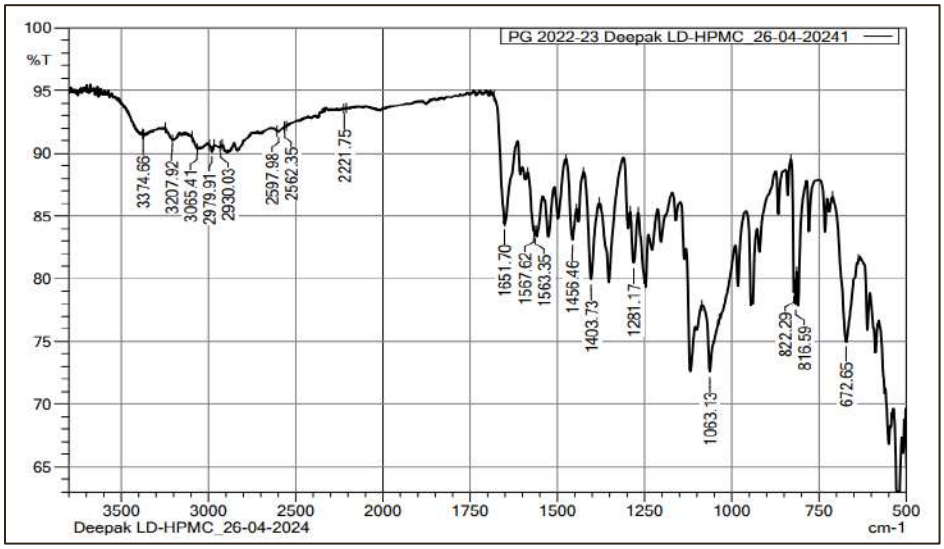

Figure 6: FTIR Spectra of Levodopa + HPMC K 100

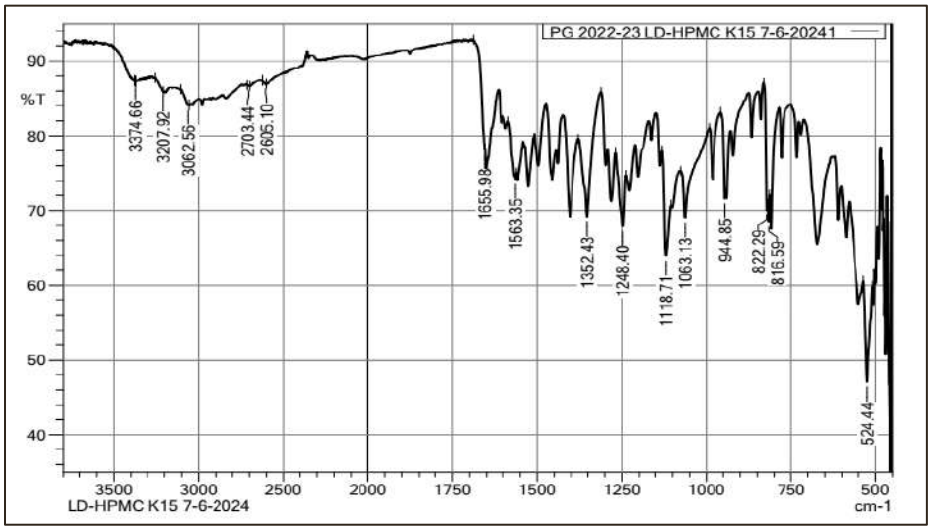

Figure 7: FTIR Spectra of Levodopa + HPMC K15

Differential Scanning Calorimetry (DSC) Studies :

DSC studies were performed on pure levodopa, polymers, a levodopa:Polymer 1:1 combination, and formulations [Figure 8 and 9]. The drug's melting endotherm was conserved in both physical combination and improved formulation. A DSC thermogram of pure Levodopa showed a sharp endothermic peak at 294.18°C. The best formulation, F2, had similar endothermic peaks at 281.18°C. The presence of all peaks indicates that all components were compatible with Levodopa, with no incompatibility between them. This compatibility suggests that the formulation is stable and retains the drug's integrity, which is essential for ensuring optimal therapeutic performance and efficacy in clinical applications.

