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Formulation Development and Characterization of Pioglitazone and Cilnidipine Buccal Tablet to Manage Diabetic Patients with Hypertension

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ABSTRACT

Diabetes mellitus is a metabolic disorder with multiple complications. Hypertension is common ailment in diabetic patient.The present research is concerned with the development of buccal tablet formulation by using Pioglitazone and Cilnidipine with an attempt toenhance the bioavailability by reducing the first pass metabolism. The buccal tablets were prepared by using carbopol 974, HPMC K15 cps, Sodium CMC, PEG, lactose, magnesium stearate, ethyl cellulose, in varying concentration by direct compression method.The prepared buccal tablets were evaluated for organoleptic properties, hardness, friability, drug content, surface pH, bioadhesion strength, ex-vivo residence time, swelling index which were found to comply with pharmacopoeial requirements. In-vitro drug release studies were carried out. Stability study indicates that buccal tablets are stable with respect to drug content and dissolution and optimized formulation has good stability in human saliva. mucoadhesive strength of tablets were found to be in the range 4.00 to 8.00 gm which is within standard limit.Experimental result showed that force of adhesion increased in ascending order of increase in polymer concentration. The surface pH of the tablets was in the range of 6.6 to 6.9 which are safe to buccal mucosa. The dissolution results were found to be in the range of 95.36 and 99.00%. These formulations showed good bio adhesion strength. It was inferred that the prepared buccal tabletswill have promising utilities in management of diabetic patient with hypertension.

Keywords:
Pioglitazone, Cilnidipine, Bioadhesion, Penetration enhancers, Buccal epithelium.

Introduction

Hypertension (defined as a blood pressure ≥140/90 mmHg) is an extremely common condition in diabetes, affecting 20-60% of patients with diabetes, depending on obesity, ethnicity, and age. Hypertension is a condition in which blood pressure is high. It can be used by genetics, diet as well as stress. It is associated with significant health problems such as stroke and heart attack.[1]

Diabetes mellitus (defined as having a plasma glucose reading ≥126 mg/dL if the participant had fasted or ≥ 200 mg/dL).[2]Often simply referred to as diabetes is a condition in which a person has a high blood sugar level, either because the body doesn't produce enough insulin (Type 1 diabetes) or because body cells don't properly respond to the insulin that is produced (Type 2 diabetes).[1]

The coexistence of diabetes and hypertension worsens clinical outcomes with respect to both microvascular and macrovascular disease. Diabetes management should therefore be comprised of a multifaceted approach that targets optimal blood pressure and lipid management in addition to glycemic control. The pathophysiology of hypertension in diabetes involves maladaptive changes and complex interactions between the autonomic nervous system, mechanical forces, rennin-angiotensin-aldosterone system as well as individual and environmental factors. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers remains the preferred agents, while combined use of these agents is not recommended due to poor renal outcomes. With the availability of newer antihyperglycemic agents, consideration should be given to their antihypertensive effects when added for additional glycemic control.[3]

Diabetes and high blood pressure tend to occur together because they share certain physiological traits. High blood pressure is a dangerous disease that becomes even more problematic in the setting of diabetes. Unfortunately, many people with diabetes are also affected by high blood pressure, and the two diseases commonly occur together. Diabetes and high blood pressure occur

together so frequently that they are officially considered to be “comorbidities” (diseases likely to be present in the same patient).[1]

The current state of *diabetes mellitus* in India is fast gaining the state of potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with disease. In 2000, India topped the world with the higher the number of the peoples with the diabetes mellitus followed by china (20.8 million) with the United States in second and third place respectively. Itis predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India,while china 42.3 and United States 30.3 million will also see significant increases in those affected by the diseases.[2]

There are several medications that are used for glycaemic control in diabetes that have modest antihypertensive effects. Medication side effects are often taken into consideration when deciding on pharmacotherapy; however it is just as important to take into consideration the beneficial effects on comorbid conditions. Thiazolidinedione’s,dipeptidyldiphosphatase (DPP-4) inhibitors, glucagon like peptide 1 (GLP-1) receptor agonists and sodium glucose co-transporters 2 (SGLT 2) inhibitors are classes of medications which have been associated witha decrease in blood pressure.[3]

The line of treatment for such patients includes separate medications for each indication. In this research work an attempt for granulating or fixed dose combination of antihypertensive and anitidiabetic drug was carried out. Cilinidipine a unique Ca^{2+} channel blocker because of its inhibitory action on the sympathethic N-type Ca^{2+} channels along with L-type Ca^{2+} channels.Cilinidipine has been classified as a fourth-generation CCB based on its action on sympathetic neurotransmitter release. Cardioprotective, renoprotective and neuroprotective effects of Cilnidipine has been reported in clinical and animal studies.[4]

Pioglitazone is a thiazolidinedione compound used in the treatment of type 2 diabetes. It is an insulin sensitizer that acts as an agonist of the peroxisome proliferators activated receptor sub-

type gamma (PPAR-γ). Pioglitazone is rapidly absorbed, its oral bioavailability 80%, and it is extensively metabolized by hydroxylation and oxidation to active and inactive metabolites in the liver.[5] Patients with hyperglycemia also suffered from hypertension, were prescribed with these two drugs. Currently as far as our literature survey goes, there is no combined dosage form available and they are available only as individual tablets FDP (Plendil) and PIO (Actos). Since FDP suffers from extensive first pass hepatic metabolism and an alternative mode of delivery system apart from oral delivery like buccal delivery system is desired.

