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Research Article

Linagliptin Buccal Films

Formulation and Evaluation of Linagliptin Buccal Films

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Abstract: Achieving steady concentration levels of drugs in the plasma for diabetics is important for an extended period. The study focussed on developing mucoadhesive buccal films incorporating linagliptin, aiming to achieve controlled drug delivery for effective type 2 diabetes management towards steady level plasma concentration. The research utilizes various mucoadhesive polymers, specifically HPMC K100, HPMC E5LV, and Eudragit RL100, exploring their potential in formulating optimized films through solvent casting technique. Our primary aim was to identify the most effective formulation, that would ensure controlled drug release over an extended period. We formulated various formulations and evaluated drug content, swelling index, in-vitro drug discharge, and ex-vivo mucoadhesive strength. The formulation, incorporated linagliptin, HPMC E5LV, HPMC K100, Eudragit RL100, glycerol, and polyethylene glycol. Results from our comprehensive evaluations showcased favorable dissolution time, robust mechanical properties, and impressive mucoadhesive characteristics in the buccal films. The sustained drug discharge and mucoadhesive strength exhibited by formulation F7 indicate its potential for effective type 2 diabetes management with a single film administration lasting up to 8 hours. This research represents a significant step forward in the field of pharmaceuticals, offering a promising avenue for developing mucoadhesive buccal films to control drug delivery precisely for enhanced therapeutic outcomes in the management of type 2 diabetes.

Keywords: Buccal, Film, Linagliptin, Mucoadhesive, Type 2 Diabetes.

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1. INTRODUCTION

Diabetes mellitus (DM) is a prevalent metabolic disorder that poses a significant global health challenge. This condition arises from an imbalance in the body's regulation of blood sugar levels, resulting in chronically elevated blood glucose levels[1]. The consequences of uncontrolled diabetes can be severe, impacting various vital organs and systems, such as the heart, kidneys, eyes, and nerves. Consequently, DM is associated with an increased risk of complications, including cardiovascular disease, kidney failure, vision impairment, and neuropathy[2]. There are two primary types of diabetes mellitus: Type 1 Diabetes (T1DM) is characterized by autoimmune destruction of the insulin-producing beta cells in the pancreas[3]. As a result, individuals with T1DM have insufficient insulin production and require external insulin administration to maintain blood sugar levels within a healthy range. T1DM typically develops in childhood or adolescence, although it can occur at any age of 4. Type 2 Diabetes (T2DM) is the more common form of diabetes and usually develops in adulthood. It is primarily characterized by insulin resistance, where the body's cells do not respond effectively to insulin signals. Additionally, T2DM often involves impaired insulin secretion from the pancreas and increased glucose production by the liver. Lifestyle factors, such as poor diet and physical inactivity, play a significant role in the development of T2DM. However, genetic predisposition also contributes to its onset. Treatment strategies for diabetes mellitus aim to manage blood sugar levels and reduce the risk of complications. These strategies [5] include lifestyle modifications: Insulin therapy, oral medications, dipeptidyl peptidase Inhibitors (they work by breaking down certain hormones that inhibit the stimulation of insulin discharge, thereby lowering blood sugar levels), and other medications. Managing diabetes requires ongoing monitoring, regular medical check-ups, and collaboration between healthcare providers and individuals with diabetes. The goal is to achieve and maintain target blood sugar levels to prevent or delay complications associated with the condition. Additionally, diabetes management often involves addressing other risk factors such as hypertension, high cholesterol, and smoking, which can further increase the risk of complications[6]. Linagliptin, a prominent member of the dipeptidyl peptidase-4 (DPP-4) inhibitor class, has garnered recognition in treatingT2DM[7]. Its unique pharmacokinetic characteristics set linagliptin apart, making it a valuable asset in diabetes management. Unlike many drugs, linagliptin exhibits non-linear pharmacokinetics, meaning its blood levels do not increase proportionally with the dose, offering dose flexibility and potentially reducing the risk of overexposure at higher doses. Additionally, its extended half-life permits convenient once-daily dosing, promoting medication adherence. Linagliptin's primary route of excretion through the intestines, mostly as an unchanged drug, distinguishes it from other T2DM medications which gets excreted through the kidneys. This intestinal excretion renders it suitable for patients with renal impairment, eliminating the need for frequent dose adjustments based on renal function. These exceptional pharmacokinetic features collectively enhance the convenience and efficacy of linagliptin in managing T2DM, making it a valuable addition to the array of treatment options available for this prevalent metabolic disorder. However, it should be prescribed, overseen by healthcare professionals familiar with its usage, and tailored to each patient's specific needs as part of a comprehensive diabetes management plan that may include lifestyle modifications and other medications. Buccal films have emerged as a promising and innovative drug delivery system with many advantages. These thin, flexible films designed for buccal administration offer several key benefits that make them an attractive choice in the pharmaceutical field[8]. Buccal films are known for their cost-effectiveness. Their efficient production methods and the potential for using fewer excipients often translate into reduced manufacturing costs, ultimately leading to more affordable medications for patients[9].Patient compliance is another significant advantage of buccal films. The ease of administration and the absence of need for water or swallowing make them convenient, especially for individuals who may have difficulty swallowing traditional oral medications. This convenience can enhance patient adherence to prescribed treatment regimens, which is crucial for managing chronic conditions like diabetes effectively[10].One of the standout features of buccal films is their potential for local and systemic drug effects. When placed in the oral cavity, these films have direct access to the systemic circulation through the internal jugular vein, bypassing the liver's first-pass metabolism. This means that drugs delivered via buccal films can achieve high bioavailability, as a significant portion of the drug enters the bloodstream directly. This is particularly valuable for drugs that may be poorly absorbed in the gastrointestinal tract, degrade in the gastric area, or require rapid onset of action[11].Compared to traditional buccal tablets, buccal films offer greater flexibility and comfort. They are typically thin, pliable, and comfortable to users, making them more acceptable to patients. This improved comfort can lead to higher patient satisfaction and adherence to treatment plans[12]. In diabetes management, buccal films represent a recent and promising development. They offer an exciting avenue for delivering diabetes medications more effectively and improving patient compliance. For a condition like diabetes, where precise medication timing and dosage are critical, buccal films provide a convenient and reliable option. As research and development in buccal drug delivery continues to advance, we can expect to see more innovative applications of this technology in diabetes care and other therapeutic areas.