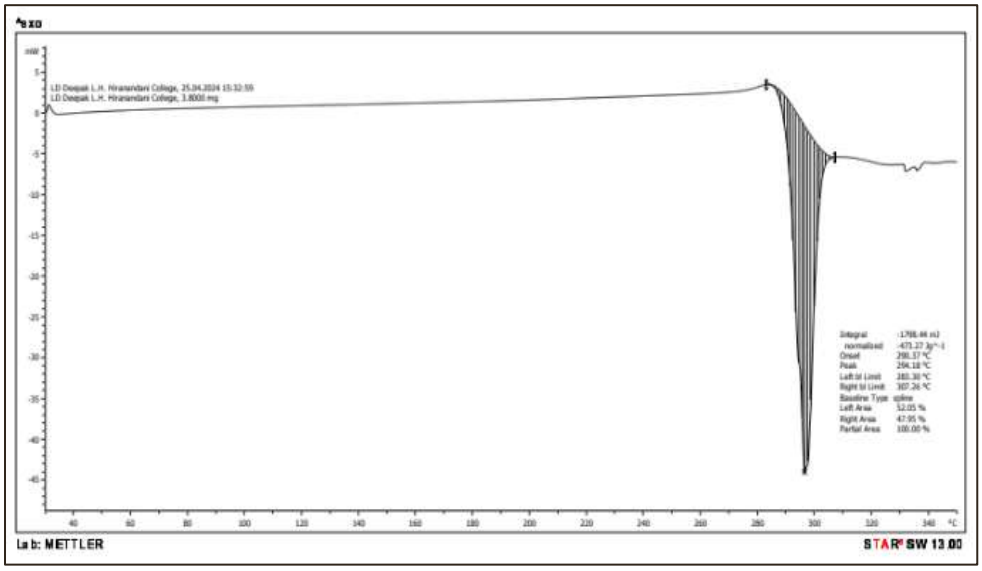

Figure 8: Thermograms of pure Levodopa

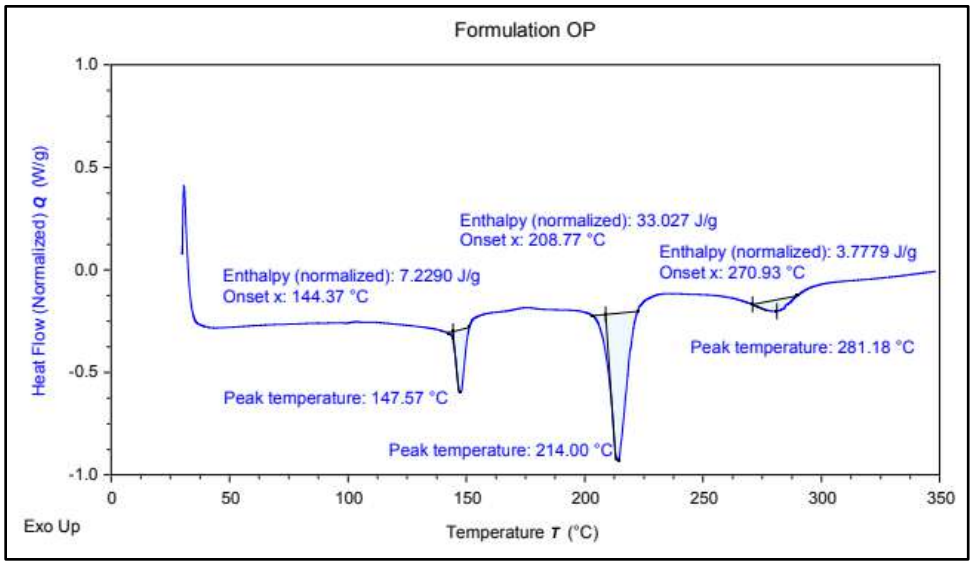

Figure 9: Thermograms of optimized formulation

Optimization of Buccoadhesive Tablet by Using 3^2 Factorial Design:

Optimization of Formulation Batches (F1 to F9):

The 3^2 factorial design was used to optimize the concentration of bioadhesive polymers. The bioadhesive polymers HPMC K15M and HPMC K100M were used as independent variables. The dependent variables included % drug release, swelling index, and mucoadhesive strength. Preliminary studies informed the selection of independent variable levels. Total 9 formulations were prepared based on the 3^2 factorial design and evaluated on the basis of tablet and mucoadhesive characteristics. All the nine formulations of 3^2 factorial design were summarized in [Table 2].`

Table 2: The 3^2 full factorial design layout of buccal tablets containing Levodopa

Ingredients (in mg)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9

Drug	50	50	50	50	50	50	50	50	50
HPMC K15M	5	10	15	5	10	15	5	10	15
HPMC K100M	10	10	10	20	20	20	30	30	30
Avicel PH102	82	77	72	72	67	62	62	57	52
Mg. Stearate	1.5	1.5	1.5	1.5	1.5	1.5	.15	1.5	1.5
Aerosil 200	1.5	1.5	1.5	1.5	1.5	1.5	.15	1.5	1.5
Total (mg)	150	150	150	150	150	150	150	150	150

Evaluation of Tablet Properties of Optimization Tablets :

Pre Compression Parameters :

Batches	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio (%)	Angle of Repose (o)
F1	0.319±0.003	0.366±0.006	12.85±0.31	1.14±0.01	27.37±0.52
F2	0.353±0.004	0.358±0.003	8.31±0.34	1.01±0.08	29.78±0.58
F3	0.328±0.008	0.372±0.004	11.82±0.61	1.13±0.04	30.19±0.51
F4	0.343±0.012	0.391±0.005	12.27±0.45	1.13±0.09	29.83±0.47
F5	0.368±0.013	0.398±0.008	7.53±0.57	1.08±0.07	34.34±0.51
F6	0.328±0.007	0.369±0.009	11.11±0.44	1.12±0.03	33.21±0.52
F7	0.356±0.003	0.392±0.004	9.18±0.38	1.1±0.04	32.06±0.45
F8	0.354±0.005	0.388±0.003	8.76±0.41	1.09±0.02	31.32±0.49
F9	0.351±0.007	0.398±0.002	11.8±0.29	1.13±0.06	33.63±0.50

Table 3: Pre compression parameter results

Precompression parameters were applied to different ratio powders, resulting in F2 formulation values with an angle of repose greater than 25 degrees. The Bulk density was 0.353, Tapped density was 0.358, Hausner's ratio was 1.01, and Carr's Index was 8.31, indicating high compressibility. These results suggest that the formulation possesses suitable flow properties for further processing and tablet compression, which is critical for ensuring uniformity and consistency in the final dosage form.