The buccal drug delivery system offers various advantages which includes easy accessibility, no first pass metabolism, withdrawal of drug action at any time and many more.

Thus it is hypothesized that the combination of anti-diabetic and antihypertensive drug for the patients suffering from hypertension induced by diabetes will provide better patient compliance as well as faster onset of action when compared with individual oral therapy.

Materials and Methods

Pioglitazone and Cilnidipinewere obtained as a gift sample from Macleods Pharmaceutical Ltd. Baddi, India. Hydroxypropylmethylcellulose (HPMC K-4M), sodium carboxymethylcellulose (Na CMC) and Carbopol 934-P wasobtained from Sigma Chemicals, USA. Aspartame wasobtained from Strides Arco Labs, Bangalore, India. Magnesium stereate and ethyl cellulose weresupplied from LobaChemie Mumbai, India.

PREFORMULATION STUDY

Physical characterization

The drug was physically characterized on the basis of color, odor and physical state. All the physical parameters were recorded and compared with literature.[32]

Determination of melting point

The melting point of Pioglitazone and Cilnidipine was obtained by using digital melting point apparatus. Small quality of drug was filled in the capillary tube with one end closed and placed in the melting point apparatus. The melting point was recorded. [33, 34, 35]

Determination of drug solubility

Solubility is directly related with the release of the drug from the dosage form: hence used to check the amount of drug absorbed into the blood stream. Pioglitazone and cilnidipine was tested for solubility in water, methanol and phosphate buffer (6.8), 0.1N HCL. Small amount of drug was mixed in 5mL of solvent. The solution was shaken thoroughly for 24 hrs using mechanical shaker. After 24 hrs, the solution was filtered and measured at 219 nm for Pioglitazone and at 236 nm for Cilnidipine using UV spectrophotometer. [35]

Determination of partition coefficient

The partition coefficient of Pioglitazone was determine using two immiscible phases (i.e. aqueous phase and oil phase) aqueous phase contains 10 mL of water and oil phase contains 10 mL of octanol. This mixture was shaken for 30 min. (Without drug) in a separating funnel. Drug (10mg) was added to the mixture and shaken for 3 hrs. The final mixture was kept for 1h to separate two layers (aqueous layer and oily layer). Pipette out (1ml) from the aqueous layer and transferred to 10 mL volumetric flask and volume was made up to 10 mL with methanol and analyzed at 219 nm for Pioglitazone and 236 nm for Cilnidipine against similarly treated blank using UV spectrophotometer. From oil layer, 1mL sample was taken and kept for 6-7 hrs at room temperature. After evaporation, remaining solution was diluted with methanol up to 10 mL and the concentration of solute was analyzed against similarly treated blank using UV spectrophotometer. The partition coefficient was calculated using following formula. [36, 37]

$$Partition\ Coefficient = \frac{concentration\ of\ drug\ in\ organic\ layer}{concentration\ of\ drug\ in\ aqueous\ layer}$$

Determination of wavelength of maximum absorption (λ_{max}) and preparation of calibration curve: [38, 39, 40, 41, 42, 43]

Determination of λ_{max} in methanol

The absorption maxima (λ_{max}) of Pioglitazone and Cilnidipine were determined in methanol by scanning the drug in the range of 400-200 nm using UV spectrophotometer.

Preparation of stock solution

For both the drugs Pioglitazone and Cilnidipine100 mg of drug was weighed accurately and transferred to 100 mL volumetric flask and small quantity of methanol was added and drug was allowed to dissolve and volume was made up to mark with methanol to obtain 1000 µg/mL concentration. From this solution, 10 mL was withdrawn and transferred to the volumetric flask and make up the volume to 100 mL to obtain 100 µg/mL concentrations. This solution was known as stock solution.

Preparation of calibration curve in methanol

From the stock solution serial dilutions of different concentration from 10-20 µg/mL were prepared in methanol. Absorbance was measured at 219 nm for Pioglitazone and 236 nm for Cilnidipine against similarly treated blank using UV-VIS spectrophotometer.

