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FORMULATION AND EVALUATION OF LINAGLIPTIN BUCCAL ADHESIVE TABLET FOR TYPE-II DIABETES

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ABSTRACT: Last few decades, the remarkable advancement in the drug delivery system has been done; the oral route remains the importance and picks up the safest route of drug delivery. Regardless of striking advancements in the oral route medication, the current study focused on the formulation of a linagliptin buccal adhesive tablet. Formulated tablets are containing linagliptin as an active drug with a combination of different polymers such as carbopol (CP), eudragit RL-100 (EU), sodium alginate (SA) at different compositions with an impermeable backing layer of ethyl cellulose (EC). The formulation was carried out by direct compression, and tablets were evaluated by different parameters for pre and post-compression study. The post-compression evaluation parameters are weight variation test, hardness, thickness, friability, drug content, swelling index, pH followed by *in-vitro* drug release studies at pH 6.8. Compatibility study between drug-polymerr interactions was investigated by FTIR studies. Formulation F6, which contains a high concentration of EU provides maximum prolong the release of linagliptin among all other formulations. Formulation F6 has shown better control of drug release 100% at 12 h. Obtained results concluded that the composition of hydrophobic and hydrophilic polymers at different ratios could be a good matrix for controlling the release rate of linagliptin buccal adhesive tablet in a prolong manner and bypass hepatic metabolism to improve bioavailability of linagliptin. *In-vitro* release kinetic study carried out for all the formulations and followed diffusion and erosion mechanism.

INTRODUCTION: Oral route drug delivery system having its significance, ease in the intake, and very convenient for the clinician. Many drugs which are prohibited by the oral route because of enzymatic degradation in GIT, irritation or pain for stomach and low absorption. Buccal route having a better advantage over the oral route and avoid hepatic first-pass metabolism and improve the bioavailability of the drug [1, 2].

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Due to the better absorption, rapid onset of action, and easy accessibility of the buccal route considered as the potential site for drug administration. The buccal route is more advantageous as compared to inhalation, transdermal route, parenteral route *etc*. [3]. Buccal adhesion generally adhere the dosage to the buccal mucosal layer and absorb the drug in presence of saliva to the systemic circulation. In the modern era, this is the new innovative approach where the attachment of a drug could be possible with a suitable carrier. Buccal adhesive tablets have a wide scope of application for both systemic and local applications [4]. The intimate contact of the tablet to the membrane due to its bioadhesive property imparts a bond between biological surface

or between synthetic and biological surface helps in penetrating the drug to the tissue or mucous membrane [5, 6]. In bioadhesive formulations, the polymer itself containing adhesive property, stick to the site of mucus membrane and release the medicament in a steady manner without any disturbances [7, 8].

Ideal polymers for buccal adhesive drug delivery should have high molecular weight, chemically inert in nature, high concentrated grade, hydrogen bonding, and hydration property [9]. In our study, we have used a combination of hydrophilic and hydrophobic polymers with hydrogel property to prolong the release rate of active drug. The bio-adhesive hydrophilic polymers are water-loving in nature. The dry form of this polymer, when applied to the buccal cavity attracts water from the saliva and forms a strong interaction with water molecule. The polymers became more viscous due to the hydration and increase retention time over mucus membrane [10] and prolong the release of the drug.

Linagliptin is a dipeptidyl peptidase-4 inhibitor, developed by Boehringer ingelheim for type-II diabetes treatment. It comes under biopharma-ceutical classification system (BCS)-III and shows high solubility and low permeability. The bioavailability of the drug also very low 30%. Type II diabetes mellitus is a chronic metabolic disorder, and its occurrence spread throughout the world. The significance of the disease gradually increasing due to the lack of advanced treatment, particularly in poorly undeveloped countries. World Health Organization (WHO) reports revealed that India is one of the leading countries having an increasing number of patients of type II diabetes [11].

The aim of the current research was to formulate and evaluate of linagliptin buccal adhesive tablet by incorporating different polymers at a different ratio to control the release rate of active drug. The pre-formulation study has been performed between active drug and a different ration of individual polymers and excipients. Drug and polymer compatibility study performed by FTIR analysis. Post-compression study for all formulations has been carried out, followed by an *in-vitro* drug release study and release kinetic study.

