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Research Article

Formulation And Evaluation Of Sustained Release Buccoadhesive Wafer Of Levodopa For The Treatment Of Parkinsonism

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ABSTRACT

The aim of the present study is to formulate and evaluate the sustained release buccoadhesive wafer of Levodopa for the treatment of Parkinsonism. Levodopa is used as an antiparkinsonian drug. To reduce the side effects and enhance the bioavailability the buccoadhesive wafers are made. They are prepared by solvent casting method using Chitosan lactate (Mucoadhesive polymer), PVP K-30 (Hydrophilic Polymer), PEG 400(Plasticizer) and aqueous acetic acid (Solvent). The prepared buccoadhesive wafer was evaluated and it was found that the wafer had good physical appearance, optimum thickness. The pH of the wafer was found to be in the range of 6.00 ± 0.09 to 6.90 ± 0.03. Tack test was found to be in the range of medium to excellent adhesion. The tensile strength was found to be in the range of 0.163±0.01 to 0.256±0.06N/cm2. The folding endurance was found to be in the range of 209±1.52 to 242±3.46. The swelling properties was found to be in the range of 89.2- 96%. Drug content was found to be in the range of 71.9 ± 0.23 to 93.6 ± 0.16%, F5 showed highest drug content 97.6 ± 0.16%. The in vitro dissolution study of the prepared wafer (F5) exhibited 96.78% ± 0.42 % and in vitro drug diffusion study was found to be 95.61 ± 0.25 % indicating that better diffusion of the drug because of the presence of PVP K-30. It was found that in vitro drug release of buccoadhesive wafer was best explained by Peppas kinetic model as plot shows highest linearity. The coefficient ((R2) was found to be 0.9816 with the N value as 0.8015 indicating that the drug release was non fickian diffusion. Based on the results obtained from the above studies, it was concluded that the buccoadhesive drug delivery system could be used to provide better therapeutic effects for Parkinsonism.

INTRODUCTION

Buccal delivery of drugs is one of the alternatives to the oral route of drug administration, mainly to those drugs that undergo first-pass metabolism and is used for increasing the bioavailability by reducing dosing frequency to mouth plasma peak levels, which results in minimizing the adverse effects [1].

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Additionally, the buccal route offers potential routes for the absorption of hydrophilic and unstable proteins, oligonucleotides, complex, high-molecular-weight polysaccharides and conventional tiny drug molecules [2].

It is also affordable and effective in geriatric and pediatric patients. In addition, wafers have improved patient compliance due to their small size and reduced thickness, compared to lozenges and tablets [3].

Over the past ten years, the use of oral cavity membranes as the location for drug administration has increased. It is known that the therapeutic compounds which are absorbed from the oral mucosa offer the direct entry of the drug into the bloodstream, thereby avoiding first-pass hepatic metabolism and gastrointestinal drug degradation, both of which are connected to perioral administration [4]. In terms of comfort and flexibility, wafers might be preferred to buccal tablets. Wafers will have direct contact the systemic circulation via the internal jugular vein, resulting in excellent bioavailability. Additionally, these dosage forms offer greater patient compliance, are self-administrable, and are pharmacoeconomic [4]. The delivery system consists of a postage stamp-sized thin film, which is placed on the patient's tongue or mucosal tissue, where it immediately hydrates by absorbing saliva; the film is then quickly dissolved and disintegrated to release the drug for oral mucosal absorption. This fast-dissolving activity is mainly caused by the film's substantial surface area, which quickly becomes wet when exposed to the moist oral environment [5]. Levodopa has a beneficial impact that is unique to PD and is more effective than any other medication used alone. It is not active on its own, but it is the transmitter DA's immediate predecessor. An oral dosage is decarboxylated in peripheral tissues (mostly the gut and liver) to a greater than 95% extent. The resulting DA is further metabolized, and the leftover substance affects the heart, blood vessels, other peripheral organs, and CTZ (although being present in the brain, namely the floor of the IV ventricle, it is not protected by the blood brain barrier). Levodopa that has been supplied enters the brain at a rate of 1% to 2%, where it is absorbed by the remaining dopaminergic neurons and converted to DA, which is then stored and released as a transmitter.

Levodopa was administered to parkinsonian patients until they passed away, and their brains had higher levels of DA than those who weren't. Furthermore, the DA levels of the patients who responded well were higher than those of the patients who responded poorly[6].

Levodopa is a model drug since it is only marginally soluble in water. Levodopa is a prodrug of dopamine and has anti-parkinsonian properties. For around five years, a traditional oral Dopa drug effectively manages the progression of Parkinson's disease. Its bioavailability is 30% [7] and it has a biological half-life of 0.75 to 1.5 hours. The dosage is between 125 and 500 mg[8].

MATERIALS AND METHODS

Levodopa was purchased from Yarrow Chem, Mumbai, India. Chitosan Lactate, Poly Vinyl Pyrrolidone K-30, Citric Acid, Vanillin was purchased from Loba chemie Pvt. Ltd, Mumbai. Poly Ethylene Glycol- 400, Glacial Acetic Acid, Aspartame was purchased from Hi- Media Laboratory Pvt. Ltd, Mumbai and ethanol was purchased from KSBCL. All other chemicals and reagents were analytical and pharmacopeial grade.

Preformulation studies

1. **Organoleptic properties9**

The color and odor of the levodopa will be observed and recorded.

2. **Determination of Melting point10**

- Melting point of drug sample was determined by using melting point apparatus.
- A few quantity of drug sample was taken and placed in a thin walled capillary tube.