Post-compression parameters :

Batches	weights (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm)^2	Friability (%)	Drug Content (%)
F1	149±0.11	2.8±0.04	9.2±0.01	6.2±0.1	0.11±0.002	95.1±0.28
F2	148±0.38	2.9±0.03	9.3±0.04	6.3±0.1	0.15±0.003	98.24±0.39
F3	147±0.22	2.8±0.11	9.1±0.08	6±0.15	0.11±0.012	93.27±0.10

F4	150±0.54	2.7±0.04	9.3±0.01	6.2±0.1	0.14±0.033	96.33±1.00
F5	147±0.37	2.9±0.07	9.0±0.05	5.8±0.11	0.33±0.021	94.22±0.54
F6	146±0.21	2.7±0.01	9.1±0.03	5.7±0.18	0.22±0.001	92.36±2.14
F7	150±0.15	2.8±0.09	9.3±0.02	5.5±0.15	0.37±0.005	93.72±0.85
F8	149±0.38	2.8±0.08	9.2±0.02	6.2±0.1	0.41±0.007	97.36±1.00
F9	150±0.22	2.9±0.09	9.0±0.05	6.1±0.12	0.45±0.014	94.61±0.25

Table 4: Post compression parameters results

The physicochemical tablet qualities of the optimization batches were assessed and are compiled in [Table 4]. Tablets ranged in thickness from 2.79 mm ± 0.030 to 2.95 mm ± 0.040 and diameter from , which was considered satisfactory. The tablets were suitable for buccal delivery due to their optimal thickness. The tablets should have optimal compactness and hardness. Tablets had a mean hardness ranging from 5.5 kg/cm^2 ± 0.037 to 6.3 kg/cm^2 ± 0.005, indicating acceptable strength. The average tablet weight was 148.4 mg. No formulation batch differed considerably from the average value. The tablet's friability ranged from 0.11 % ± 0.003 to 0.45 % ± 0.006. Tablet formulations stayed within 1 % of the IP limit. All formulations had satisfactory drug content uniformity, with values ranging from 92.36 % ± 2.45 to 98.24 % ± 0.39, indicating proper tablet component mixing and F2 formulation showed highest drug content as compared to others.

The surface pH of buccal tablets was evaluated to assess potential adverse effects in vivo. To avoid irritation to the buccal mucosa, it was decided to maintain a neutral pH on the surface. This requires a combination glass electrode. To allow the tablet to swell, soak it in 5 ml of SSF pH 6.8 at room temperature for 2 hours. To determine the pH, place the electrode on the tablet surface and wait 1 minute for equilibration. The tablet's surface pH affects the release of drugs and causes buccal discomfort. To prevent mucosal irritation and side effects, buccal tablets should have a pH close to neutral. Surface pH for all formulations ranged from 6.20 ± 0.02 to 6.88±0.03 [Table 5], which is near to neutral. These buccal tablets do not cause irritation to the buccal mucosa, supporting their suitability for safe and effective use in buccal drug delivery. Maintaining a pH close to neutral is crucial for enhancing patient comfort and ensuring optimal therapeutic outcomes.

Surface pH:

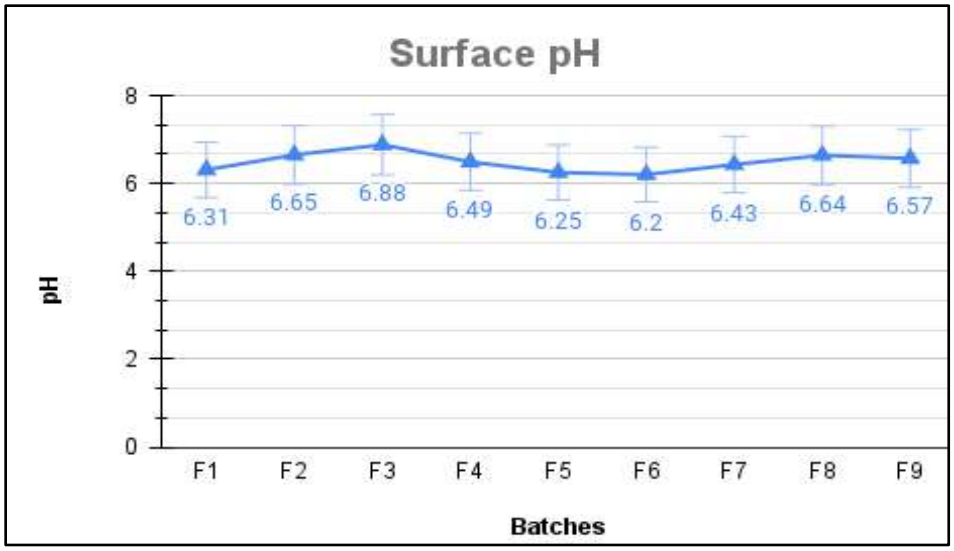

Figure 10: Surface pH of F1-F9 Batches

Swelling Index :

HPMC is a hydrophilic polymer that expands when exposed to liquid, such as water or bodily fluids. The swelling is necessary for controlling drug release rate and ensuring adequate mucoadhesivity. Therefore, studying the hydration rate is crucial for understanding swelling patterns and effect on mucoadhesion. Throughout the investigation, all formulation batches demonstrated a significant swelling index. All tablets maintained their integrity following the study period. The swelling index was modified by the combination of HPMC grades at varying concentrations. Increasing the concentration of HPMC K15 and HPMC K100 resulted in a higher swelling index (F9 was highest and F1 was the lowest). Figure 12 depicts the swelling behavior of F2 formulations over time, whereas Figure 11 compares the swelling behavior of these tablets.