MATERIALS AND METHODS:

Materials: Linagliptin, carbopol, and eudragit RL-100 were purchased from Sigma Aldrich, India. Sodium alginate and PVP K-30 analytical research-grade were purchased from the Nice laboratory, India. Similarly, ethylcellulose, talc, magnesium stearate, and remaining excipients were of analytical research-grade and used as received from Divya Chemicals, India.

Formulation of Linagliptin Buccal Adhesive Tablets: The tablets were prepared by direct compression method, using different combinations of polymers **Table 1**. The ingredients of the core layer of different combinations were accurately weighed and mixed in a mortar and pestle to obtain a homogeneous mixture. The obtained mixture was then passed through 60 µm mesh. Hydraulic press was used at a pressure of 15 psig using flat faced punch of 9 mm diameter for compression [12, 13, 14, 15, 16]. The buccal adhesive tablets were prepared using CP, EU, SA polymers as individually and at different compositions shown in **Table 1**.

The effect of individual polymers and their compositions at different ratios has been studied considering the % of drug release. Ethylcellulose used as a backing layer, which works as an impermeable membrane from all sides except one.

TABLE 1: FORMULATION OF LINAGLIPTIN CONTAINING BUCCAL MUCOADHESIVE TABLET (%)

Drug		CP	EU-RL-100	SA	PVP	Talc	MS (%)	EC
Batch no.	(%)	(%)	(%)	(%)	K-30	(%)		(Backing layer)
F1	5	30	-	-	15	5	5	40
F2	5		30	-	15	5	5	40
F3	5			30	15	5	5	40
F4	5	10	10	10	15	5	5	40
F5	5	20	5	5	15	5	5	40
F6	5	5	20	5	15	5	5	40
F7	5	5	5	20	15	5	5	40

Pre-Compression Study:

Bulk Density: Bulk density is the ratio of the mass by the volume of an untapped powder sample. The bulk density is measured in g/ml. The bulk density depends on both the density of the powder particles and on the arrangement of the powder particles.

The bulk density influence preparation, storage of the sample. The mathematical representation is given below.

Bulk density = Weight of the drug / Bulk volume

Tapped Density: In tapped density, the bulk powder mechanically tapped in a graduated cylinder until the change in volume is observed. Here the tapped density is calculated as mass divided by the final volume of the powder.

Tapped density = Weight of the granules / Tapped volume

Angle of Repose: It gives an idea of the flowability of a powder or a bulk solid. There is some factor which responsible for the flowability of powders such as particle size, size distribution, shape, surface area, *etc*. Flowability of the powder depending on the different environment and can be changed easily. The angle of repose was calculated by the following formula.

$$\theta = \tan^{-1} h/r$$

Where, θ = angle of repose, h = height of the formed cone. r = radius of the circular base on the formed cone.

Carr's Index: It is one of the most important parameters to characterize the nature of powders and granules.

Carr's index (%) = Tapped density - Bulk density / Tapped density × 100 Hausner's ratio

It is an important character to determine the flow property of powder and granules. This can be calculated by the following formula.

Hausner's ratio = Tapped density / Bulk density

Values less than 1.25 indicate good flow, and greater than 1.25 indicates poor flow.

Weight Variation: Twenty tablets were selected randomly from each formulation. Individually weighed tablets and then collectively, the average weight of the tablets was calculated, then weight variation was calculated.

Hardness: The hardness of the tablets was determined using a Monsanto hardness tester. Hardness is one of the important factors in having a significant role in transportation. The hardness of ten tablets was measured using Pfizer hardness tester. It is expressed in kg/cm^2.

Thickness: The thickness and diameter of the prepared tablets were evaluated with the help of Vernier calipers and screw gauge.

Friability: The tablets were tested for friability testing using Roche friabilator. For this test, twenty tablets from each formulation have been selected. All tablets weighed properly and subjected to the friabilator plastic chamber, revolving at 25 rpm for 4 min, and the tablets were then dusted and reweighed. The friability was then calculated using the formula.

% loss = Initial wt. of tablets - Final wt. of tablets × 100 / Initial wt. of tablets

Drug Content Estimation: Twenty tablets were crushed into powder, the quantity of powder equivalent to average weight of formulation was weighed and taken in a volumetric flask dissolved in 15 ml of methanol, the solution is filtered through Whatman filter paper, from this 1 ml of solution is withdrawn and after suitable dilution analyzed by UV spectrophotometer at 296 nm.