- The tube was approximately 10-12 cm in length with 1mm in diameter and closed at one end.
- The capillary which contains sample was placed in melting point apparatus and heated and when drug sample was melted the melting point of sample powder was noted.

3. Solubility studies10

- It was determined by dissolving drug in 0.1M HCl, Phosphate buffer pH 6.8, aqueous acetic acid.
- The solubility study was conducted by taking excess quantity of the drug in 10ml of solvent.
- Then the sample were kept in magnetic stirrer and agitated for 24 hrs at 37±0.5˚C.
- The sample were filtered and diluted suitably with solvent.
- The samples were analyzed spectrophotometrically.

1. Drug-Excipient Compatibility Study by FTIR11

FT-IR spectroscopy was employed to ascertain the compatibility between Levodopa and other excipients. The FT-TR spectra of Levodopa, Chitosan lactate, PVP K-30 and excipients mixture were carried out to investigate the changes in chemical composition of drug after combining with excipients. The wave number of a characteristic peak of the physical mixture were compared with the pure sample and interpreted.

Procedure: The pure drug, mixture of drug and excipients were prepared and scanned from 4000 - 400 cm^{-1} in FTIR spectrophotometer. The IR spectrum of pure drug, mixture of drug and excipients were recorded by FTIR spectrometer.

2. Determination of absorption maxima (λ max) of the drug

Stock solution of the drug was prepared using 0.1M HCl and phosphate buffer solution (PBS) of pH 6.8 to give a concentration of 1000µg/ml. 10ml from above solution was diluted up to 100ml in a volumetric flask to give concentration of 100µg/ml. Wavelength was scan from 400-200 nm was done to find the absorbance maxima.

Method

Solvent casting technique

Sufficient quantity of polymer was dissolved in a suitable solvent under magnetic stirrer for 24 hr. Resulting viscous solution is filtered through nylon mesh to remove the suspended particles. The drug and water-soluble hydrophilic polymer is added into the polymeric solution under constant stirring. Plasticizer, flavoring agent, sweetening agent is added into the solution under constant temperature to ensure a clear solution. Then the solution is poured to the glass petri dish and allowed to dry at 37ºC till a complete, flexible layer is formed. Dried wafers is cut into desired shape and size[12].

Preparation of buccoadhesive wafer

Buccoadhesive wafer of Levodopa was prepared by a solvent casting technique using mucoadhesive polymer as per the formula given in table 1. Initially, the polymer Chitosan lactate was weighed accurately and dissolved in 10ml of aqueous acetic acid. The beaker containing polymers was stirred for 24hr on the magnetic stirrer to get the viscous solution. Drug and plasticizer and excipients were added to the polymeric solution with continuous stirring. Then the whole solution was poured into the pre – lubricated glass petri- plate and left for 12hrs. The wafer was removed carefully after drying and cut into 2×2 cm^2. The film was stored in butter paper covered with aluminum foil and stored at room temperature.

Table No. 01: Formulation chart of Sustained release buccoadhesive wafer

Formulation code	Drug (mg)	Chitosan lactate (mg)	PVP K-30(mg)	PEG-400 (ml)	Aqueous acetic acid (ml)	Aspartame (mg)	Citric acid (mg)	Vanillin (mg)
F1	40	100	10	0.5	10	12	0.2	5
F2	40	100	10	1	10	12	0.2	5
F3	40	100	20	0.5	10	12	0.2	5
F4	40	100	20	1	10	12	0.2	5
F5	40	100	30	0.5	10	12	0.2	5
F6	40	100	30	1	10	12	0.2	5

Calculation

Calculation of the amount of drug for one cast wafer

Internal diameter of the Petri dish = 9.2cm

Radius of the Petri dish = 4.6 cm

Internal surface area = 3.14 ×21.16

= 66.44 cm^2 Surface area of film

2 cm^2 contains 40 mg of Levodopa.

66.44 cm^2 contains = 664.4 mg of Levodopa.

Evaluation of Buccoadhesive Wafers

1. Color[13]

Color and transparency of each wafer is inspected visually.

2. Thickness[14]

The thickness of wafer can be measured by micrometer screw gauge.

3. Weight variation[14]

Weight variation is used to measure the reproducibility of the wafer production process.

Two square inch wafer was cut at five different places in the cast film. The weight of each film/ strip was taken and the weight variation was calculated.

$$\%\ Weight\ variation = \frac{Weight\ of\ each\ wafer\ strip - Average\ weight\ of\ wafer\ strip}{Average\ weight\ of\ wafer\ strip} \times 100\%$$

4. pH of wafer[15]

The wafer was placed in a petri dish and slightly moistened with 1 ml of distilled water and kept for 30 seconds. pH was measured by bringing the electrode in contact with the surface of the wafer and allowing it to stand for 1 minute. This study was performed three times for each wafer and the mean ± S.D was calculated.

5. Tack test[16,17]

Thumb tack test was performed to determine the tackiness by gently squeezing a thumb on a wafer for ~5 s and then quickly removing it. The parameters which represents the adhesive property of wafer is expressed by following value ranges: No adhesion (-), Poor adhesion (+), Medium adhesion (++) and Good/excellent adhesion (+++).

6. Tensile strength[18]

Mucoadhesive buccal wafer of size 2 cm^2 was placed between the clamp of the stand and clip through which the weighing pan was attached above the ground level in the air. For the measurement of tensile strength of the wafer the weights were added to the pan till the wafer breaks. The load causing the deformation and rupture of wafer was calculated by the following formula:

$$\text{Tensile strength} = \frac{Weight\ placed\ on\ pan\ (kg)}{Width\ of\ wafer(cm)} \times Thickness\ of\ wafer(cm)$$

Unit Kg/cm^2.