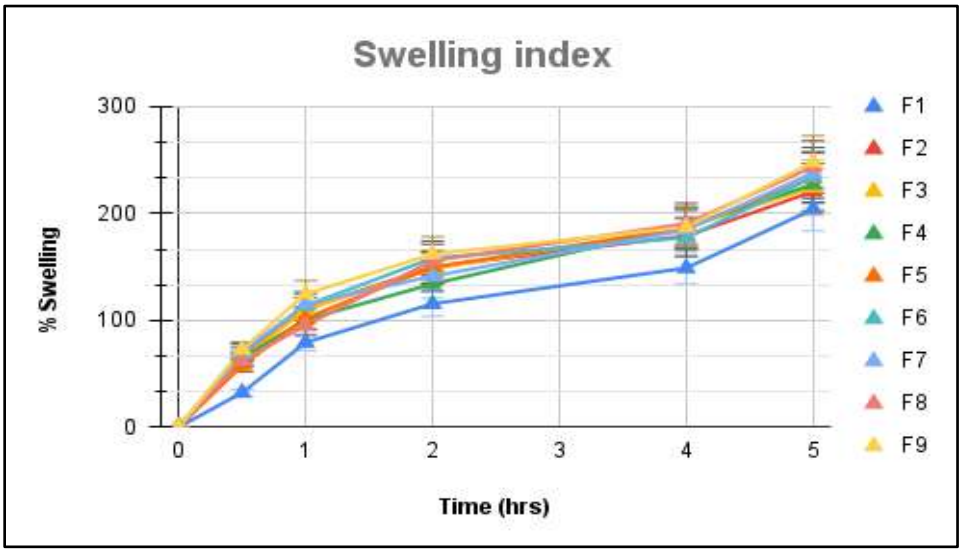

Figure 11: Swelling study of F1-F9 formulations

When levodopa tablets come into contact with the solution medium, HPMC K15 and HPMC K100 will swell and form a gel-like matrix around the tablet core.

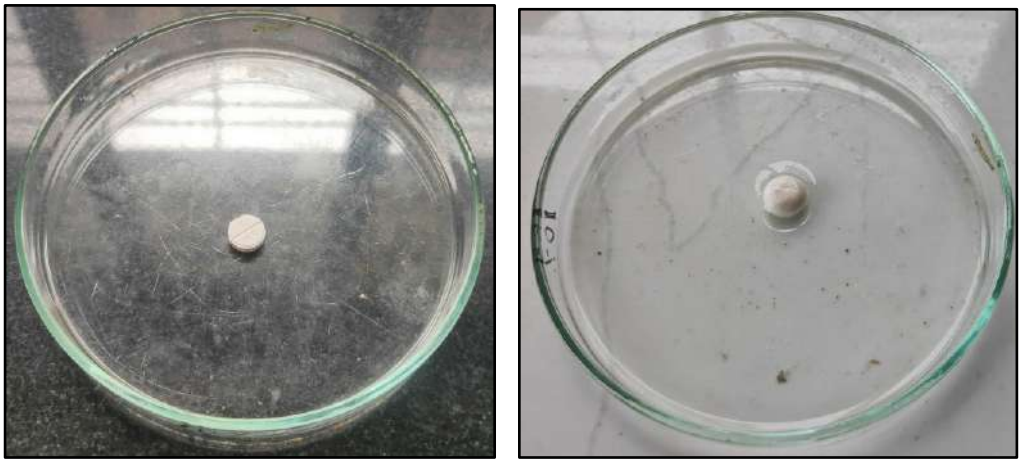

Figure 12: Before and After swelling behavior of Optimized formulation

***Ex - vivo* Bioadhesive Strength :**

Bioadhesion is influenced by the type of polymer, swelling ability, and contact time between the polymer and the mucus membrane. Ex vivo bioadhesive strength was assessed for all optimization batches (F1–F9) (Table 5). Increasing polymer concentration led to enhanced bioadhesive force. The batch F9 had the maximum

force, 34.30 gm. This could be ascribed to the high concentration of HPMC K15M and HPMC K100M. The high concentration may have formed a strong gel at the tablet-mucosa interface, penetrating deeply into the mucus layer[35]

Figure 13. Measurement of bioadhesive strength by physical balance

Ex vivo Residence Time

The ex vivo residence time is proportional to the ex vivo bioadhesion strength, possibly due to interaction between buccal mucin and hydrophilic polymer chains. The ex vivo residence time for all formulations ranged from 393 to 594 min (Table 5). The varying quantities of HPMC K 15 and HPMC K100 in different formulations may have contributed to the observed variance in mucosal adhesion time. Batch F9 had the highest residence time (594 min) due to its high concentration of bioadhesive polymers HPMC K15M and HPMC K100M (15 mg and 30 mg) in combination. The presence of hydrophilic polymers may have formed a firm viscous gel upon hydration, leading to extended retention duration on the mucosal surface and sticky interactions between mucin and tablets.

Figure 14: *Ex vivo* Residence Time of Buccal Mucoadhesive Levodopa tablet

In vitro Drug Release/Dissolution Studies :

HPMC is classified as a hydrophilic polymer. When exposed to water, in vitro drug release from a mucoadhesive levodopa tablet occurs in three phases. The first stage involves introducing the dissolving fluid into the polymer matrix, which may lead to hydration of the material. The second stage involves swelling polymers, followed by erosion and breakdown of the polymer matrix. In the third step, drugs diffuse through the polymer matrix or are released from degraded tablets. All formulations studied showed sustained drug release over an 8-hour period, promoting prolonged therapeutic effects and enhancing patient compliance [Table 5]. F2 demonstrated the highest drug release of the nine batches [Figure 16].