% Swelling Study: Buccal tablets were weighed individually (W1) and placed in buffer solution pH 6.8 in a petridish at room temperature. The tablets were removed from the petridish at regular intervals of time and excess water removed from the surface carefully using filter paper. The swollen tablet was then reweighed (W_2), and the swelling index was calculated using following formula [17].

% SI = Final weight (W_2) – Initial weight (W_1) × 100 / Initial weight (W_1)

Surface pH: Surface pH studies were carried out in order to find out any side effects or any irritation. This has to be due to the alkaline or acidic pH, which could irritate buccal mucosa.

***In-vitro* Drug Release:** The USP type II dissolution apparatus was used to find out the % of drug release at a regular interval of time from the buccal cavity. The dissolution medium consists of 900 ml of phosphate buffer pH 6.8. The temperature was maintained at 37 ± 0.5 °C, at a revolution per minute 100 rpm. The impermeable layer or the backing layer of the tablet was attached

to a glass slide with instant adhesive. The slide was put in the bottom of the dissolution vessel so that the tablet surface stayed on the upper side of the slide. Dissolution was carried out, and a regular interval of time 5 ml of sample is pipetted and the same amount of fresh buffer medium replaced in the basket. The collected samples were analyzed under UV Spectrophotometer at 296 nm with suitable dilution. Phosphate buffer pH 6.8 chosen as a blank for the detection of absorbance [13, 15] Pharmacokinetic modelings of drug dissolution profile

In order to examine the release mechanism of the drug from the tablets, the *in-vitro* drug release data of linagliptin was carried out for all the formulations with the following release models mentioned below [18, 19, 20].

- Zero-order: $M_t = M_o \pm K_o t$
- First-order: $\ln M_t = \ln M_o \pm K_1 t$
- Higuchi model: $M_t = K_H \sqrt{t}$
- Korsmeyer–Peppas model: Mt/Mo = Kktn

Where M_t is the amount of drug dissolved at time t, Mo the initial amount of drug, K_1 is the first-order release constant, K_0 the zero-order release constant, K_H the Higuchi rate constant, K_k the Korsmeyer–Peppas model release constant and n is the diffusional release exponent indicative of the operating release mechanism. The correlation coefficient (R^2) value was used as an indicator of the best fitting for each of the models considered.

RESULTS AND DISCUSSION:

Pre-formulation Study for all Formulations: Bulk density and tapped density mainly depends on the nature of the compound and its size. These properties of a compound may vary due to the crystallization, milling or in the formulation. It also provides true knowledge of the size of the final dosage form. The density of the solid also affects their compression and flow property after final production. The Precompression results of linagliptin have been reported in **Table 2**. The bulk density of the formulations was found to be 0.299 to 0.455 gm/ml, tapped density shows the range between 0.27 to 0.46 gm/ml, angle of repose between the range of 24.01 to 30.21, carr's index within the range of 13.93 to 22.11 and Hauser's ratio value lies between 1.02 to 1.13. Obtained results were within limits and observed excellent flow properties.

TABLE 2: PRE-FORMULATION STUDY FOR LINAGLIPTIN FORMULATIONS (F1 TO F7)

Pre-compression Parameters	F1	F2	F3	F4	F5	F6	F7
Bulk density	0.299±0.01	0.321±0.08	0.343±0.11	0.371±1.02	0.402±0.07	0.441±1.24	0.455±0.29
Tapped density	0.39±0.73	0.27±1.52	0.45±0.91	0.29±1.72	0.43±0.83	0.41±0.51	0.46±0.31
Angle of repose	27.21±0.1	24.01±0.72	29.8±0.09	25.32±0.11	27.09±0.84	24.01±0.02	30.21±0.05
Carr's index	17.33±0.76	22.11±0.03	18.07±1.99	15.71±1.09	14.03±1.71	13.93±0.04	16.01±0.02
Hausner's ratio	1.13±0.06	1.11±0.01	1.09±0.02	1.13±0.01	1.02±0.03	1.03±0.02	1.08±0.03

FTIR Study: Drug compatibility is a very important factor in maintaining the safety, effectiveness, and physical appearance of the active drug. The drug-polymer mixtures were taken, and their compatibility was performed.