Multiply Kg/cm^2 by 0.098 (acceleration due to gravity) to get N/mm^2.

7. Folding Endurance19

Folding endurance is determined by repeated folding of the wafer at the same place till the strip breaks. The number of times the wafer is folded without breaking is computed as the folding endurance value.

8. Swelling properties 20

The wafer of 2 cm² was weighed and put in a Petri-dish containing 10 ml of double distilled water and were allowed to soak. Increase in weight of the wafer was determined at preset time intervals, until a constant weight was observed. The degree of swelling (% S) was calculated using the formula

$$S\ (\%) = \frac{Wt - Wo}{Wo} \times 100$$

Where, S is percent swelling,
W is the weight of wafer at time t
W is the weight of wafer at time zero.

9. Drug content21

A wafer cut into three pieces of equal diameter and added into 100 ml of pH 6.8 phosphate buffer and continuously stirred for 24 hrs. The solutions shall be filtered, suitably diluted and analyzed in a UV Spectrophotometer. The average of drug content of three wafer will be taken as final reading.

10. In vitro Dissolution test22

By this method cumulative drug release and cumulative percentage of drug retained were calculated. In vitro drug dissolution was performed using USP basket type apparatus.

The studies were carried out at 37°C with stirring speed of 75 rpm in 900 ml phosphate buffer (pH 6.8). 5 ml of samples were withdrawn at predetermined time intervals of 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420 min and replaced with the same volume of buffer. The samples were collected and the concentration was determined at appropriate wavelength using UV spectrophotometer.

11. In vitro drug diffusion test23

The In vitro drug release of buccoadhesive wafer was performed using a cellophane membrane over a diffusion cell. The cellophane membrane was soaked overnight in a buffer solution (pH 6.8), then stretched over an open end of a glass tube 3 cm diameter and made water-tight by rubber band. The formulated wafers were cut into size of 2 cm² and placed over the cellophane membranes.

The tubes were then immersed in a 250 ml beaker containing 100 ml buffer (pH 6.8). The tubes were adjusted, so the membrane shall be below the surface of the release medium. Then, the beakers were transferred to shaker water bath adjusted at 37 ± 1oC and 100 rpm. 3ml samples were withdrawn at different time intervals (15, 30, 45, 60, 90, 120, 180 and 240 min) from the receptor medium and replaced by equal volumes of PBS (pH 6.8) maintained at the same conditions.

Drug Release Kinetics Study 24

In order to determine the release mechanism that provides the best description to the pattern of drug release, the in vitro release data were fitted to zero order, first-order, Higuchi matrix model and Korsmeyer – Peppas model. The release data were also kinetically analyzed using these models. The release exponent (n) describing the mechanism of drug release from the matrices was calculated by regression analysis using the following equation.

a. Zero order release kinetics25

It refers to the process of constant drug release from a drug delivery device independent of the concentration. In its simplest form, zero order release can be represented as

$Q = Q0 + K0t$

Where Q is the amount of drug released or dissolved,

Q0 is the initial amount of drug in solution (it is usually zero), K0 is the zero order release constant.

b. First order release kinetics

The first order Equation describes the release from system where release rate is concentration dependent, expressed by the equation:

$dC / dt = - Kt$

Where K is first order rate constant expressed in units of time-1.

c. Higuchi Model

This model is applicable to study the release of water soluble and low soluble drugs incorporated in semisolid and solid matrices.

Model expression is given by the equation:

$Q = A [D (2C - Cs) Cs t] 1/2$

Where Q is the amount of drug released in time t per unit area A, C is the drug initial concentration, Cs is the drug solubility in the media,

D is the diffusivity of the drug molecules (diffusion coefficient) in the matrix.

d. Korsmeyer - Peppas Model

Korsmeyer and Peppas developed an empirical equation to analyze both Fickian and non-Fickian release of drug from swelling as well as non-swelling polymeric delivery systems. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer – Peppas model

$Mt / M\alpha = K\ tn$

Where Mt/Mα is fraction of drug released at time t, K is the rate constant (having units of tn) incorporating structural and geometric characteristics of the delivery system.

n is the release exponent indicative of the mechanism of transport of drug through the polymer. To study the release kinetics, data obtained from in-vitro drug release studies were plotted as[112]

i. Cumulative percent drug released versus Time (zero-order kinetic model).

ii. Log cumulative percentage drug retained versus Time (first-order rate kinetics model).

iii. Cumulative percent drug released versus square root of time (Higuchi's model).

iv. Log cumulative percent drug released versus log Time (Korsmeyer-Peppas equation).

Based on the "R2" value, the best-fit model was selected.

12. Stability test26

A piece of wafer preparation was stored in an aluminum package at 25 ºC with 50-60% humidity (normal condition) and another wafer at 40 ºC with 75% humidity (accelerated conditions) and both are observed.

RESULTS AND DISCUSSION

Determination of melting point of the drug

Melting point of Levodopa was found to be in the range of 284-286 °C and it complies with the IP standard, thus indicating the purity of the sample.

Drug excipient compatibility studies by FTIR

IR spectrum of Levodopa (drug), physical mixture with excipients was recorded and it was found in accordance with the reported peaks. There are no observed significant peak shifts and no generation of a new peak, although there might be no possible interaction between drug and excipients of buccoadhesive wafers. FTIR spectra were found to be pure, stable and unaltered.