Fourier transformer infrared spectroscopy (FT-IR)

FT-IR spectroscopy of pure drugs Pioglitazone and Cilnidipine was carried out using Fourier transformer infrared spectrophotometer. The spectrum was obtained using press pellet technique. The pellets were prepared by KBr after mixing with drug in the ratio 1:100 and by applying the pressure of 10 ton in KBr for 1 minute for both the drugs individually. The pellets weretransferred to the sample holder and placed in the spectrophotometer and sample was

scanned at 4000 to 400 cm $^{-1}$ at a resolution of 4 cm^{-1} and interpretation of spectrum was further done.[44, 45, 46, 47]

Drug – Drug compatibility study

A mixture of Pioglitazone and Cilnidipine was prepared and their spectrum was obtained by using KBr press pellet technique. Pellet was prepared by mixing the drugs and KBr in the ratio 1:100 and by applying the pressure of 10 ton for 1 minute. The sample disc was prepared and placed in the sample holder and was scanned at 4000 to 400 cm^{-1} and the interpretation of the spectrum was further done by comparing the spectrum with the spectrum of individual drug.[32, 44]

Drug excipients compatibility study

The compatibility study of the Pioglitazone and Cilnidipine was done by different excipients viz., HPMC K15cps, carbopol, polyethylene glycol, lactose, magnesium stearate, ethyl cellulose. The infrared spectrum of individual excipient was developed in pure form by using KBr pellet technique taking excipient and KBr in the ratio 1:100. The pressure of 10 ton was applied in KBr press for 1 minute. The pellets were then transferred to sample holder and placed in FT -IR spectrophotometer and scanned at wavelength of 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}. Similarly, the spectrum of a mixture of excipients with both the drugs Pioglitazone and Cilnidipine weredeveloped individually. All selected excipients viz., HPMC K15cps, carbopol, polyethylene glycol, lactose, magnesium stearate, ethyl cellulose were mixed with Pioglitazone and Cilnidipine individually in the quantity of equal ratio 1:100. The sample discs were prepared with KBr, drugs and excipients by using KBr press at pressure of 10000 to 15000 psi. The sample disc was placed in the sample holder and scanned at 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}and the interpretation of spectrumwas further done.[32, 44, 48]

Preparations of powder blend by direct compression method

In the present study direct compression method was used for the development of buccaltablets. Direct compression method is most easy and suitable method used by various formulation

scientists. In this method all ingredients weighed according to their decreasing order to make a blend, all ingredients passed through sieve #60. For blending we mixed for 30 minutes by using double cone blender (Rolex double cone blender). After blending it was analysed for the organoleptic properties and Micromeritics properties. In the preliminary studies concentration of HPMC and Carbopol was optimized by changing the concentration from 5 mg to 20 mg. The optimized concentration was used in the formulation.[55, 56]

Table 1: Different formulation for buccal tablets

Sr.no.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)
1	**Pioglitazone**	20	20	20	20	20
2	**Cilnidipine**	30	30	30	30	30
3	**HPMC K15 cps**	10	10	10	10	10
4	**Carbopol**	10	10	10	10	10
5	**PEG 6000**	10	20	30	40	50
6	**Lactose**	60	50	40	30	20
7	**Magnesium stearate**	10	10	10	10	10
8	**Ethyl cellulose**	50	50	50	50	50

Evaluation of Powder Blends (Pre-compression Studies)

The blend was prepared for the preparation of the tablets and before the compression; the pre-compression study was done. The various parameters like Bulk density, Tapped density,Hausner's ratio, Carr's compressibility index, Angle of repose (θ), Percentage porosity were performedfor core powder blend. [57]

Compression of Tablet by Direct Compression Method

Buccal tablets containingPioglitazone and Cilnidipine werepreparedby direct compression method. The ingredients of the core layer were weighed accurately andmixed by trituration in a glass mortar and pestle for 15minutes. All the ingredients were screened through sieveno. 60.[59] The prepared blend of each formulation was pre-compressed, on 10-station rotary tablet

punching machine at a low compression force to form single layered flat-faced tablet of 9 mm punch diameter. Then, 50 mg of ethyl cellulose powder was used as backing layer to prevent the bidirectional flow and final compression was done at a high compression force. After compression of tablets, the upper punchwas removed carefully without disturbing the set up and mixed ingredients. [60, 61]

Evaluation of Buccal Tablets (Post Compression Studies)

The prepared tablets were evaluated for post compression studies which are as follows: [62, 63]

General appearance

General appearance of a tablet, its visual identity and overall elegance is essential for patient acceptance. The tablet's size, shape, color, presence or absences of an odor, legibility of any identifying marking were studied as the general appearance characteristic.

Weight Variation, Hardness and Thickness

Twenty tablets were randomly selected from each batchand individually weighed using digital balance (Citizon,Model No. CG 203). Hardness was measured usingMonsanto hardness tester and the thickness was measuredby using digital verniercalliper (International BiologicalLaboratories).