2. MATERIALS AND METHODS

2.1. Materials

Pure linagliptin was purchased from Chemland India,. Throughout the study, analytical-grade chemicals were employed.

2.2. Linagliptin characterization

2.2.1. Solubility test

The solubility assessment of linagliptin in various solvents, including methanol, ethanol, 0.1N HCl, phosphate buffer at pH 6.8, and phosphate buffer at pH 4.5, is a fundamental step in pharmaceutical research and formulation. This comprehensive evaluation provides essential insights into the drug's solubility characteristics, influencing its potential applications and formulation strategies[13]. Methanol and ethanol represent commonly used solvents, offering insight into the drug's overall solubility behavior and potential use in oral solutions or suspensions. The assessment in 0.1N HCl

replicates the stomach's acidic environment, which is crucial for drugs intended for oral administration. Phosphate buffer solutions at pH 6.8 and pH 4.5 simulate physiological and acidic conditions, respectively, aiding in predicting how the linagliptin may behave in the body and its stability in specific environments. This data guides researchers and formulators in making informed decisions about the drug's formulations, routes of administration, and analytical methods for quality control, ensuring consistent performance in pharmaceutical applications.

2.2.2. *Melting point*

The melting point of linagliptin was determined using Thiel's tube method. This approach introduced finely powdered linagliptin into one end of a capillary tube, which was subsequently sealed at the other end. This capillary tube, attached to a thermometer, was immersed within a Thiel's tube filled with liquid paraffin. The temperature at which the linagliptin underwent melting was recorded upon heating the Thiel's tube[14].

2.2.3. *Determination of λ_{max}*

In the analytical process, a standard solution of linagliptin was prepared at a precise concentration of 10 µg/ml. This standardized solution was subjected to absorbance scanning utilizing a UV double-beam spectrophotometer. The scanning process covered a broad wavelength range from 200 to 400 nm. This UV-visible spectroscopy technique allows for the measurement of absorbance across a spectrum of wavelengths, revealing the drug's characteristic absorption pattern or peaks. The resulting data was used for the quantitative determination of linagliptin. These data are valuable in analytical methods and quality control procedures in pharmaceutical research and manufacturing[15].

2.2.4. *Standard calibration curve*

25 mg of pure linagliptin was transferred into a clean and dry 50 ml volumetric flask. 25 ml of methanol, which serves as the solvent, was added and thoroughly mixed. The volume was adjusted to 50 ml using methanol, ensuring complete homogenization. 2 ml of this solution was taken and transferred into another clean 50 ml volumetric flask. It was then diluted with methanol to reach a total volume of 50 ml. This resulting solution was a standard stock concentration of 20 µg/ml. The absorbance of these solutions was measured using a UV-visible spectrophotometer at a wavelength of 294 nm[16]. The data was analyzed using linear regression after generating a graph depicting absorbance against concentration.

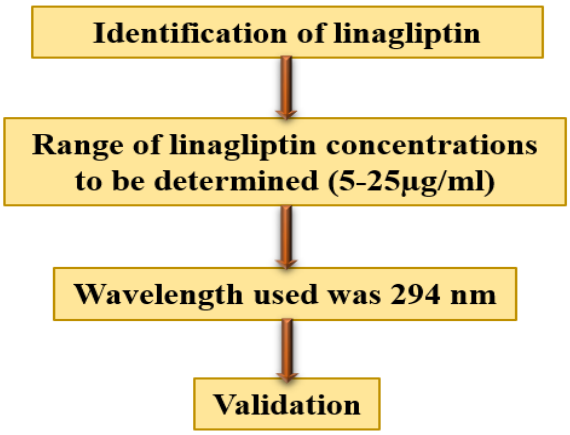

Fig.1: Analytical method development steps

2.3. *Compatibility studies*

2.3.1. *FTIR studies*

The Fourier Transform Infra-red (FTIR) spectral analyses were conducted on both pure linagliptin and the excipients to assess the compatibility of the linagliptin with the used formulation components. The peaks in the spectra were compared against the peaks of linagliptin and the polymer mixture to evaluate any potential interactions[17].

2.4. *Mucoadhesive buccal film preparation*

Linagliptin mucoadhesive buccal films were prepared using the solvent casting method. The mucoadhesive polymers employed in this process included HPMC K100, HPMC E5LV, and eudragit RL 100. The drug, polymers, and other excipients were accurately weighed following the batch formula. Water-soluble ingredients, i.e., the polymers, were dissolved in water to create a homogenous and viscous solution. Simultaneously, the linagliptin and other excipients were dissolved in a suitable solvent to form a transparentand viscous solution. These two solutions were combined, resulting in a final mixture, casted into a film, and allowed to dry[18]. Once dried, the films were fashioned into the desired sizes and stored for future use. The composition of the formulation of the linagliptin buccal films is given in Table 1.