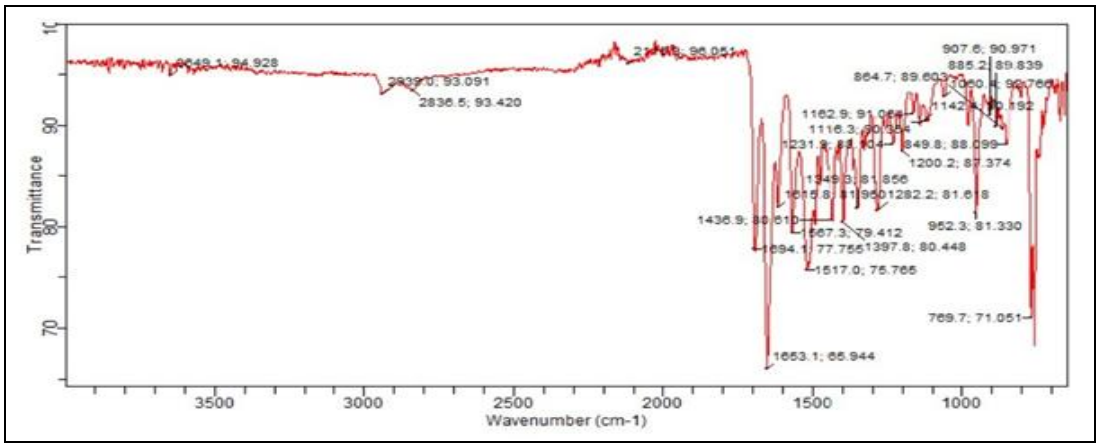

FIG. 1: FTIR SPECTRA OF PURE LINAGLIPTIN

The FTIR spectrum of individual polymers (Carbopol, eudragit, and sodium alginate), drug (Linagliptin), and drug combined with individual polymers have shown in **Fig. 1** to **7**. The obtained result reveals that individual polymers and linagliptin shows different spectra that are different from each other.

Whenever the drug-polymer combination has been taken into consideration, it is observed that there is no shifting or change in the spectra of linagliptin. The FTIR spectra confirmed that there is no interaction between drug-polymer and reported polymers that are compatible with the active drug.