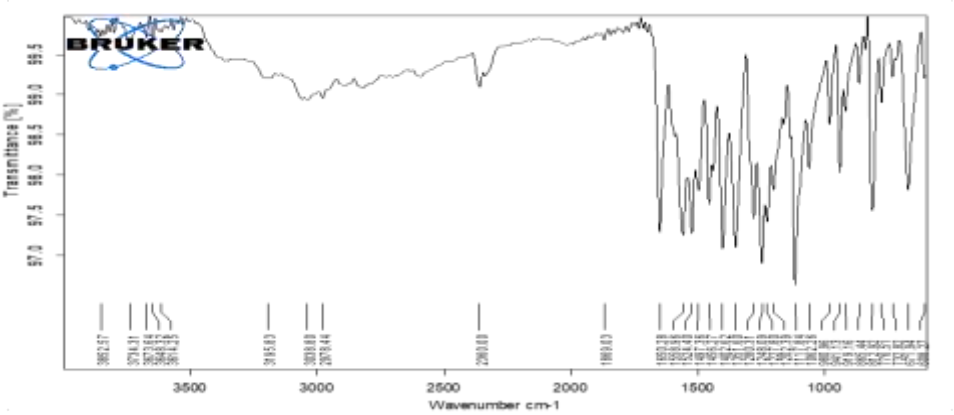

Figure no. 1: FT-IR spectrum of Pure Levodopa

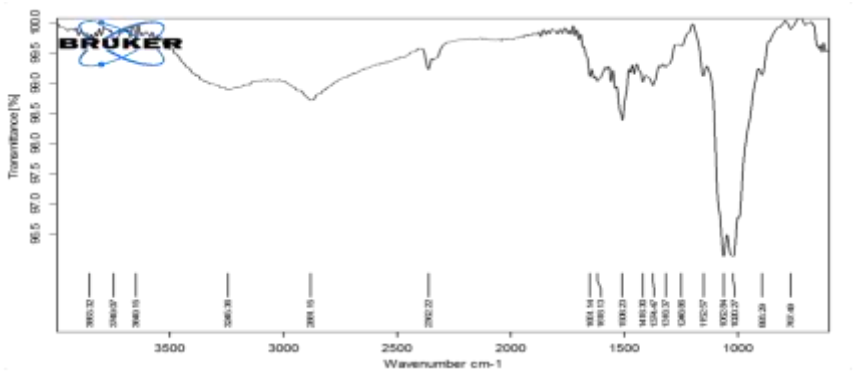

Figure no. 2: FT-IR spectrum of Chitosan Lactate

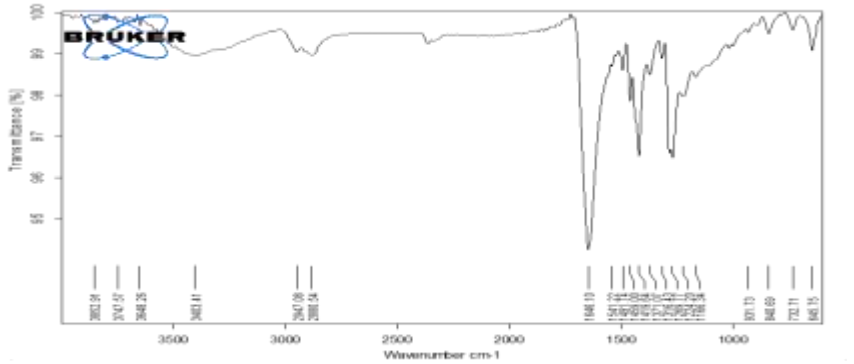

Figure no. 3: FT-IR spectrum of PVP K- 30

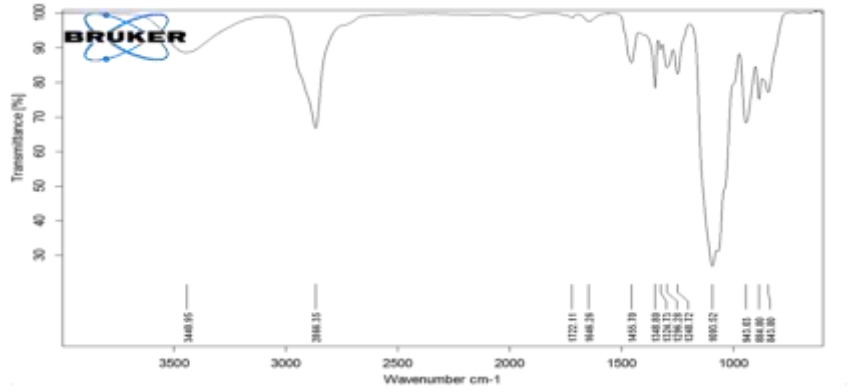

Figure no. 4: FT-IR spectrum of PEG 400

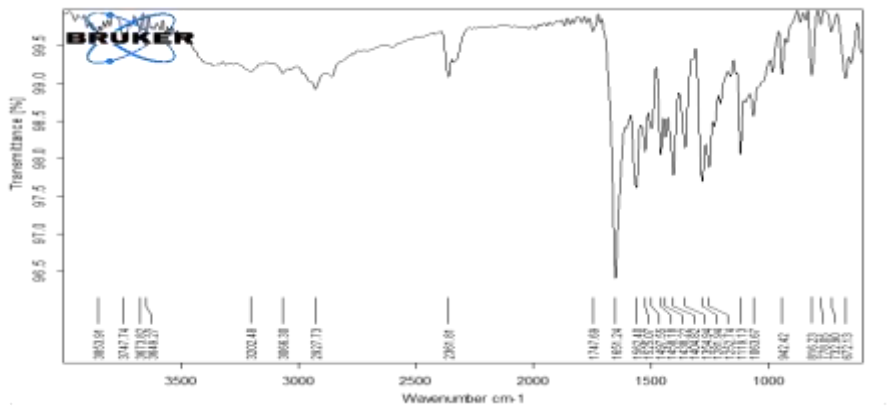

Figure no. 5: FT-IR spectrum of Levodopa: Chitosan Lactate: PVP K-30 (1:1:1:)) Physical mixture