Table 1: Various formulations of linagliptin buccal films

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Linagliptin	80	80	80	80	80	80	80	80	80
HPMC K100	640	-	-	320	320	-	320	160	160
HPMC E5LV	_	640	_	320	_	320	160	320	160
Eudragit RL100	_	_	640	_	320	320	160	160	320

Mannitol	100	100	100	100	100	100	100	100	100
Tween 80(ml)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
PEG-400 (ml)	1	1	1	1	1	1	1	1	1
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Ethanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

2.5. Evaluation of mucoadhesive buccal films

2.5.1. The weight and thickness of the films

Three films from each formulation are chosen for film weight assessment, and their weights were measured using a digital balance. The average weight is then calculated from these measurements. Likewise, three films of each formulation are selected for evaluating film thickness. Measurements are taken at three different locations on each film using a Vernier caliper. The resulting mean value of these measurements is then determined[19].

2.5.2. Surface pH of films

Three films from each formulation were allowed to undergo a 2h swelling process on a petri plate to determine the surface pH. After swelling, pH paper was placed on the surface of the swollen area to assess the surface pH. The resulting pH readings are recorded, and the mean value is calculated from these three measurements [20].

2.5.3. Swelling index

Each buccal film was individually weighed ($W_{initial}$) and then placed in separate Petri dishes containing pH 6.8 phosphate buffer. Afterward, the buccal films were removed and gently blotted with filter paper to remove excess surface water[21]. Then, finally weighed (W_{final}). Using the following formula, the swelling index (SI) was calculated (Eq.1):

$$Swelling\ Index = \frac{W\ (final) - W\ (initial)}{W\ (initial)} X100 \text{--- (1)}$$

2.5.4. Folding endurance

Three films was cut to an appropriate size to measure folding endurance. One film was repeatedly folded at the same spot or folded up to 300 times until it breaks [22]. The folding endurance value was determined by the point at which the film does not break even after being folded multiple times[23].

2.5.5. Drug content uniformity

Drug uniformity was assessed by dissolving 5 pre-weighed films in 100 ml phosphate buffer at pH 6.8 using a magnetic stirrer for 2 h. Subsequently, the solution was then filtered using Whatman filter paper. The linagliptin content was analyzed using a UV spectrophotometer[24] after appropriate dilution.

2.5.6. Moisture content

The prepared films was weighed and placed in a desiccator containing activated silica at room temperature for 24 hours. The individual films was weighed every other day until a stable weight is achieved[25]. The percentage moisture content was calculated by determining the difference between the initial and final weights about the final weight (Eq.2)[26].

$$\%\ moisture\ content\ = \frac{W\ (initial) - W\ (Final)}{W\ (initial)} X100 \text{--- (2)}$$

2.5.7. Moisture Uptake

The buccal patches was weighed and placed inside a desiccator containing a saturated sodium chloride solution at 74% RH. After the initial week, the patches was removed and weighed[27]. The water absorptive capacity (moisture uptake) will calculated usiing the percentage difference between the initial and final weights to the initial weight (Eq.3)[28].

$$\%\ moisture\ uptake\ = \frac{W\ (Final) - W\ (Initial)}{W\ (initial)} X100 \text{--- (3)}$$

2.5.8. In-vitro drug discharge evaluation

Dissolution studies was conducted for each formulation using the USP dissolution apparatus, set at 37±0.5 °C. Continuous rotation at 50 rpm was maintained with the help of 900 ml of dissolution medium. A specimen of the linagliptin film was introduced into each test. A sample portion was withdrawn and substituted at specific intervals with an equal volume of fresh dissolution medium[29, 30]. The sample analysis was performed through spectrophotometry at a predetermined wavelength.

2.5.9. Mucoadhesion strength

The assessment of mucoadhesion strength for the buccal film was conducted using a modified physical balance method. Fresh buccal mucosa from sheep was procured from a nearby slaughterhouse and used within 2 h of collection. The mucosal membrane underwent rinsing with distilled water followed by treatment with phosphate buffer at pH 6.8. A double-beam physical balance was employed, and a durable thread of suitable length was suspended from the left arm of the balance. A glass stopper with a consistent surface was attached to the lower end of the thread. The buccal mucosa was securely tied with the mucosal side facing upward, using thread underneath an inverted 50 ml glass beaker. This assembly was placed within a 500 ml beaker containing phosphate buffer at pH 6.8, maintained at 37 °C to ensure

the mucosal surface remained moist[31].The buccal film was affixed to the glass stopper on one side of the membrane using adhesive (feviquick). Before the experiment, equilibrium between the two sides of the balance was established by placing a weight on the right pan. Subsequently, a 5 g weight was removed from the right pan, causing the glass stopper and film to descend over the mucosal membrane. This configuration was maintained for three minutes. The weights on the right pan gradually increased until the film gently detached from the mucosal membrane. The additional weight on the right pan (total weight minus 5 g) was to determine the mucoadhesive strength. The mean of three trials was calculated for each set of formulations to ensure reliable results. To ensure consistent outcomes for the formulation, the tissue was precisely rinsed with phosphate buffer after each measurement, with a 5-minute interval before introducing a fresh film[32, 33].After calculating the mucoadhesion strength, the adhesion force was determined using the provided equations (Eq.4)[34].

$$Force\ of\ adhesion\ (N) = \frac{Mucoadhesive\ strength}{1000} X9.8 \text{--- (4)}$$

2.5.10. Ex-vivo permeation study

Permeation studies was conducted using a modified Franz diffusion cell setup, which includes two compartments: a donor compartment and a receptor compartment, each having a capacity of 18 ml and an effective diffusion area of 0.785 cm². For these experiments, porcine or sheep buccal mucosa was employed. The mucosal membrane was carefully separated from adipose tissue and muscles using a scalpel. The buccal epithelium, free from underlying tissue, was isolated and utilized within 2 h of extraction [35,36]. The isolated buccal epithelium was placed between the two chambers of the diffusion cell, with the receptor chamber containing pH 6.8 PBS. A stabilization period of 1 h was allowed for the buccal epithelium. Once the buccal epithelium was stabilized, the film was be positioned on it, and periodic samples was withdrawn, with an equal volume of fresh medium introduced (Figure 2). These collected samples was subjected to spectrophotometric analysis[22].