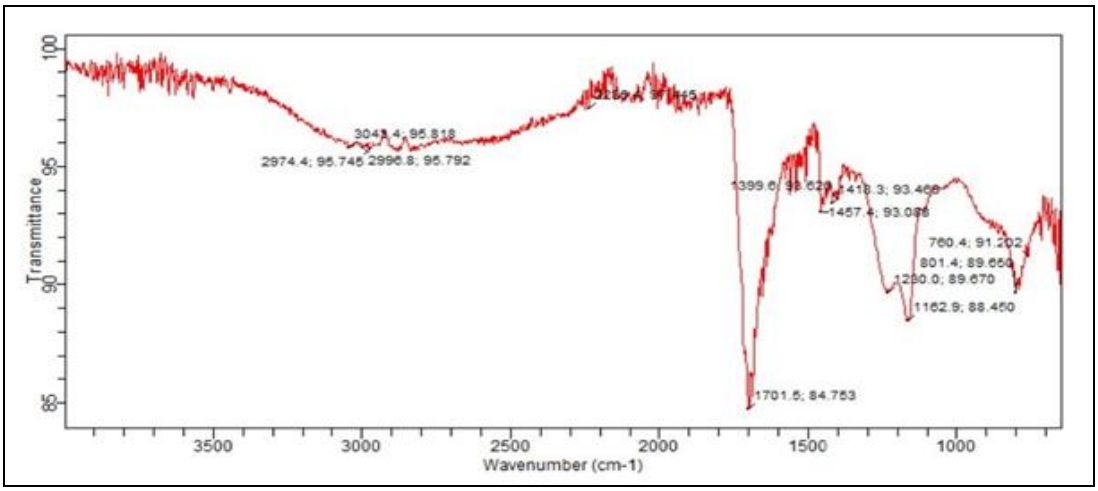

FIG. 2: FTIR SPECTRA OF CARBOPOL

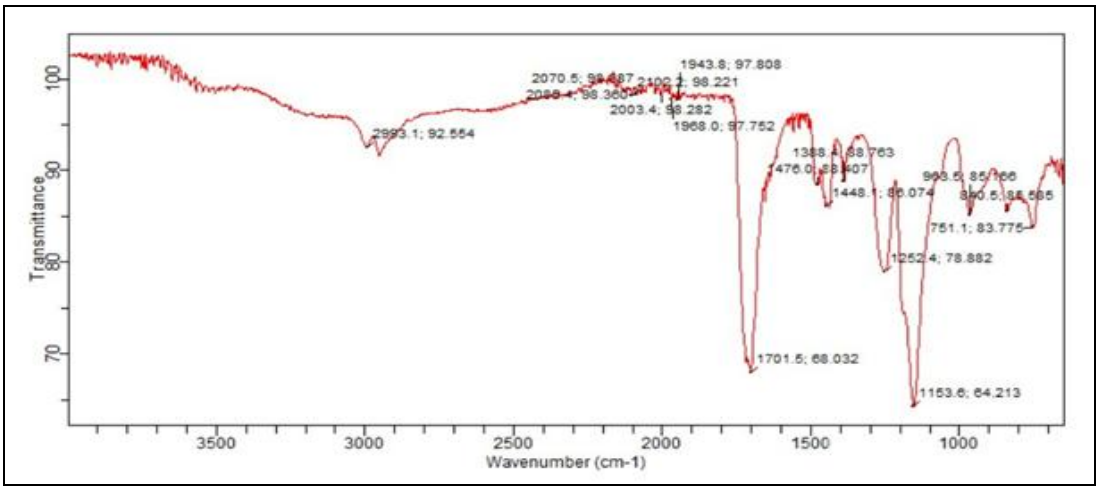

FIG. 3: FTIR SPECTRA OF EUDRAGIT RL-100

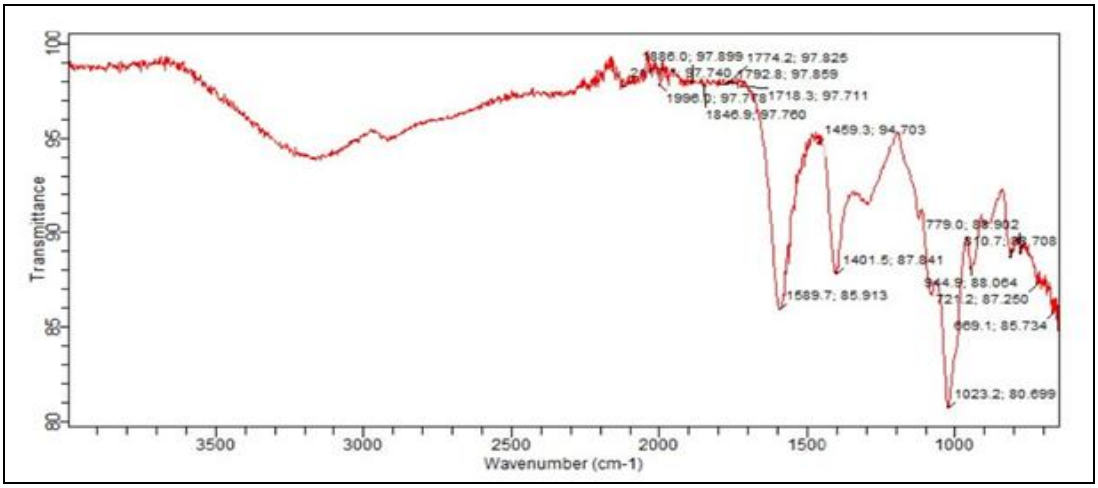

FIG. 4: FTIR SPECTRA OF SODIUM ALGINATE

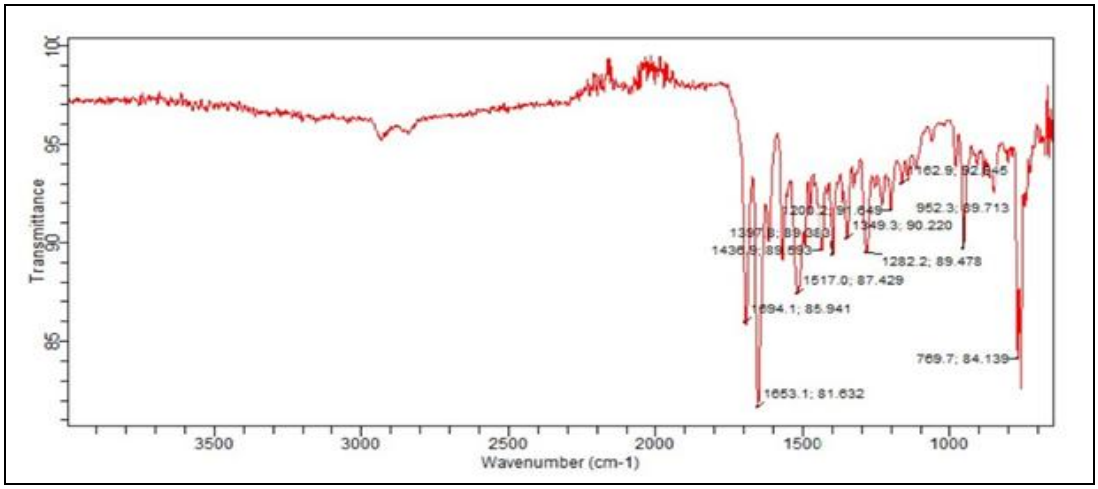

FIG. 5: FTIR SPECTRA OF LINAGLIPTIN AND CARBOPOL

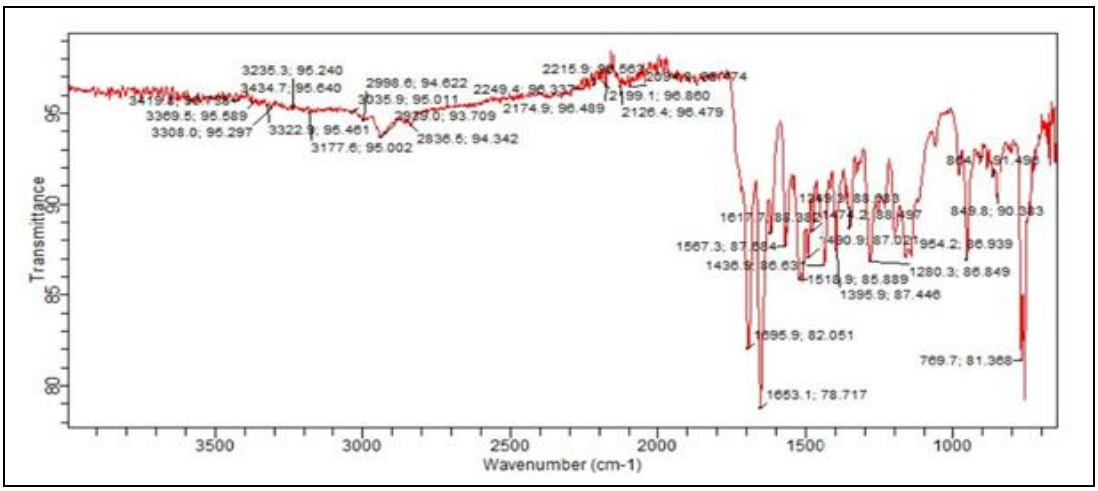

FIG. 6: FTIR SPECTRA OF LINAGLIPTIN AND EUDRAGIT

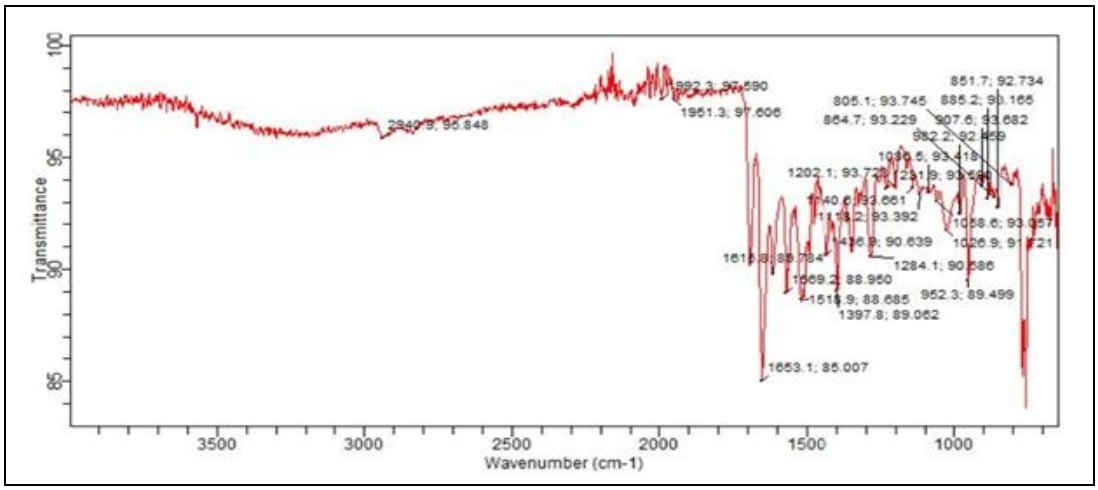

FIG. 7: FTIR SPECTRA OF LINAGLIPTIN AND SODIUM ALGINATE

Post-compression Study of Linagliptin Buccal Tablets: Linagliptin buccal adhesive tablets (Formulation F1-F7) were evaluated for their physicochemical properties that play a vital role in the drug release pattern. A comparison of physico-chemical properties of all the formulations is listed in **Table 3**. The weight variation was found to be within the limit of ± 7%. The average weight for all formulations was found to be in the range of 148 to 152 mg. The measurement of thickness has been carried out by Vernier caliper. Thickness is an important parameter which helps in ease of

swallowing of tablets. Obtained results concluded that uniform thickness has been observed for all formulations and found within the range of 2.28 to 3.31 mm. The formulated tablets passed through the hardness and friability tests as per the standard limits, the