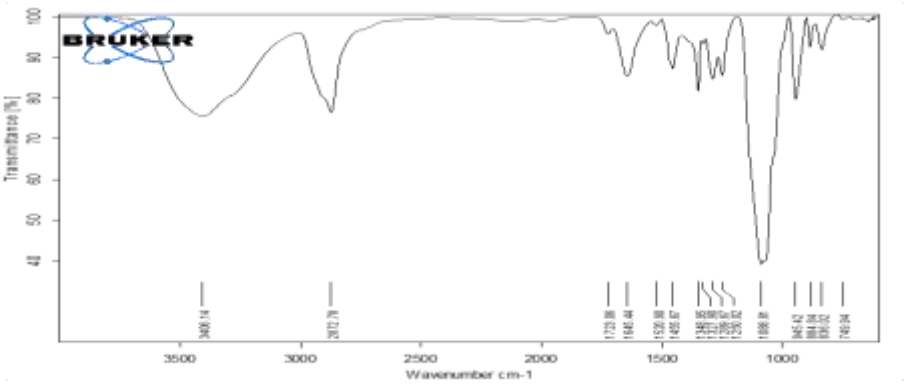

Figure no. 6: FT-IR spectrum of buccoadhesive wafer of Levodopa

Table no.02: Interpretation of FT-IR spectra of the drug, Chitosan Lactate, PVP K-30, PEG- 400 physical mixture and buccoadhesive wafer

Characteristic band	Characteristic wavenumber (cm^2)	Compounds observed frequencies (cm^{-1})					
		Levodopa	Chitosan Lactate	PVP K- 30	PEG - 400	Physical mixture	Buccoadhesive wafer formulation
C-H stretching	~2800		2881.15	2880.54	2866.35		2872.78
C=C aromatic stretching	1620-1650					1651.24	1645.44
O-H bending	2500-3300	2978.44	3245.36		3440.95	2927.73	
C=O stretching	1650-1750	1650.28		1646.10		1747.69	1723.06
N-H stretching	3300-3500	3614.25	3649.15	3403.41		3649.27	3406.14
C-O stretching	~2100				1348.88		
C-N stretching	1266-1342			1269.77		1281.94	1289.67

Figure no. 7: Prepared Formulation of Sustained release buccoadhesive wafer of Levodopa.

Figure no. 8: Prepared F5 formulation of Sustained release buccoadhesive wafer.

Determination of λ max

Concentration of 0- 50µg/ml was prepared from a standard Levodopa solution scanned by a UV-visible spectrometer in the range of 200-400 nm using 6.8 PBS as blank then the maximum wavelength (λ max) was determined.

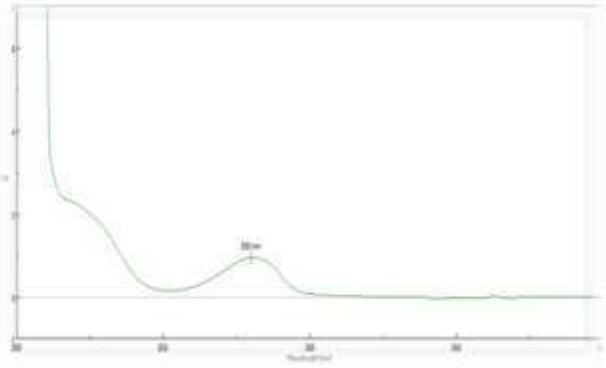

Figure no.9: λ_{max} of Levodopa in Phosphate buffer pH 6.8

EVALUATION OF BUCCOADHESIVE WAFERS

Color

The color was noted visually, for all the wafers from F1 to F6 were brownish yellow in color, transparent in appearance.

Thickness

The thickness of the six wafers were determined and it was found to be in the range of 0.18 ± 0.020mm to 0.33 ± 0.014mm which was easy to handle and can be easily placed on the buccal cavity because of presence of proper amount of polymers.

Weight variation

The weight of the six wafer formulations were determined and it was found to be in the range of 160.7 ± 0.15 to 179 ± 0.35 mg which indicated that the drug was uniformly distributed.

pH of wafer

The surface pH of the six wafer formulations were conducted and it was found to be in the range of 6.00 ± 0.09 to 6.90 ± 0.03 which indicating it to be compatible with buccal pH.

Tack test

The tack test of the prepared six formulations were determined and found to be satisfactory which indicates it to stick well to the buccal cavity.

Tensile strength

Tensile strength of the six formulations were performed and it was found to be in the range of 0.163±0.01 to 0.256±0.06N/cm^2 which showed that it is having enough strength to maintain elasticity.

Folding Endurance

The folding endurance of the prepared six wafer formulations were determined and it was found to be in the range of 209±1.52 to 242 ±3.46 which shown that it has proper mechanical handling and flexibilities.