Friability

Friability is the loss of tablet mass in the container due to removal of fine particles from the surface during transpiration or handling.USP tablet fraibilator (EF-2, electro lab, Mumbai) was employed for the determination of tablet friability. Pre-weighted tablets, (20 tablets) were placed in the fraibilator. Fraibilator consist of a plastic chamber that revolves at 25 rpm, dropping tablets at a distance of 6 inches with each revolution. The fraibilator was rotated for 4 minutesat

the end of test, tablets were dusted and re-weighedthe loss in tablet weight was measured and friability was calculated using following formula.[64,65]

$$\text{Friability (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Determination of drug content

10 tablets from each batch were crush and the mass equivalent to one tablet was taken ina 100mL volumetric flask, mass equivalent to one tablet was taken and volume was made to mark with phosphate buffer (pH6.8). The flask was shaken for 24hrs using a water bath shaker incubator. The solution was filter and analyzed after suitable dilutions using UV –visible spectrophotometer.

Determination of surface pH

The Surface pH of the prepared buccaltablets was determined to evaluate the possible irritation effects onthe mucosa. The buccal tablets were placed in glass tubes and allowed to swell in contact with distilled water (12 mL) and the pH was measured by bringing the pH paper, in contact with the surface of the tablet and allowing it to equilibrate for 1minute. [67]

Swelling Studies

For conducting the swelling study, the tablet was weighed (Wo) and placed in a petridish containing 5 mL ofphosphate buffer (pH 6.8) for 8 hours. After that, thetablets were taken out from the petridish and excess waterwas removed carefully by using filter paper and weighedagain (Wt). The swelling index was calculated using thefollowing formula. [67, 68]

SI = (Wt-Wo) / Wo × 100

Where SI = Swelling index

Wt = Weight of tablets after time (t)

Wo = Weight of tablet before placing in the Petri dish

Bioadhesive Strength

A modified physical balance was used for determiningthe bio adhesive strength. The left pan was removed. The buccaltablet was then stuck to glass stopper through its backing membrane using an adhesive (Feviquick). To left arm of balancethe glass stopper along with the tablet was hanged. A clean glassmortar was placed below hanging glass stopper. The balance wasso adjusted that right hand side was exactly 5 g heavier than theleft. Fresh porcine buccal mucosa was obtained from a localslaughter house and used within 2 hrs of slaughter. The mucosalmembrane was separated by removing the underlying fat and loosetissues, washed with distilled water and then with phosphate bufferpH 6.8 at 37°C. The fresh porcine buccal mucosa was cut intopieces and washed with phosphate buffer pH 6.8. A piece ofbuccal mucosa was tied with the mucosal side upwards usingthread over the hollow cylinder, the cylinder was used because itwas gave strength to the buccal mucosa and it was not float duringthe adhesion. The cylinder was then lowered into the glass beaker(250 mL) which was then filled with 200 mL phosphate buffer pH 6.8kept at 37 ± 0.5°C to keep mucosal membrane moist. This was then kept below the left hand setup of the balance. The tablet to betested for bioadhesion was then stuck with a little moisture. The 5g weight on the right pan was removed. This lowered the tablet over the mucosa, with a force of 5g. The balance was kept in this position for 3 minutes and then the weight was added slowly to theright hand pan until the tablet detached from the mucosal surface. The detachments force gave the bioadhesive strength ofthe buccal tablet in g. From the bioadhesivestrength, force of adhesion and then the averages of threedeterminations were calculated:[69,70,71]

Force of adhesion (F) = [W x g] / 1000

Where g is acceleration due to gravity (9.80665 m/sec^2)

Residence Time

The *ex-vivo* residence time was determined using a locally modified USP disintegration apparatus. The disintegration medium was composed of 900mL (pH 6.8) of phosphate buffer maintained at 37±1°C. The porcinebuccal mucosa was tied to the surface of a glass slab, vertically attached to the disintegration apparatus. The buccal tablet was hydrated using phosphate buffer (pH 6.8) and the hydrated surface was brought in contact with the mucosal membrane by keeping the backing membrane outside. The glass slide allowed moving up and down, so that the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time taken for complete displacement of the tablet from the mucosal surface was noted and repeated thrice.[72]

***In-vitro* drug release study**

This is carried out in USP XXIII tablet dissolution testapparatus-II, employing paddle stirrer at 50 rpm and 200 ml of pH6.8 phosphate buffer as dissolution medium. The release study was performed at 37±0.5 °C. The backing layer of the buccal tablet is attached to glass disk with cyanoacrylate adhesive. The disk isplaced at the bottom of the dissolution vessel. Samples of 5 mLwere withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.45µmmembrane filter disc (Millipore Corporation) and analyzed after appropriate dilution by measuring the absorbance at 219 nm and 236 nm. The experiment was run in triplicate.[73,67]