hardness ranging from 5.61 to 6.91, and the percentage of friability obtained below 1%. The friability and hardness of the tablet are directly implicated to the strength of the tablet and an important factor in controlling the damage during the transportation and handling of the tablet. Similarly, drug content%, swelling index %, and surface pH for all the formulation lies in the range between 98 to 100.5%, 78 to 98%, and 5.99 to 6.82, respectively. Eudragit based formulation has shown less swelling as compared to carbopol and sodium alginate. Obtained results confirm that evaluation parameters are within the limit as per Indian pharmacopeia for all the formulations.

TABLE 3: POST-COMPRESSION PARAMETERS FOR LINAGLIPTIN BUCCAL ADHESIVE TABLETS FORMULATION F1-F7

Formulation	Tablet Weight variation (mg)	Tablet Hardness (kg/cm^2)	Tablet Thickness (mm)	Tablet Friability (%)	Drug content (%)	% Swelling	Surface pH
F1	148.33±2.11	6.02±0.17	2.97±1.03	0.37±0.51	99.09±0.15	98	6.71±0.08
F2	150.11±1.06	6.91±0.04	3.31±0.93	0.3±0.09	98.01±0.06	78	5.91±0.03
F3	149.03±1.7	5.61±0.01	2.28±0.37	0.58±0.37	100.3±0.91	97	6.82±0.11
F4	151.09±1.91	5.89±1.02	2.96±0.09	0.43±0.09	99.87±0.93	89	5.99±0.01
F5	152.13±0.01	5.61±1.03	3.31±0.01	0.81±0.03	99.92±0.73	95	6.71±0.9
F6	150.11±1.37	5.91±0.97	2.99± 0.48	0.39±0.08	98.85±0.81	87	6.53±0.06