Swelling properties

The swelling properties of the six wafer formulations were determined and it was found in the range of 89.2- 96% which indicated that it has helped to establish intimate contact of the film with buccal surface.

Drug content

The drug content of prepared six wafer formulations were conducted and it was found to be in the range of 76.9 ± 0.23 to 97.6 ± 0.16% which showed that drug was in proper amount along with polymers and delivered its dose accurately.

***In vitro* Dissolution test**

In vitro Dissolution test of six wafer formulations were determined and it was found to be in the range of 83.64 ± 0.25 –to 96.78 %±0.42.

The dissolution studies of prepared Buccoadhesive wafer were carried out and at the end of 420min F5 formulation showed 96.78% which is shown in Table No.15 and which showed that the wafer exhibited good dissolution thereby enhancing the bioavailability and therapeutic effectiveness.

***In vitro* drug diffusion study**

In vitro drug diffusion study of six wafer formulations were determined and it was found to be in the range of 90.44-95.61%.

The diffusion study of prepared Buccoadhesive wafer were carried out and at the end of 420min F5 formulation showed 95.61% indicating better diffusion of the drug because of presence of high amount PVP K-30.

Drug release kinetics study

The data obtained from the *in vitro* drug diffusion studies were fitted to zero order, first order, Higuchi model and Korsmeyer - peppas model. The results obtained were given in the table no.17. The release constants was calculated from the slope of appropriate plots, and the regression coefficient (R^2) was determined. It was found that *in vitro* drug release of Buccoadhesive wafer was best explained by Peppas kinetic model as the plots shows highest linearity. Correlation coefficient (R^2) was found to be 0.9816 with the N value as 0.8015 indicating that the drug release was non fickian diffusion.

Stability study

Stability Studies were carried out at selected temperature conditions based on ICH guidelines and results are mentioned below.

Based on Swelling property, drug content and *in vitro* drug release studies and results showed that there is no significant change in the selected parameters at normal and accelerated conditions and was stable throughout the time period of 3 months.

Table 03: Evaluation of buccoadhesive wafer of levodopa

Formulation code	Thickness (mm)	Weight variation(mg)	pH	Tenacity
F1	0.21 ± 0.017	165 ± 0.11	6.43 ± 0.02	++
F2	0.18 ± 0.020	159.4 ± 0.26	6.57 ± 0.06	+++
F3	0.22 ± 0.080	175.5 ± 0.10	6.67 ± 0.10	++
F4	0.24 ± 0.012	172.1 ± 0.32	6.91 ± 0.03	+
F5	0.26 ± 0.028	160.7 ± 0.15	6.81 ± 0.05	+++
F6	0.29 ± 0.014	179 ± 0.35	6.00 ± 0.09	++

All data are given in mean±SD

Table 04: Evaluation of buccoadhesive wafer of levodopa

Formulation code	Tensile strength N/cm^2	Folding Endurance	Swelling properties (%)	Drug content (%)
F1	0.163±0.01	213 ± 2.30	90.1 ± 0.16	86.8 ± 0.17
F2	0.223±0005	224 ±1.73	89.2 ±0.35	76.9 ±0.23
F3	0.186±0.02	237 ±3.05	95 ±0.19	84.3 ±0.18
F4	0.254±0.06	217 ±2.64	93 ±0.13	89.8 ±0.14
F5	0.247±0.05	242 ±3.46	96 ±0.62	97.6 ±0.16
F6	0.231±0.02	209 ±1.52	95.2 ±0.11	92.4 ± 0.25

All data are given in mean±SD

Table no.05: *In vitro* Dissolution test of buccoadhesive wafer

Formulation code	% cumulative drug release (±SD)											
	0 min	15 min	30 min	45 min	60 min	90 min	120 min	180 min	240 min	300 min	360 min	420 min
F1	0	11.58 ±0.35	17.29 ±0.04	23.20 ±0.21	28.00 ±0.28	31.89 ±0.39	35.79 ±0.19	56.79 ±0.31	65.24 ±0.16	76.60 ±0.3	80.55 ±0.22	86.52 ±0.26
F2	0	10.40 ±0.26	13.89 ±0.41	21.47 ±0.18	29.91 ±0.5	35.20 ±0.10	49.60 ±0.14	54.02 ±0.09	63.57 ±0.5	70.61 ±0.8	83.02 ±0.09	88.44 ±0.18
F3	0	7.40± 0.15	19.80 ±0.25	24.67 ±0.23	31.54 ±0.24	40.96 ±0.35	59.17 ±0.03	64.99 ±0.15	73.23 ±0.35	77.86 ±0.23	81.88 ±0.09	87.12 ±0.05
F4	0	8.08± 0.17	14.70 ±0.58	22.34 ±0.19	30.17 ±0.17	38.39 ±0.08	43.92 ±0.09	55.49 ±0.05	63.83 ±0.12	74.13 ±0.7	83.14 ±0.21	86.95 ±0.01
F5	0	7.60± 0.28	14.32 ±0.25	20.60 ±0.09	27.78 ±0.10	34.97 ±0.16	40.37 ±0.42	52.05 ±0.9	61.95 ±0.41	75.44 ±0.34	88.05 ±0.27	96.78 ±0.42
F6	0	8.29± 0.23	13.32 ±0.38	25.01 ±0.16	32.97 ±0.05	39.48 ±0.06	44.99 ±0.33	53.34 ±0.27	63.89 ±0.31	71.98 ±0.19	74.25 ±0.6	83.64 ±0.25