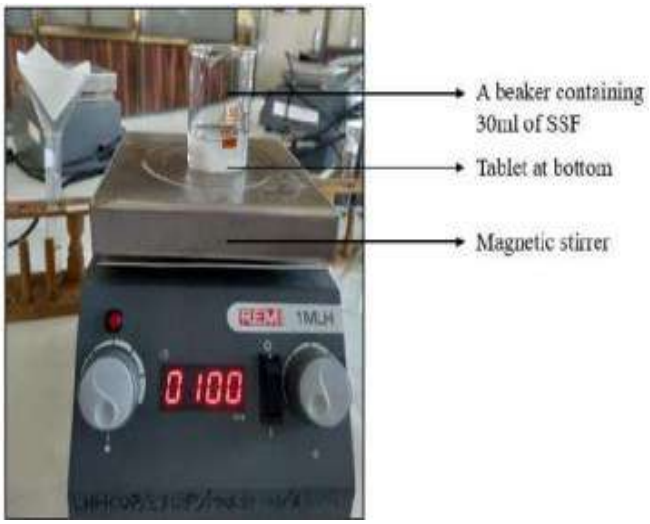

Figure 15: In-vitro dissolution of Buccal Mucoadhesive Levodopa tablet

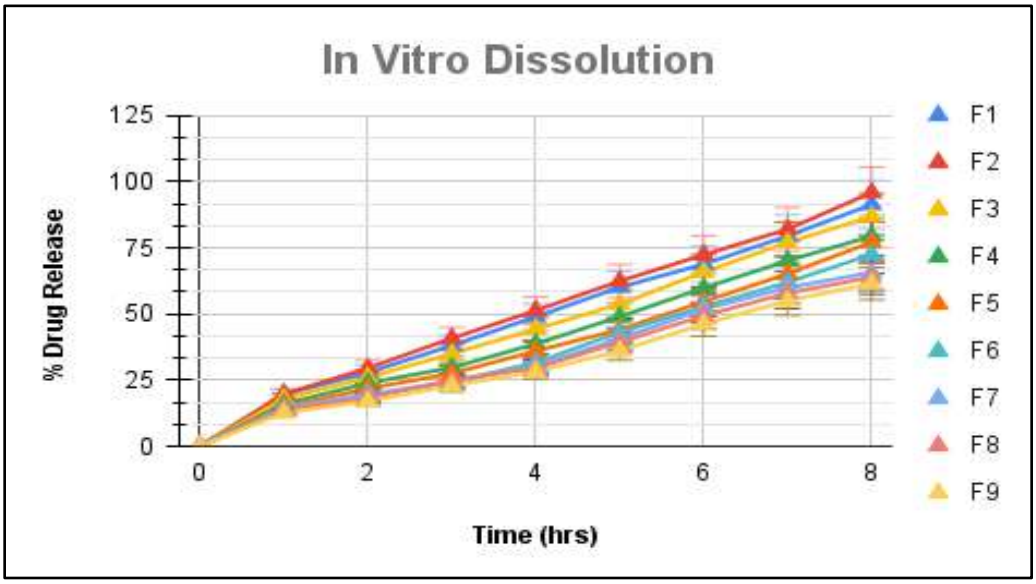

Figure 16: In-vitro dissolution of F1-F9 Batches

Batches	Surface pH	Swelling Index (%)	Mucoadhesive Strength (gm)	Residence Time (min)	In vitro Drug Release (%)
F1	6.31±0.02	204.02±1.82	16.1±0.15	393±5.2	91.30±0.35
F2	6.65±0.02	220.45±0.97	20.5±`0.12	468±1.1	95.82±0.22
F3	6.88±0.03	224.48±1.38	21.8±0.33	483±3.4	86.73±0.14
F4	6.49±0.05	227.33±1.47	22.35±0.57	528±2.2	79.35±0.85
F5	6.25±0.01	233.33±0.37	24.3±0.12	521±1.4	77.07±0.45
F6	6.20±0.03	234.24±0.65	27.1±0.65	554±3.4	72.52±0.63
F7	6.43±0.07	238±1.52	29.55±0.34	555±2.6	65.59±0.14
F8	6.64±0.08	243.6±1.34	31.5±0.42	576±3.1	63.85±0.25
F9	6.57±0.01	248±0.91	34.3±0.25	594±2.4	61.49±0.48

Table 5: Results of ex-vivo parameters for designed mucoadhesive tablets of levodopa.

***Ex-vivo* permeation study :**

The optimized batch F2 was chosen for the ex vivo permeation research. Goat buccal mucosa closely matches human buccal mucosa in form and biology, making it ideal for drug permeation research. After 8 hours, 84.07% of levodopa was able to pass through the buccal mucosa [26]. The result of the ex vivo permeation study is shown in [Figure 18]. This significant permeation rate indicates the formulation's potential effectiveness for oral delivery, suggesting that the optimized tablets could enhance therapeutic outcomes by facilitating efficient drug absorption across the buccal membrane. Further investigations could explore long-term stability and clinical applicability.