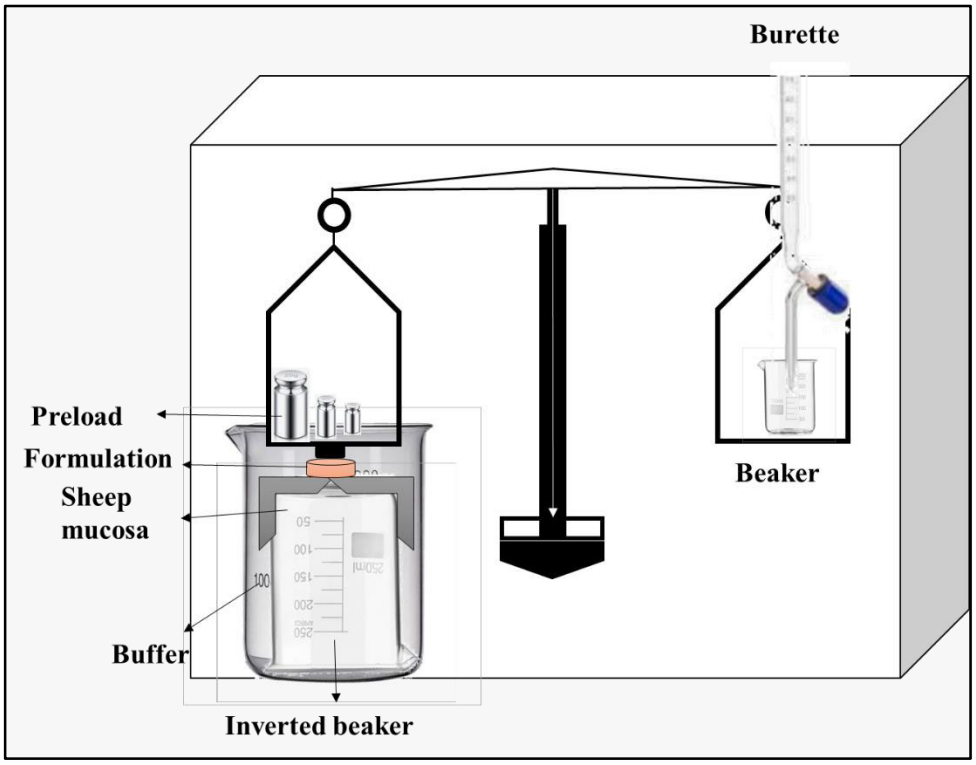

Fig.2: *Ex-vivo* mucoadhesion assembly

3. RESULTS

3.1. Results of solubility, melting point, and λ_{max}

The solubility assessment of linagliptin across various solvents revealed distinct characteristics. Linagliptin exhibited insolubility in both water and pH 6.8 phosphate buffer. However, it displayed high solubility in methanol and notable solubility in ethanol and 0.1 N HCl. Additionally, linagliptin demonstrated solubility in phosphate buffer at pH 4.5.The melting point of pure linagliptin was determined to be 194±1.12 °C, providing valuable information about its thermal properties. Furthermore, when a standard solution of linagliptin (10 µg/ml) was analyzed within the wavelength range of 200 – 400 nm, the UV-visible spectrum exhibited maximum absorbance at 293 nm. This absorbance peak is essential for quantitatively determining linagliptin using spectroscopic techniques.

3.2. Standard calibration curve

The standard calibration curve for linagliptin in methanol exhibits a robust linear relationship between linagliptin concentration and absorbance, with a high r^2 value of 0.995 (Figure 3).

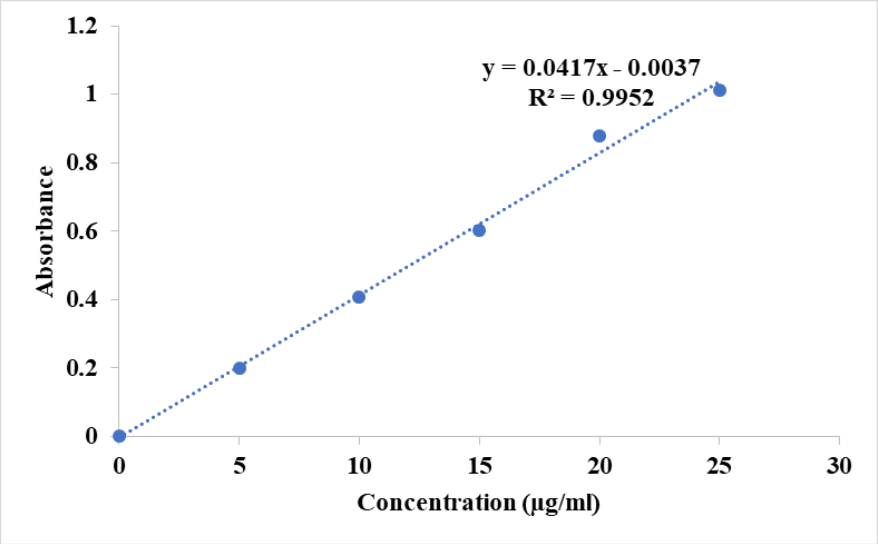

Fig. 3: Standard calibration curve of linagliptin

3.3. FTIR data

The FTIR spectra exhibited distinctive peaks corresponding to the drug at their respective characteristic wavelengths. Importantly, no significant shifts were observed in these peaks, indicating that the drug remains compatible with the chosen excipients. This observation is crucial as it suggests that the excipients do not induce chemical changes or interactions with the drug molecules that could compromise their stability or efficacy (Figure 4).