***Ex-vivo* permeation studies**

Thepermeation study ofbuccal tabletwas carried out on porcine buccal membrane using modified Franzdiffusion cell with a diffusion area of 17.35 cm^2 and the acceptorcompartment volume of 30 mL. A semi permeable membrane(porcine buccal mucosa membrane) was clamped between thedonor and acceptor compartments. The water in the acceptorcompartment was continuously stirred at 100 rpm using amagnetic stirrer and maintained at 37 ± 0.5°C. The buccal tabletwas

placed into the donor compartment and was wetted with 1ml of 7.4pH phosphatebuffer. The diffusion was carried out for 10 hrs. The amount of drug permeated through themembrane was determined by removing samples periodically andreplaced with an equal volume of 7.4 pH phosphate buffer. Thesealiquots after filtration were diluted suitably and analyzedspectrophotometrically at 219 nm and 236 nm or absorbed against similar treated blank.[74, 75]

Stability of buccal tablets

Stability studies ofbuccal tablets wereperformed for best formulation in normal human saliva. Thehuman saliva was collected and filtered through filter paper. Buccaltablets were immersed in separate petridish containing 5 mL ofhuman saliva and placed in a temperature-controlled oven for 10hrs 37°C ± 0.5°C. At predetermined time interval thebuccal tablets were evaluated by observing change in colour, shape,collapse of the tablet and change in pH. The experiments wererepeated in triplicate.[76,77]

Result and Discussion

Preformulation Study

The results of Physical characterization, melting point, Solubility, Partition coefficientare shown in Table 2.

Table 2: Parameters for Preformulation study of Cilnidipine and Pioglitazone

Parameters	**Results**	
	Cilnidipine	**Pioglitazone**
Physical characterization	Color: Light yellowish powder Odor: Odorless	Color: White crystalline powder Odor: Odorless
Melting point	105 ºC ± 0.02	188 ºC ± 0.05

Solubility	Freely soluble in methanol (519.0 ± 0.03 mg/mL)	Freely soluble in methanol (595.0 ± 0.29 mg/mL)
Partition coefficient	4.7 ± 0.123	2.3 ± 0.03

Determination of wavelength of maximum absorption (λ_{max}) and preparation of calibration curve:

For Pioglitazone and Cilinidipine, the determination of maximum absorption was done using methanol as solvent, using solution of 12µg/mLand 10µg/mL concentration, respectively. The spectrum for Pioglitazone and Cilinidipine was obtained at 219 nm and 236 nm, respectively.

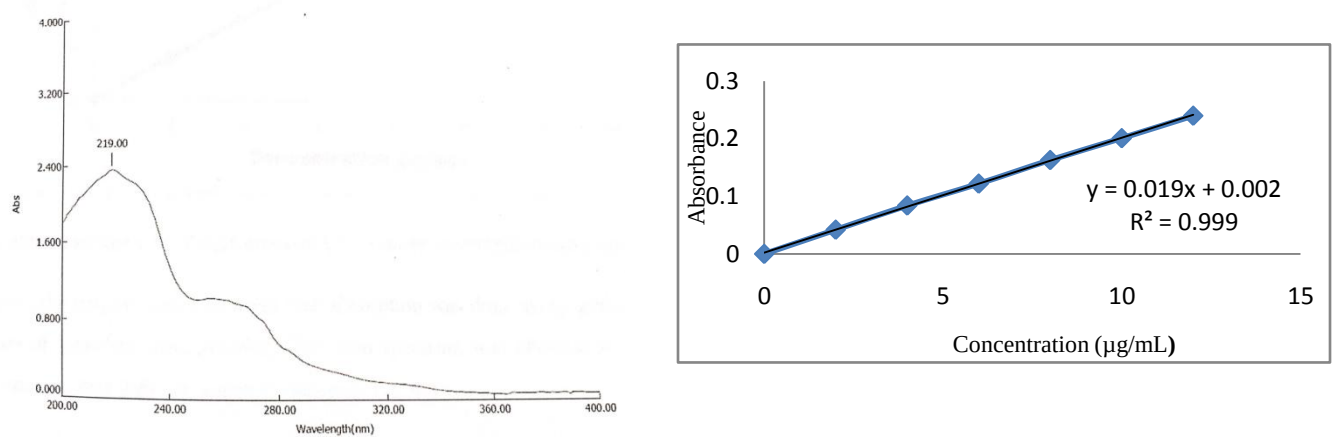

Figure 1: UV – visible spectrophotometer scan spectrum of Pioglitazone in Methanol and Calibration curve for Pioglitazone