F7	150.92±2.02	6.09±0.3	3.01±0.31	0.76±0.06	100.5±0.93	94	6.81±0.01

Results are expressed as of mean ±SD (n=3)

***In-vitro* Drug Release:** The dissolution was carried out triplicate by utilizing the diffusion medium Phosphate buffer with the pH 6.8. The percentage of drug release for all linagliptin buccal adhesive formulations F1 to F7 ranged from 95% to 100.63% at the end of 12 h. Maximum drug release in a controlled manner was observed in the formulation F6 after 12 h. The reason for maximum release may be due to the combination of different polymers at different concentration and the viscosity nature of polymers. Eudragit RL-100 as a hydrophobic polymer, prolongs the release rate of the linagliptin up to 12 h. High viscosity nature of carbopol with its gelling nature control the release rate of linagliptin whereas sodium alginate as a swelling polymer creates pores in the polymer matrix and release linagliptin from the core of the buccal tablet in a steady manner. Ethylcellulose used as a baking layer and considered an impermeable layer to stop the release of the drug. Used polymers played a significant role in the preparation of buccal adhesive tablet by controlling the release rate of linagliptin and provide a steady plasma drug concentration. Drug release % were calculated for linagliptin buccal adhesive tablet formulations F1 to F7 shown in **Table 4** and **Fig. 8**.