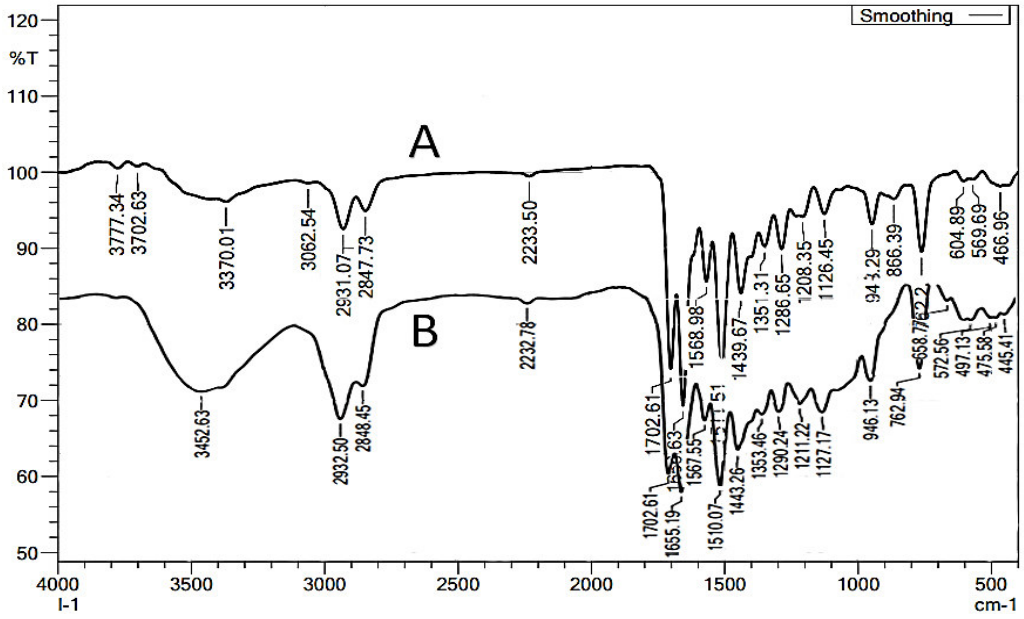

Fig.4: FTIR spectra of A) Pure drug; B) linagliptin with excipients

3.4. Physical evaluation of mucoadhesive buccal films

Across all formulations, the film thickness remained consistently within a narrow range, with measurements ranging from 0.22±0.01 to 0.29±0.02 mm. This uniformity in thickness indicates precision in the manufacturing process. Additionally, each of these films passed the weight variation test, demonstrating that the average percentage deviation adhered to acceptable limits set by pharmacopoeial standards, ensuring quality and consistency. Folding endurance values exhibited a range of 120±10 to 300±07, signifying varying degrees of mechanical strength and flexibility among the formulations. This range provides insights into the films' ability to withstand folding stresses, which is crucial for their practical application. Surface pH values for all batches fell from 6.87±0.07 to 7.07±0.01, closely approximating neutrality. This observation suggests that the formulated product is unlikely to irritate the oral cavity, making it suitable for buccal administration.Furthermore, the linagliptin content across all formulations remained consistent and within the range of 93.73±0.18% to 99.58±0.37% (Table 2). This alignment with quality standards defined by pharmacopeias assures the reliability of linagliptin content, which is critical for the efficacy and safety of the buccal films. These comprehensive evaluations of film thickness, weight variation, folding endurance, surface pH, and linagliptin content collectively ensure the quality and performance of the formulations in pharmaceutical applications.

Table 2: Physical evaluation data of the films

Formulation	Thickness (mm)	Weight (mg)	Surface pH	Folding endurance	Moisture Content (%)	Moisture Uptake (%)	Linagliptin content (%)
F1	0.26±0.02	0.32±0.03	7.03±0.03	220±15	16±1.1	8.4±0.2	99.58±2.3
F2	0.22±0.01	0.31±0.02	6.87±0.07	150±11	13±1.2	6.4±0.5	98.42±3.3
F3	0.21±0.02	0.30±0.01	6.95±0.02	120±10	9±0.2	4.2±0.2	92.57±4.1
F4	0.24±0.03	0.33±0.02	7.07±0.01	250±12	18±0.3	9.1±0.4	96.65±2.1
F5	0.25±0.02	0.32±0.01	6.92±0.06	210±9	15±1.0	6.8±0.8	97.76±2.6
F6	0.24±0.01	0.31±0.02	6.98±0.03	200±13	14±1.2	5.7±0.8	95.49±4.1
F7	0.29±0.02	0.34±0.03	7.01±0.02	300±07	19±0.2	9.6±0.8	98.08±3.2
F8	0.26±0.01	0.32±0.02	6.94±0.01	260±05	15±0.6	7.9±0.5	96.98±1.8
F9	0.23±0.02	0.31±0.01	6.97±0.04	247±20	14±0.3	6.9±0.4	93.73±1.7

3.5. Swelling data

In the assessment of swelling characteristics across multiple formulations, it was observed that the degree of swelling increased over time. Among the various formulations studied, formulation F1, which incorporates HPMC K100 as the primary polymer, exhibited the most pronounced swelling behavior with a swelling index of 125.5±1.53% (Figure 5A). In contrast, formulation F3, which utilizes eudragit RL100 as its primary polymer, displayed the lowest swelling index, measuring 76.7±0.67. % These findings stress the influence of the polymer type on the swelling behavior of the buccal films, with HPMC K100 promoting the highest degree of swelling and eudragit RL100 resulting in comparatively lower swelling over the specified time intervals. This information is valuable in tailoring buccal film formulations for specific drug delivery applications, considering the desired swelling characteristics.