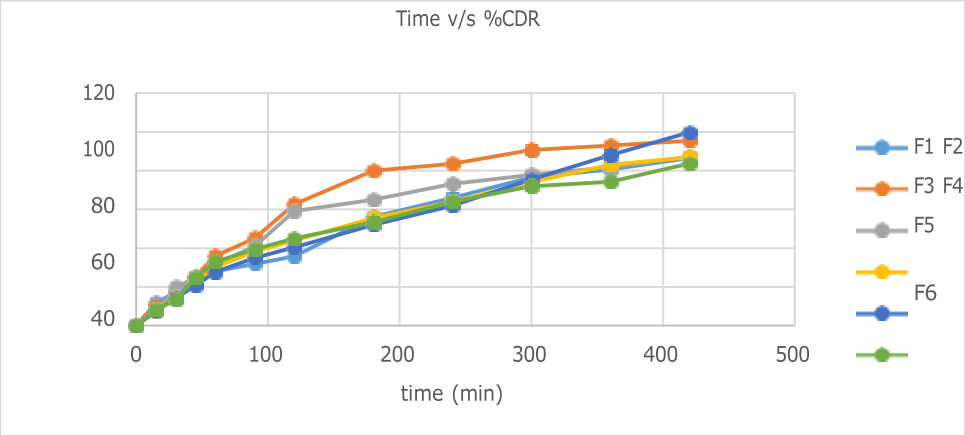

Figure no. 10: In-vitro dissolution test of Buccoadhesive wafer of Levodopa

Table no.06: In vitro drug diffusion study of buccoadhesive wafer

Formulation code	% Drug diffusion											
	0 min	15 min	30 min	45 min	60 min	90 min	120 min	180 min	240 min	300 min	360 min	420 min
F1	0	6.40 ±0.32	13.04 ±0.04	22.45 ±0.6	29.94 ±0.27	41.58 ±0.34	52.74 ±0.24	59.87 ±0.614	68.93 ±0.5	79.12 ±0.28	87.02 ±0.25	94.48 ±0.12
F2	0	6.46 ±0.2	14.0 2±051	23.4 5±0.22	30.8 9±0.3	41.5 ±0.6	50.9 4±0.31	61.4 5±0.19	72.0 1±0.39	78.9 3±0.28	87.3 2±0.21	90.44 ±0.04
F3	0	6.86 ±0.23	12.8 9±0.26	23.4 1±0.09	31.4 0±0.08	39.4 8±0.16	51.0 3±0.09	62.0 3±0.14	71.0 5±0.10	78.5 3±0.02	85.1 2±0.18	91.75 ±0.41
F4	0	8.90 ±0.31	16.1 3±0.05	21.0 9±0.21	32.1 6±0.7	48.9 3±0.35	57.8 5±0.05	65.1 2±0.09	76.5 9±0.08	86.0 8±0.24	88.6 7±0.19	94.07 ±0.58
F5	0	6.48 ±0.12	11.2 3±0.42	20.6 9±0.27	31.2 9±0.34	42.5 5±0.12	57.6 3±0.09	69.1 7±0.42	78.4 5±0.16	88.5 4±0.19	94.4 0±0.09	95.61 ±0.25
F6	0	6.68 ±0.32	10.5 4±0.25	21.0 9±0.6	30.1 4±0.19	41.0 7±041	50.1 1±0.27	68.1 0±0.33	75.4 0±0.0	85.9 4±0.10	92.6 9±0.16	93.1± 0.38

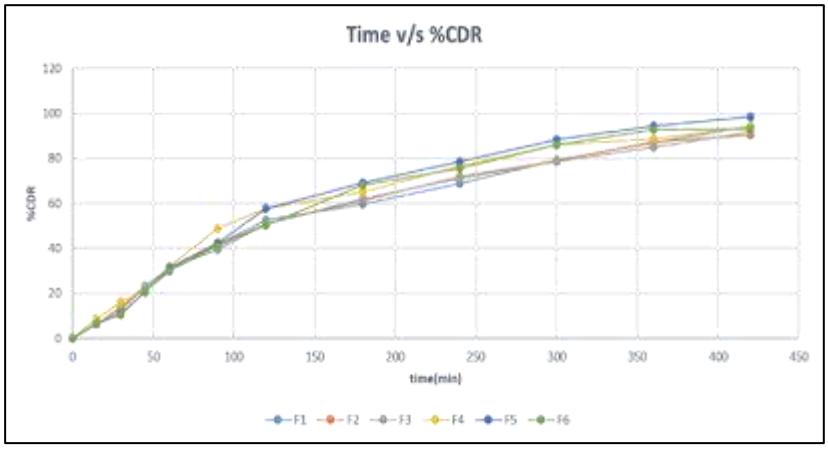

Figure no. 11: *In vitro* drug diffusion study of Buccoadhesive wafer of Levodopa