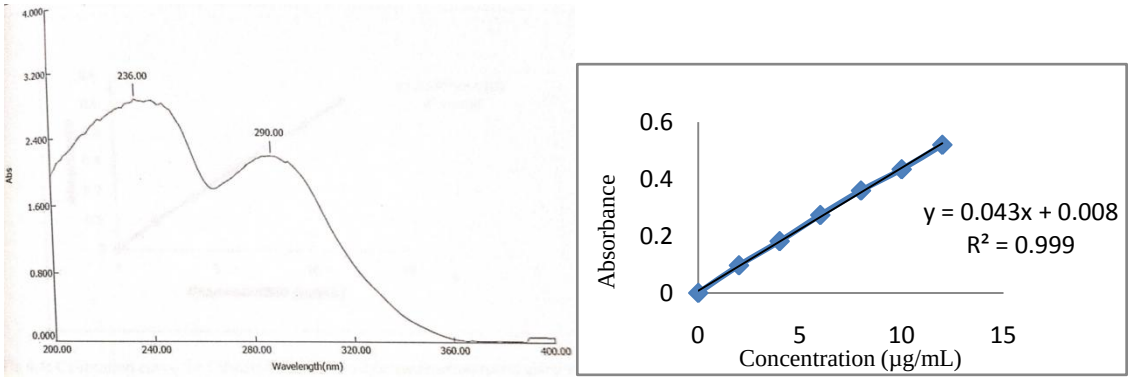

Figure 2: UV- visible spectrophotometer scan spectrum of Cilnidipine in methanol and Calibration curve for Cilnidipine

Fourier transformer infrared spectroscopy (FT-IR)

The infrared spectrum of Pioglitazone and Cilnidipine was obtained with the help of FT-IR spectrophotometer, using KBr pellet technique as shown in Figure 3,4, 5 & 6). The FTIR spectrum of Pioglitazone showed the presence of N-H (2967), C=O (1734), NH-C=O (1692), C-CH_3 (1460),S=O (1030).The FTIR spectrum of Cilnidipine showed the presence of N-H stretch (3084), -OCH3 (2878), C=O (1743), C-N stretch (1373), N-O (1333).The interpretation of FT-IR spectrum of Pioglitazone and Cilnidipine confirm the identity of Pioglitazone and Cilnidipine. The comparision of FT-IR of mixture of Pioglitazone and Cilnidipine was done with individual spectrum of Pioglitazone and Cilnidipine. No interaction was observed and as all of important peaks of individual drugs were present in the spectrum of mixtureand both the drugs are compatible and formation can be developed for the combination of Pioglitazone and Cilnidipine.