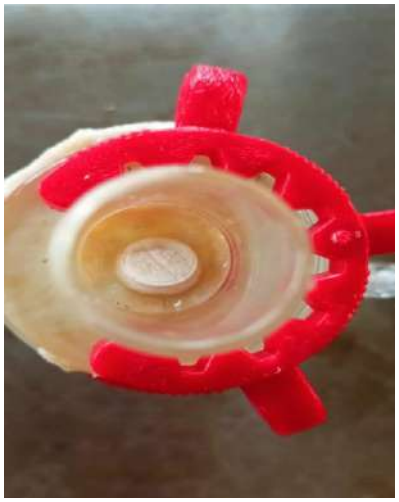

Figure 17: Ex-Vivo Permeation On Franz-Diffusion Cell

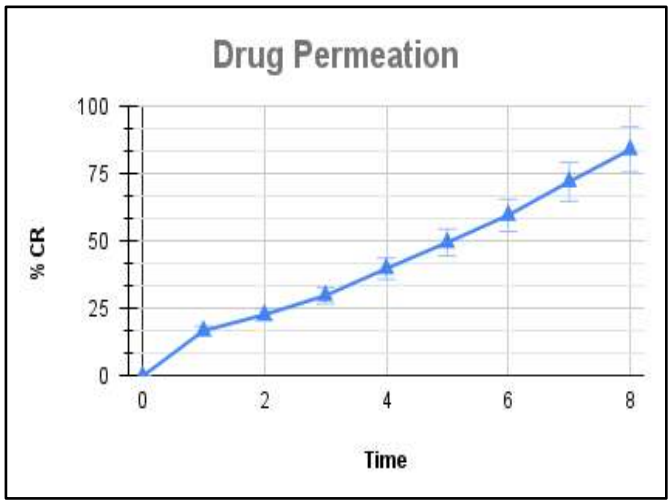

Figure 18: Ex-Vivo Permeation of F2 Batch

Dissolution Kinetics Study :

Drug release data from F1 to F9 batches has been examined using mathematical models for dissolution. The n and R^2 values were determined and represented for zero order, first order, Hixson Crowell, Higuchi and Peppas-Korsmeyer dissolution models. The selected dissolving model accurately describes drug release kinetics from buccal mucoadhesive tablets based on these results. The value of n describes the release of these dose forms. The optimized F2 formulation exhibited zero-order kinetics and Korsmeyer-Peppas dissolution kinetics, indicating a consistent drug release rate. Additionally, F2 follows non-Fickian release, suggesting that both diffusion and swelling contribute to the overall release mechanism, enhancing therapeutic efficacy.

Statistical Analysis of Optimization Data And Validation of Model :

The DOE (Stat Ease version 13) program predicted nine batches for two independent variables, HPMC K15M and HPMC K100M, at three levels (-1, 0, and +1), utilizing a 32 complete factorial statistical optimization design technique. The software was instrumental in fitting the dependent variable results to various polynomial regression equations, including linear, quadratic, and cubic forms. To assess model performance, several statistical measures were employed, such as standard deviation, squared correlation coefficient (R^2), adjusted R^2, predicted R^2, sequential P-values, and lack of fit P-values, which were thoroughly compared across the equations presented in Table 7. Following this rigorous evaluation, a linear model was identified as the most suitable for all dependent variables (Y1, Y2, and Y3), indicating a clear relationship between the independent variables and responses. The derived polynomial regression equations not only provided insights into the impact of HPMC K15M and HPMC K100M on the selected responses but also established a solid foundation for further optimization of drug release profiles. This comprehensive analysis highlights the effectiveness of statistical design techniques in formulation development, ultimately guiding future research efforts toward enhanced drug delivery systems.

Formulation	Factor 1 A: HPMC K 15	Factor 2 B: HPMC K100	Response 1 Drug Release (Y1)	Response 2 Swelling Index (Y2)	Response 3 Muco Adhesive Strength (Y3)

F1	5	10	91.30	204.02	16.10
F2	10	10	95.82	220.45	20.50
F3	15	10	86.73	224.48	21.80
F4	5	20	79.35	227.33	22.35
F5	10	20	77.07	233.33	24.30
F6	15	20	72.52	234.24	27.10
F7	15	30	65.59	238	29.55
F8	10	30	63.85	243.62	31.50
F9	15	30	61.49	248	34.30

Table 6: Experimental plan of 3^2 factorial design with observed responses

Model	R^2	Adjusted R^2	Predicted R^2	p Value
Y1 (Drug release)				
Linear	0.9701	0.9601	0.9340	0.0001
Y2 (Swelling index)				
Linear	0.9376	0.9168	0.8365	0.0002
Y3 (Mucoadhesive strength)				
Linear	0.9840	0.9787	0.9679	0.0001

Table 7: Regression values reflecting the effect of variables over responses

Study of Influence of Independent Variables :

Drug Release (Y1) :

All nine formulations in the optimization research demonstrated sustained drug release for up to 8 hours, with F2 exhibiting the highest release rate among them. F2 was selected as the optimal formulation due to its superior in vitro drug release rate, strong bioadhesion force, and favorable swelling index. The final equation representing drug release in terms of the coded independent variables is expressed as:

Drug release Y1 = +77.08 - 2.58*A - 13.82*B

The coefficients indicate the contributions of each independent variable to the dependent variables. [Figure 19] illustrates a 3-D response surface plot and contour graph, effectively showcasing the relationship between the independent variables

and drug release. These plots were instrumental in extrapolating drug release data within the confines of the experimental design, providing valuable insights for further optimization and formulation strategies.