3.6. In-vitro drug discharge studies

Linagliptin discharge studies were conducted throughout 8 h using the USP paddle method with phosphate buffer at pH 6.8 as the dissolution medium (Table 3 and Figure 5B). Notably, Formulation F1, which incorporated HPMC K100 as a mucoadhesive polymer, exhibited the highest linagliptin discharge percentage of 80.66%. On the other hand, Formulation F7, which contained a combination of HPMC K100, HPMC E5LV, and eudragit RL 100, displayed a sustained linagliptin discharge profile, with a linagliptin discharge percentage of 59.32% at the end of 8 h. This sustained discharge characteristic sets it apart from the other formulations.

3.7. Kinetic modelingof drug discharge

In a study assessing linagliptin discharge patterns, various kinetic models were employed to analyze the in-vitro discharge data of different formulations. Formulations F2, F3, F4, F6, and F9 exhibited zero-order discharge kinetics, indicating a consistent rate of linagliptin discharge over time. Formulation F5 followed first-order discharge kinetics, where the rate of linagliptin discharge decreased exponentially. While the Higuchi model was mentioned, specific formulations adhering to this model needed to be specified. However, formulations F1, F7, and F8 conformed to the Korsemeyer-Peppas model. Formulation F7 exhibited non-Fickian transport, suggesting a complex discharge mechanism involving factors beyond simple diffusion, while F1 and F8 demonstrated super case-II transport within the Korsemeyer-Peppas model (Table 3, Figure 5C, 5D, and 5E).

Table 3: Kinetic modeling plot of linagliptin buccal films

Formulation	Zero-order	First order	Higuchi model	Korsmeyer- Peppas	
				R^2	n
F1	0.9965	0.9067	0.9889	0.9985	0.9318
F2	0.9976	0.9461	0.9116	0.9966	0.9855
F3	0.9979	0.9376	0.9302	0.9952	0.8882
F4	0.9976	0.9343	0.9092	0.9976	0.9552
F5	0.9723	0.9905	0.8415	0.9606	0.9481
F6	0.9962	0.9564	0.9197	0.9911	0.8656
F7	0.9946	0.9415	0.9229	0.9958	0.8701
F8	0.9950	0.9224	0.9164	0.9957	0.9758
F9	0.9969	0.9648	0.9106	0.9824	0.8857

3.8. Ex-vivo mucoadhesive strength

The study investigated the mucoadhesive strength of prepared mucoadhesive buccal films (Figure 5F). Among the formulations tested, formulation F7, which has a combination of HPMC K100 and Sodium alginate as mucoadhesive polymers, exhibited the highest mucoadhesive strength, with a maximum value of 39.0±2.50 g. This strong adhesive property is likely attributed to the synergistic effects of the two polymers. In contrast, formulation F3 displayed the lowest mucoadhesive strength, measuring only 25.7±1.25 g.