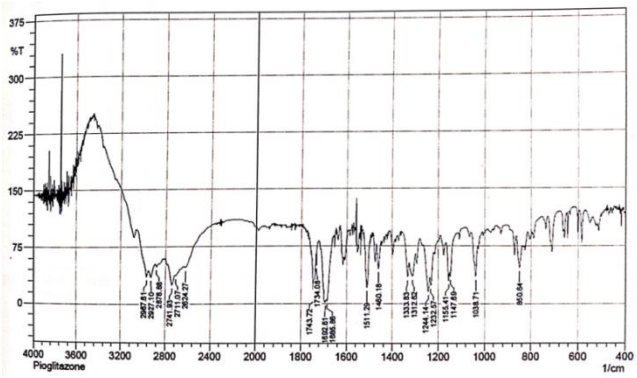

Figure 3: FT-IR spectrum of Pioglitazone

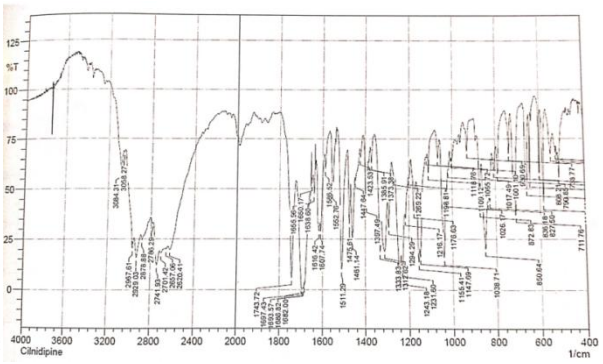

Figure 4: FT-IR spectrum of Cilnidipine

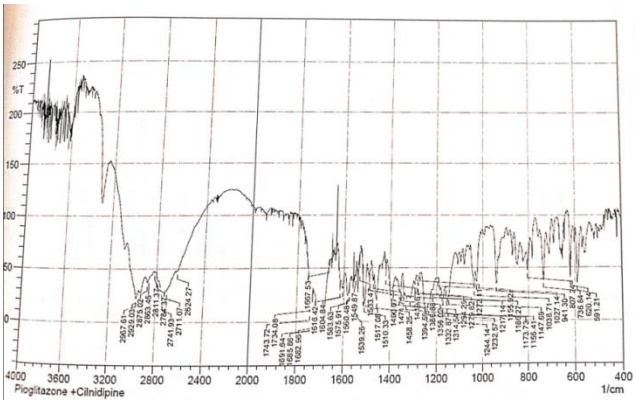

Figure 5: FT-IR spectrum of mixture of Pioglitazone and Cilnidipine

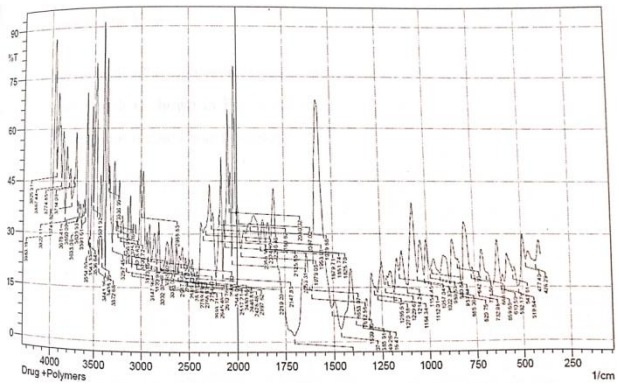

Figure 6: FT-IR spectrum of drugs and polymers

FORMULATION DEVELOPMENT

Preparation of powder blend by direct compression method

In this method all ingredients weighed according to their decreasing order to make a blend, all ingredients passed through sieve #40. The mixture was blended for 30 minutes by using double cone blender. After blending pre-compression study was performed.

EVALUATION OF POWDER BLENDS (PRECOMPRESSION STUDIES)

The pre-compression study was done for the blend of various formulation in which various parameters such as bulk density, tapped density, Angle of repose, Carr's index, Hausner's ratio, Percentage porosity, were studied. The result of pre compression study is shown in table 3.

Table 3:Results of pre-compression study of various formulations

Parameters	Formulation code				
	F1	**F2**	**F3**	**F4**	**F5**
Bulk density (g/mL)	0.370± 0.005	0.371± 0.004	0.310± 0.005	0.357± 0.005	0.355± 0.011
Tapped density (g/mL)	0.428± 0.006	0.414± 0.012	0.363± 0.007	0.373± 0.003	0.447± 0.006
Carr's index (%)	13.523±2.380	10.66± 1.485	14.495± 2.452	4.453± 1.874	18.317± 1.457
Hausner's ratio	1.352± 0.319	1.119± 0.019	1.170± 0.034	1.046± 0.021	1.220± 0.030
Angle of repose (θ)	13.54± 0.588	15.87± 0.997	16.140± 0.936	11.28± 0.980	24.013± 0.702
% Porosity	16.78± 2.820	11.96± 1.878	17.012± 3.399	4.437± 2.043	21.627± 0.703

*Result in Mean ±SD, where n=3

COMPRESSION OF TABLET BY DIRECT COMPRESSION METHOD

Buccal tablets containing Pioglitazone and Cilnidipine wereprepared by direct compression method.All the tablets were off white color, round in shape. The textures of tablets were smooth. The prepared tablets were subjected for the post compression evaluation.

EVALUATION OF BUCCAL TABLETS (POST COMPRESSION STUDIES)

The evaluation of tablets of various formulations was done and the different parameters were studied such as general appearance, thickness, diameter, weight variation, hardness, friability, disintegration time, drug content (as shown in table 4).

General appearance

All the tablets of different formulation were round in shape and smooth surface. The prepared tablets were white in color and odorless.

Weight Variation Hardness Thickness, Friability and Drug Content

All the formulationshowed almost uniform mass, thickness and showedfavorable drug content. For Cilnidipine, the drug content was found in the range of 90.603- 95.835%. While in case of Pioglitazone, the drug content was found to be in the range of 97.420- 105.643%. The maximum weight variation was 9.599, which shows all the formulation have weight variation in the limit and thickness ranged between 3.390 ± 0.05 and 3.494 ± 0.04 mm. The hardness and friability lies between 5.333 Kg/cm^{2}and6.333 Kg/cm^2, andthe minimum friability loss was found 0.062 for F5 while the maximum friability loss was found 0.276 for F4. In all the formulation,friability fallen below 1%, which is an indication of goodmechanical resistance of tablets.

Table 4: Results of evaluation of tablets of different formulations

Parameter	**Formulation code**				
	F1	**F2**	**F3**	**F4**	**F5**
Hardness (Kg/cm^2)	6.167± 0.289	6.333± 0.289	6.033± 0.153	5.933± 0.115	5.333± 0.306
Thickness (mm)	3.452± 0.027	3.390± 0.066	3.456± 0.045	3.457± 0.045	3.494± 0.047
Diameter (mm)	9.832± 0.043	9.803± 0.033	9.831± 0.048	9.805± 0.037	9.781± 0.022
Friability (%)	0.081± 0.041	0.095±0.054	0.128± 0.054	0.276± 0.086	0.062± 0.009
Weight variation (mg)	251.600±9.599	248.600±8.525	250.000±0.050	252.15±7.315	250.700±5.342
%Drug content (Cilnidipine)	91.570± 0.110	90.603± 0.561	92.403± 0.064	92.403± 0.064	95.835± 0.983
%Drug content (Pioglitazone)	97.420± 4.192	105.120±0.970	101.447±0.803	102.11± 0.069	105.64± 1.450

*Result in mean ± SD, where n=3

Determination of surface pH

The surface pH wasdetermined in order to investigate the possibility of any side-effects, in the oral cavity as acidic or alkaline pH is bound to causeirritation to the buccal mucosa. Surface pH of all formulations wasfound to be almost in neutral pH and ranged between 6.03 and6.71 and no mucosal irritation was expected.