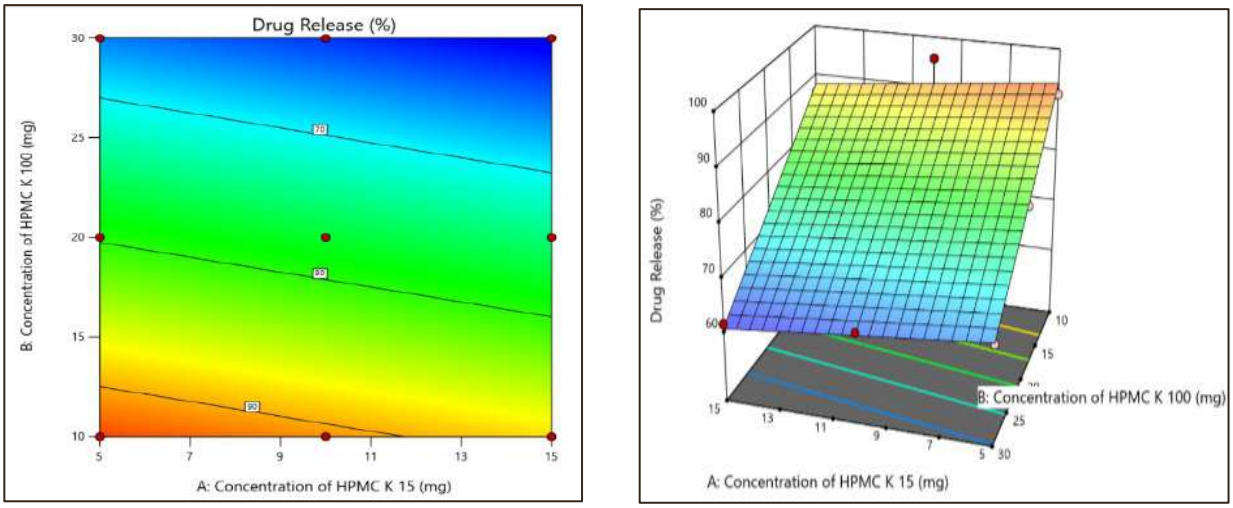

Figure 19: Drug release 3 D surface response and Contour plot

Swelling Index (Y2) :

The formulation F9 had the highest concentration of both independent variables, HPMC K15 and HPMC K100. The highest swelling index value of 248 indicates the combined effect between the two polymers. The formulation's high viscosity was caused by a high concentration of polymers, resulting in the highest SI value. It is supported by a polynomial equation, where the positive sign indicates a direct association between independent variables and response. As a result, the HPMC K15M and HPMC K100M variables in this equation were positive, indicating a direct association with the response Y2. Final equation in terms of coded independent factors can be obtained as follows.

Swelling index Y2 = +230.39 + 76.23*A + 13.44*B

This relationship is visually represented through both the surface plot and contour plot, effectively illustrating the interactions and confirming the findings. These insights highlight the importance of polymer concentration in optimizing the swelling properties of formulations.

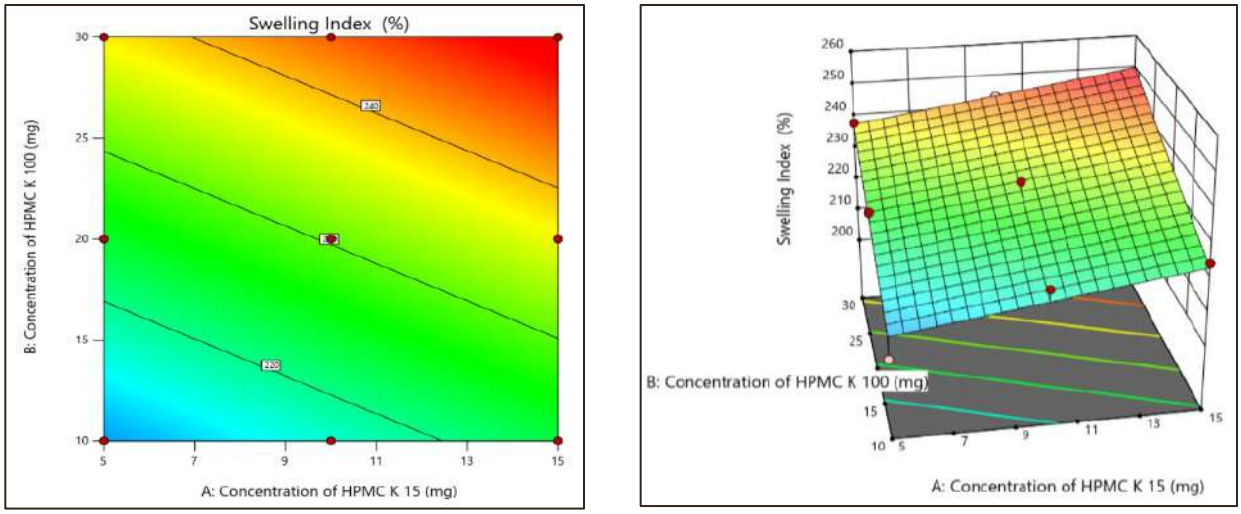

Figure 20: Swelling index 3 D surface response and Contour plot

Mucoadhesive Strength (Y3) :

Batch F9 had the highest ex vivo mucoadhesion strength of 34.30 gm ± 0.25, attributed to its high content of HPMC K15 (10 mg) and HPMC K100 (30 mg) (Table 8). These findings suggest that increasing the concentration of bioadhesive polymers leads to a corresponding increase in bioadhesion strength. Hydrophilic polymers can make intimate contact with mucus by creating a gel-like substance when hydrated and swelling. The final coded equation for independent variables can be expressed as follows.

Mucoadhesive strength Y3 = +25.28 + 2.53*A + 6.16*B

This equation underscores the positive impact of both polymers on mucoadhesive strength. Additionally, surface and contour plots visually represent this mathematical relationship, providing a clear illustration of how variations in polymer concentration influence mucoadhesion, thereby guiding future formulation strategies to optimize therapeutic effectiveness.