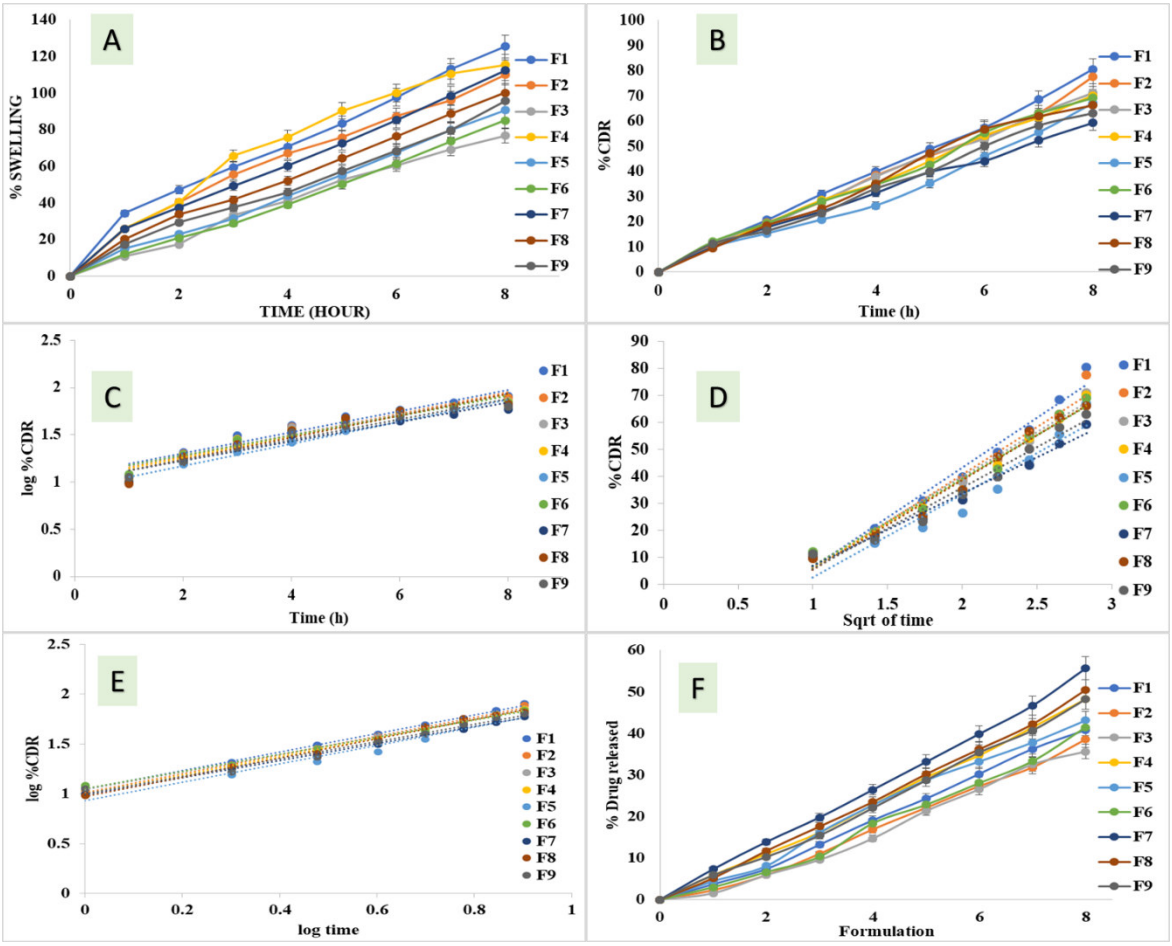

Fig. 5: A) Swelling index B) *In-vitro* linagliptin discharge; C)First order plots; D) Higuchi's plots; E) Korsmeyer-Peppa's plots; F) *Ex-vivo* linagliptin permeation of the formulations

3.9. *Ex-vivo permeation results*

In the ex-vivo permeation study of mucoadhesive buccal films, various formulations were tested, and the results revealed significant variations in mucoadhesive strength. Formulation F7 emerged as the standout performer, displaying a remarkable mucoadhesive strength of 39.0±2.5g. This exceptional adhesive capability can be attributed to the synergistic combination of HPMC K100 and Sodium alginate as mucoadhesive polymers within this formulation. In contrast, formulation F3 demonstrated the lowest mucoadhesive strength, measuring only 25.7±1.25g. This reduced adhesion can be attributed to its limited propensity to swell. These findings showed the importance of polymer selection and their combinations in designing mucoadhesive buccal films, with F7 proving the potential for enhanced adhesion in such drug delivery systems (Figure 6).

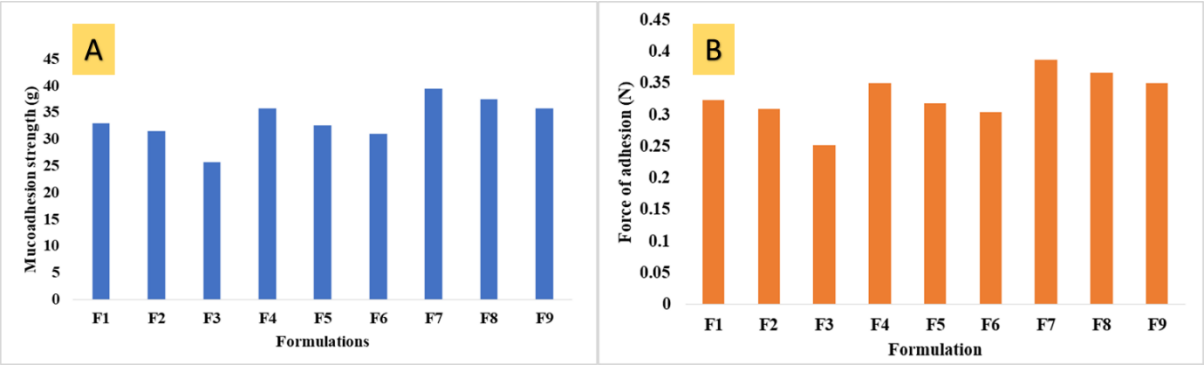

Fig. 6: Mucoadhesive strength of linagliptin buccal film formulations (F1-F9).

4. DISCUSSION

The solubility assessment of linagliptin across different solvents is a critical starting point for drug formulation. It reveals the challenges of dissolving linagliptin in water and phosphate buffer at pH 6.8, commonly used as dissolution media [37, 38]. The low solubility in these aqueous solutions suggests that formulating this drug for oral administration or other applications may require specific strategies to enhance its solubility. On the other hand, linagliptin's high solubility in methanol and its solubility in ethanol and 0.1 N HCl opens up possibilities for using these solvents in formulation