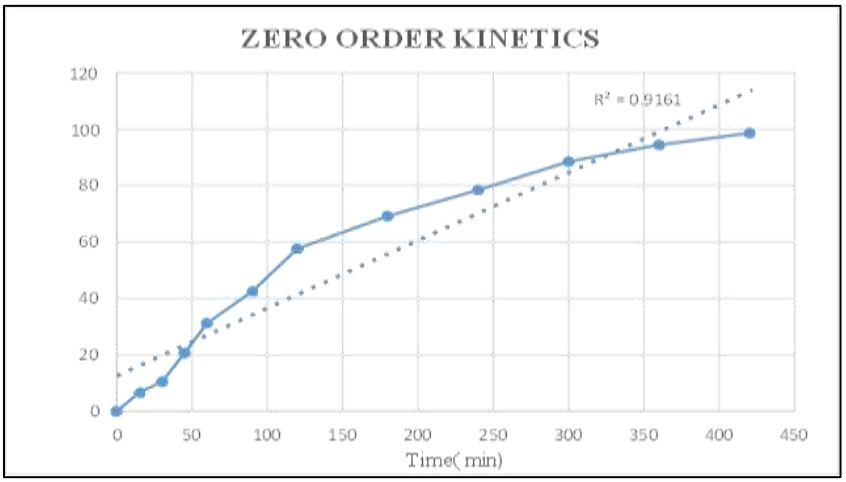

Figure no.12: Plot of % CDR Vs Time (Zero order kinetics)

Figure no. 13: Plot of Log % of drug retained Vs Time (First order kinetics)

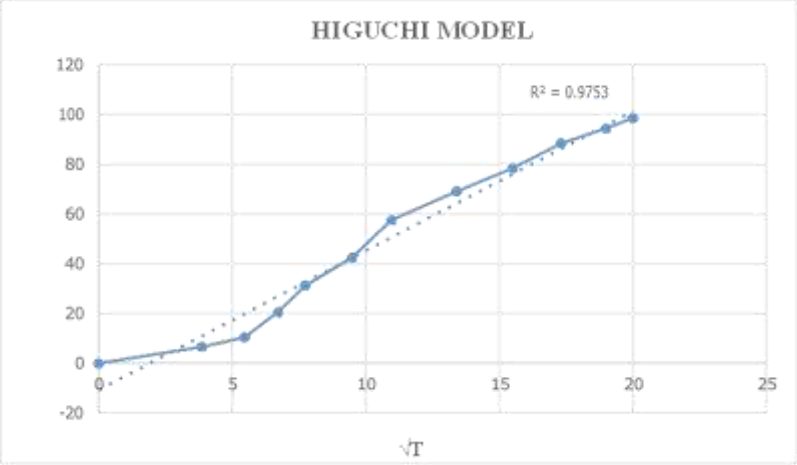

Figure no. 14: Plot of % CDR Vs. square root of time

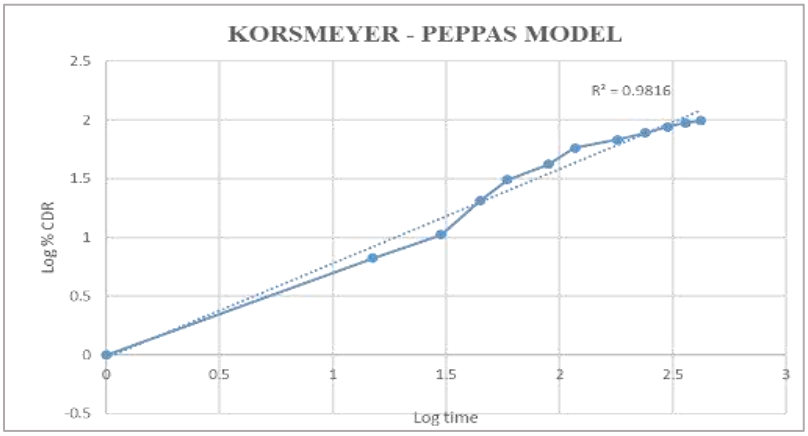

Figure no. 15: Plot of Log % CDR Vs Log time

Table no.07: Kinetic release study of Buccoadhesive wafer of Levodopa

Formulation	Zero order model	First order model	Higuchi model	Korsmeyer-Peppas model	
	R^2	R^2	R^2	R^2	N
F5	0.9161	0.9522	0.9753	0.9816	0.8015

Table No: 08 Stability data of F5 Sustained release buccoadhesive wafer formulation

Time (Days)	Swelling property	Swelling property	Drug content	Drug Content	*In vitro* drug diffusion study	*In vitro* drug diffusion study
	25±2°C and 50-60% RH	40±2°C and 75% RH	25±2°C and 50-60% RH	40±2°C and 75% RH	25±2°C and 50-60% RH	40±2°C and 75% RH
0	96±0.62%	96±0.62%	97.6±0.16%	97.6±0.16%	95.61±0.25	95.61±0.25
30	95.9±0.1%	57.02±0.1%	94.23%	94.1±0.21%	97.95%	97.16%
60	96.4±0.09%	96.4±0.1%	93.91%	93.52±0.14%	97.45%	97.04%
90	95.89±0.78%	95.59±0.78%	92.2%	92.14±0.06%	98.68%	98.09%

CONCLUSION

Buccal delivery is an appealing alternative route for the administration of drugs that has low bioavailability because of extensive first-pass metabolism. The following conclusion could be drawn from the various experiments. FTIR studies concluded that there was no drug and excipients interaction. The buccoadhesive wafer containing backing layer, which acts like a patch providing unidirectional drug release of Levodopa, could be prepared by the solvent casting technique with buccoadhesive polymers like Chitosan Lactate and PVP K-30. The prepared wafers were smooth, flexible and elegant in appearance with uniform in weight, thickness, drug content uniformity and showing good folding endurance. The physicochemical properties of all formulations were shown to be within limits. The surface pH of all formulations was in an acceptable salivary pH (6.00- 6.91). Among that formulation, F5 shows better drug release, drug content, tensile strength and accelerated stability conditions were found to be stable at specified by ICH. So that F5 batch considered as best formulation. Hence, present study concludes that the Levodopa could be delivered through the buccal route.

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