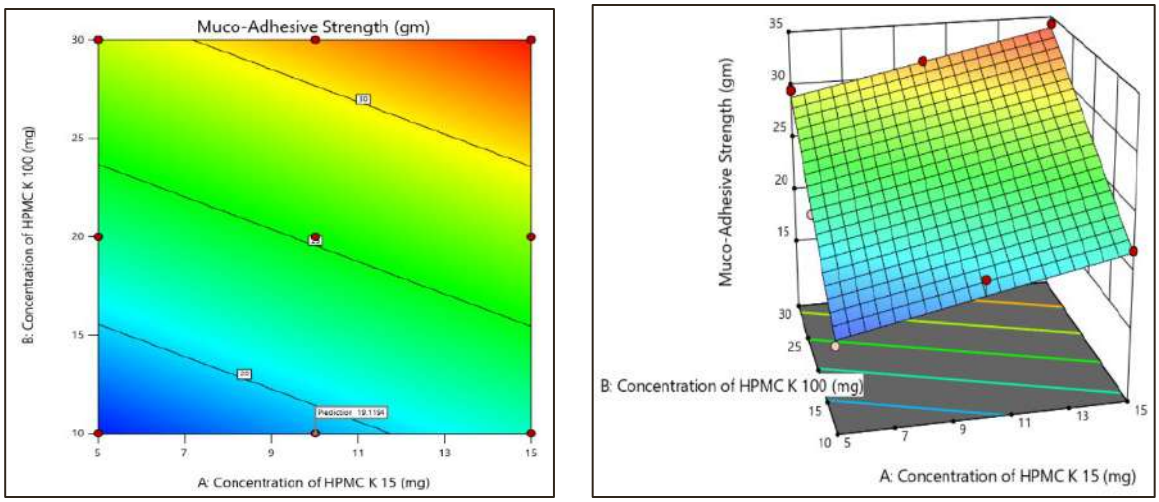

Figure 21: Mucoadhesive strength 3 D surface response and Contour plot

Constraints	Goal	Lower limit	Upper limit
HPMC K15M	is in range	5	15
HPMC K100M	is in range	10	30
Drug release	maximize	61.49	95.82
Swelling index	maximize	204.02	248
Mucoadhesive strength	maximize	16.10	34.30

Table 8: Constraints limit of optimization model

Validation of the Optimization Model :

The relationship between independent and dependent variables was established using polynomial regression equations. Design expert software was then used to optimize and validate the formula for levodopa buccal mucoadhesive tablet. The optimal formula for levodopa buccal mucoadhesive tablet was developed by optimizing all dependent responses (Y1, Y2, and Y3) simultaneously using design software. The design

expert software was used to maximize all dependent responses (Y1, Y2, and Y3) simultaneously. Constraints were given to both responses and independent variables based on preliminary study findings and literature. Y1, Y2, and Y3 responses were programmed to be maximized. Design expert software was used to do an extensive grid and feasibility search, using polynomial equations and response surface plots to identify the most desirable formulation. The optimized formulation of HPMC K15 (10 mg) and HPMC K100 (10 mg) had the maximum desirability value of 1.000. To confirm the predicted formulation, a new buccal mucoadhesive tablet of levodopa was established based on the suggested amounts of independent variables and evaluated experimentally.

The experimental outcomes were compared as predicted. The prediction error % was calculated to determine the closeness to projected results [Table 9]. The experimental results for Y1, Y2, and Y3 were extremely close to the projected outcomes. The 3^2 factorial design successfully implemented for optimization levodopa buccal tablets.

Response	Experimental Value	Predicted Value	Percentage Prediction Error %
Drug Release (Y1)	94.26	90.90	3.56
Swelling Index (Y2)	220.22	216.93	1.49
Mucoadhesive Strength (Y3)	18.40	19.11	-3.85

Table 9: Experimental and predicted values for the optimized buccal adhesive tablet

Short-term Stability Studies :

After 1 month of stability studies, the optimized formulation tablets were evaluated for physical appearance, uniformity of drug content, and % drug release. During the trial, there was no noticeable change in the look of the buccal mucoadhesive tablets. The drug content and percentage of release remained similar to the initial values, showing that the optimized formulation was stable [Table 10].

Sr. No.	Parameter	Observations	
		Before Stability Study	After Stability Study
1	Appearance	Off white	Off white
2	% Drug Release	94.26	94.07
3	Uniformity of Drug Content	98.12	97.81

Table 10: Results of stability studies

CONCLUSION

Levodopa buccal mucoadhesive tablets can be successfully prepared using polymers such as Carbopol 971P NF, HPMC K15, and HPMC K100 in different amounts and combinations. These tablets demonstrated adequate physicomechanical

and mucoadhesive properties. The properties of buccal tablets are affected by the type and proportion of HPMC polymers used. In a preliminary study, tablets containing HPMC K15M and HPMC K100M had the highest mucoadhesive characteristics. The 3^2 factorial design was successfully used to determine the concentration of HPMC K15M and HPMC K100M when combined. The formulation F2 containing 10 mg and 10 mg of HPMC K15M and HPMC K100M respectively was found to be optimum with the highest % drug release and required mucoadhesive properties. From the present study, it can be concluded that such buccal tablets of levodopa may provide extended release of drug through the buccal route which may provide a better alternative route for administration avoiding hepatic passage of drug, preventing the metabolism, enhancing the bioavailability and improving the patient compliance.

ACKNOWLEDGEMENTS

We would like to express our sincere gratitude to all those who contributed to the success of this research article. First and foremost, we thank our research guide, Mrs. Rachana Sarawade, for their invaluable guidance and support throughout the project. Their expertise and encouragement were instrumental in shaping our work. We also extend our appreciation to our colleagues in the Dr. L H Hiranandani college of pharmacy for their insightful feedback and collaboration. Additionally, we are grateful to Molychem Pvt Ltd, Mumbai for providing drug i.e. Levodopa, Colorcon Asia Pvt Ltd, Mumbai for providing HPMC polymers and NMIMS for performing DSC samples that made this research possible. Thank you all !

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HOW TO CITE: Rachana Sarawade, Deepak Rathod, Formulation And Evaluation of Novel Drug Delivery System Containing Anti Parkinson's Agent, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 12, 1530-1555. https://doi.org/10.5281/zenodo.14406680