processes. Furthermore, the drug's solubility in phosphate buffer at pH 4.5 could be leveraged for designing formulations targeting specific pH environments in the body.The melting point of pure linagliptin, found to be 194±1.12°C, provides valuable information about its thermal stability[39]. This is crucial during drug manufacturing, as it ensures that the drug can be handled and processed at appropriate temperatures without degradation. Additionally, knowing the drug's melting point is important for storage conditions, as it helps prevent the drug from undergoing undesirable changes during storage. The UV-visible spectrum analysis is an essential tool for quantitatively determining linagliptin using spectroscopic techniques. The maximum absorbance at 293 nm is a reference point for accurate and reliable measurements. This is especially significant in pharmaceutical analysis, where precise quantification of the drug is crucial for quality control and dosage accuracy[40].The standard calibration curve for linagliptin in methanol demonstrates a robust linear relationship between linagliptin concentration and absorbance, as indicated by the high r^2 value of 0.995. This strong correlation ensures that the data adheres closely to the Beer-Lambert law, which is fundamental in spectroscopy[41]. Moreover, the slope of the calibration curve confirms the consistent relationship between concentration and absorbance, making it suitable for precise quantitative analysis of linagliptin in methanol. This calibration curve's linearity is vital for analytical procedures, ensuring accurate and reliable drug concentration measurements. The FTIR spectra analysis provides critical information about the compatibility of linagliptin with excipients used in pharmaceutical formulations. The absence of significant shifts in characteristic peaks in the spectra indicates that the excipients do not induce chemical changes or interactions with the drug molecules[42]. This is essential for ensuring that the selected excipients maintains the drug's integrity and therapeutic properties throughout the formulation process and patient administration. Compatibility assessments like this are fundamental steps in pharmaceutical formulation to guarantee the safety and effectiveness of the final product. The evaluation of film properties, including thickness, weight variation, folding endurance, surface pH, and linagliptin content, underscores the quality and consistency of the formulations. The uniformity in film thickness indicates precision in the manufacturing process. Passing the weight variation test ensures that the average percentage deviation adheres to acceptable limits set by pharmacopoeial standards, ensuring quality and consistency in production [43]. The folding endurance values provide insights into the films' mechanical strength and flexibility, which are crucial for their practical application. Surface pH values within a close range of neutrality suggest that the formulated product is unlikely to irritate the oral cavity, making it suitable for buccal administration. Furthermore, the consistent drug content across all formulations assures the reliability of drug dosage, which is critical for the efficacy and safety of the buccal films. These comprehensive evaluations collectively ensure the quality and performance of the formulations in pharmaceutical applications [44]. The assessment of swelling characteristics across multiple formulations reveals how different polymers affect the behavior of buccal films over time. Notably, formulation F1, featuring HPMC K100 as the primary polymer, exhibited the most pronounced swelling behavior, with a swelling index of 125.5±1.53%. In contrast, formulation F3, utilizing eudragit RL100 as its primary polymer, displayed the lowest swelling index at 76.7±0.67%. These findings underscore the significant influence of polymer type on the swelling behavior of buccal films[45]. Such information is invaluable for tailoring buccal film formulations to achieve specific drug delivery objectives, considering the desired swelling characteristics. The linagliptin discharge studies conducted using the USP paddle method with phosphate buffer at pH 6.8 as the dissolution medium provides a critical understanding of how the formulated buccal films discharge the linagliptin over time[30]. Formulation F1, with HPMC K100 as a mucoadhesive polymer, exhibited the highest linagliptin discharge percentage of 80.6659%. In contrast, Formulation F7, containing a combination of HPMC K100, HPMC E5LV, and eudragit RL 100, displayed a sustained linagliptin discharge profile, with a drug discharge percentage of 59.32% at the end of 8 h. This sustained discharge profile distinguishes it from the other formulations and has potential applications in controlled drug delivery. Various kinetic models were applied to the *in-vitro* discharge data to understand the linagliptin discharge patterns further. Formulations F2, F3, F4, F6, and F9 exhibited zero-order discharge kinetics, indicating a consistent rate of linagliptin discharge over time. Formulation F5 followed first-order discharge kinetics, where the rate of linagliptin discharge decreased exponentially[46]. Formulations F1, F7, and F8 conformed to the Korsemeyer-Peppas model, with F7 exhibiting non-Fickian transport, implying a complex discharge mechanism beyond simple diffusion [47]. F1 and F8 demonstrated super case IItransport within the Korsemeyer-Peppas model. These findings provide valuable insights into the linagliptin discharge mechanisms of these formulations, guiding the development and optimization of linagliptin delivery systems. Assessing mucoadhesive strength in buccal films is crucial for their practical use in linagliptin delivery. Formulation F7, which combined HPMC K100 and Sodium alginate as mucoadhesive polymers, displayed the highest mucoadhesive strength, while F3 showed the lowest strength due to its limited swelling behavior[48]. These findings underscore the importance of polymer selection and their combinations in designing effective mucoadhesive buccal films, with F7 showcasing strong potential. These comprehensive studies contribute to a thorough understanding of linagliptin's properties, formulation, and potential pharmaceutical applications. The insights gained from these assessments guide the development of drug delivery systems, ensuring the quality, efficacy, and safety of pharmaceutical products. Further research and refinement in these areas promise advancements in drug delivery and therapeutic options for patients.

5. CONCLUSION

The study demonstrates the development of buccal films containing linagliptin, utilizing a combination of mucoadhesive polymers and a penetration enhancer, Tween 80. The formulations exhibited physicochemical properties, including adequate swelling, neutral surface pH, and compatibility between the drug and excipients. Formulation F7, combined with HPMC K100, HPMC E5LV, and eudragit RL100, displayed exceptional mucoadhesive strength, sustained drug discharge, and enhanced bioavailability, making it a promising candidate for Diabetes mellitus treatment. The diverse discharge kinetics observed in various formulations offer flexibility in tailoring drug discharge patterns.

6. AUTHORS CONTRIBUTION STATEMENT

Suprith D contributed to the conception, study design, and data analysis. K. Mahalingan supervised the work. P. Kumar contributed to the literature search, P. Dhamala checked the grammar and punctuation, and Hindustan Abdul Ahad drafted the manuscript. All the authors read and approved the final manuscript.

7. ABBREVIATIONS

HPMC-Hydroxy Propyl Methyl Cellulose; pH-Negative logarithm of hydrogen ion concentration; FTIR-Fortier Transform Infra-red spectroscopy; DM-Diabetes Mellitus; T1DM- Type 1 Diabetes Mellitus; T2DM- Type 2 Diabetes Mellitus; DPP-dipeptidyl peptidase inhibitors; RH- Relative humidity; PBS- Phosphate Buffer Solution; µg-microgram; ml-milliliter; UV-Ultra violet; mg- milligram; nm- nanometer; min- minutes; h- hours, %- percent; rpm- rotations per minute; g- grams; °C- degree Celsius.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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