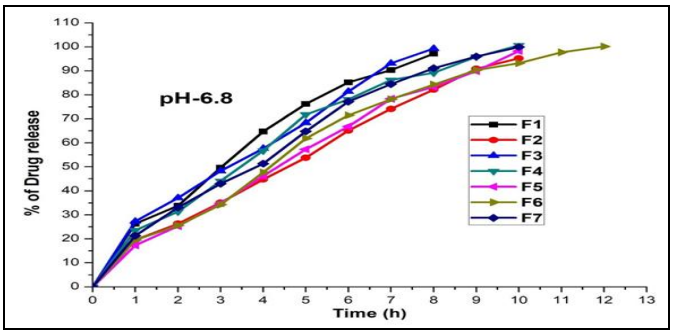

FIG. 8: *IN-VITRO* DRUG RELEASE OF LINAGLIPTIN BUCCAL ADHESIVE TABLET (FORMULATIONS F1-F7)

TABLE 4: *IN-VITRO* DISSOLUTION PROFILE FOR LINAGLIPTIN BUCCAL ADHESIVE TABLET FORMULATIONS F1- F7

Formulation	60 min (1h)	120 min (2h)	180 min (3h)	240 min (4h)	300 min (5h)	360 min (6h)	420 min (7h)	480 min (8h)	540 min (9h)	600 min (10h)	660 min (11h)	720 min (12h)
F1	26.33	33.81	49.71	64.71	76.22	85.18	90.33	97.19	-	-	-	-
F2	19.56	26.34	35.12	44.77	53.82	65.12	74.17	82.21	90.87	95.22	95.02	-
F3	27.31	37.11	48.32	57.68	68.35	81.39	93.12	99.32	-	-	-	-
F4	23.56	31.34	44.12	56.77	71.82	78.12	86.17	89.21	95.87	100.63	-	-
F5	17.32	25.34	34.81	46.21	57.32	66.81	78.38	83.31	89.91	98.29		
F6	19.45	25.61	34.27	47.71	61.87	71.52	78.22	84.32	90.31	93.21	97.73	100.2
F7	21.31	33.09	42.98	51.37	64.8	77.22	84.53	91.09	96.01	99.93	-	-

Pharmacokinetic Modeling of Drug Dissolution Profile: Keeping in mind the end goal to decide the correct system of medication discharge from the formulation, the *in-vitro* dissolution studies were assessed by zero-order, first-order, Higuchi, and Peppa's equations. The standard of picking the most proper model was in accordance with the highest R^2 value as the best fit. The results are shown in **Table 5**. Drug release is both diffusions, and erosion-controlled mechanism observed in all formulations F1 to F7.

TABLE 5: RELEASE KINETICS OF LINAGLIPTIN BUCCAL ADHESIVE TABLET (FORMULATIONS F1-F7)

Formulation	Zero-order plots	First-order plots	Higuchi plots	Korsmeyer-peppas plots r^2	Diffusional exponent (n)	Order of release
F1	0.998	0.879	0.887	0.999	0.9095	Diffusion & Erosion
F2	0.782	0.897	0.988	0.989	0.927	Diffusion & Erosion
F3	0.887	0.983	0.991	0.966		Diffusion
F4	0.902	0.863	0.927	0.998	0.979	Diffusion & Erosion
F5	0.911	0.917	0.918	0.997	0.972	Diffusion & Erosion
F6	0.952	0.956	0.953	0.985	0.97	Diffusion & Erosion
F7	0.917	0.954	0.918	0.933	0.988	Diffusion & Erosion

CONCLUSION: The current research focused on the development of linagliptin buccal adhesive tablets incorporating by different types of polymers at different composition ratios. Polymers are of hydrophilic and hydrophobic in nature, and containing gelling property is useful for control the release rate and linagliptin. Pre and post-compression evaluation parameter value shows within the limit of IP. The *in-vitro* dissolution study conducted for all the formulations (F1-F7) and found that CP and SA as an individual polymer have shown complete drug release of linagliptin, whereas EU shows incomplete release. In formulation F6, which contains CP: EU: SA in the ratio of 5:20:5 respectively has shown better control in the release rate of linagliptin buccal adhesive tablet 100% at 12 h. A combination of the hydrophobic and hydrophilic polymer could be a good carrier for controlling the release rate of the buccal adhesive tablet. The release kinetics for all the formulations has followed diffusion and erosion mechanism.

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CONFLICTS OF INTEREST: Nil

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