Swelling Studies

Among all the formulations, F5 showed maximum swelling index of 105 % after 5 hrs and followed by F4, F3, F2, and F1. It was concluded that swelling increases as the timeproceeds because the polymer gradually absorb water due tohydrophilicity of polymer. The outermost hydrophilic polymer gethydrated which results in and swelling and a gel barrier is formedat the outer surface. As the gelatinous layer progressively dissolvesor disperses. The swelling behavior provides an idea regardingthe moisture intake capacities of polymers and the differences in swelling of the hydrophilic polymers may be due to the differencein resistance of the matrix network structure.

Bioadhesive Strength

The bioadhesion strength ofbuccal tablets**.**Adhesion occurs shortly after the beginning ofswelling but the bond formed between mucosal layer and polymer not very strong. The adhesion will increase with the degree ofhydration until a point where over-hydration leads to an abruptdrop in adhesive strength due to disentanglement at thepolymer/tissue interface. The formulation F5 showed maximummucoadhesion strength. The mucoadhesivestrength of the formulation F5 was found to be maximum of0.0754 Newton. This may be due to fact that positive charges onsurface of Carbopol 974-P could give riseto strong electrostatic interaction with mucous or negativelycharged mucous membrane.

Residence Time

0.0512	7.0 ± 0.41

The formulation F5 showed maximum residence time.Theresidence time of buccal tabletsranged between 6.4- 9.2 hrs and noted this much time required forbuccal tablets to detach from the buccal mucosa.

Table 5: Results of evaluation of tablets of different formulations

Formulation code	Surface pH	Bioadhesive Strength (N)	Residence Time (Hours)	Percentage Swelling
F1	6.19 ± 0.04	0.0512	7.0 ± 0.41	42
F2	6.34 ± 0.01	0.0481	6.4 ± 0.54	57
F3	6.18 ± 0.02	0.0667	8.3 ± 0.58	84
F4	6.71 ± 0.06	0.0608	8.0 ± 0.36	98
F5	6.36 ± 0.30	0.0754	9.2 ± 0.46	105

*Result in mean ± SD, where n=3

In-vitro drug release study

Among all the five formulations, F4 and F5werefound to behighest percentage drug release. During the study itwas observed that the tablets were initially swell and no erodible over the period of 4 hrs. For the preliminary studies it was concluded that by increasing the concentration of HPMC in the formulation, the drugrelease rate from the tablets was found to be decreased therefore the optimum and fixed concentration of HPMC was used in all the formulation. But when the concentration of PEG increased, the drug release ratewas found to be increased. This may be due to increased hydration(or) swelling characteristics of polymers with increasedconcentrations. From the overall data it was found that theformulation F4 and F5 showed the maximum percentage release.

Ex-vivo permeation studies

Based on *ex vivo* mucoadhesion, *ex-vivo* residence time and *in-vitro* release studies formulation F5 wasselected for *ex-vivo* permeation study. Pigs resemble that ofhumans more closely than any other animal in terms of structureand composition and therefore porcine buccal mucosa was selectedfor permeation studies. The results of drugpermeation frombuccal tablets through the porcinebuccalmucosa revealed that Pioglitazone and Cilnidipine was released from thetablet and

permeated through the porcine buccal membrane andcould possibly permeate through the human buccal membrane. The drug permeation for F5 formulation was slow and steady and 71.57 % for Pioglitazone and 75.84 % for Cilnidipine could permeate through the buccal membrane in 4hrs.

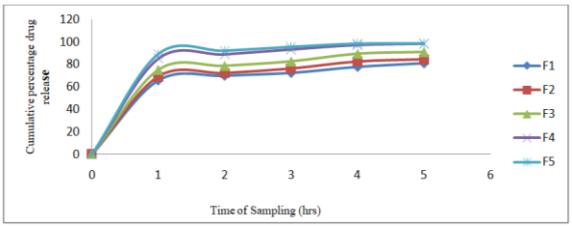

Figure 7:*In vitro*Cumulative percentage release of Pioglitazone

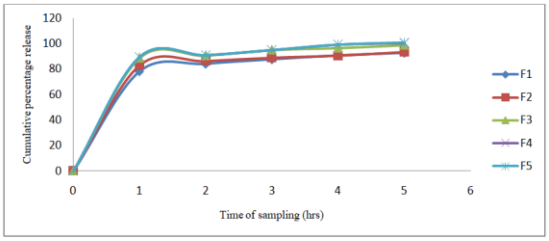

Figure 8:*In vitro*Cumulative percentage release of Cilnidipine

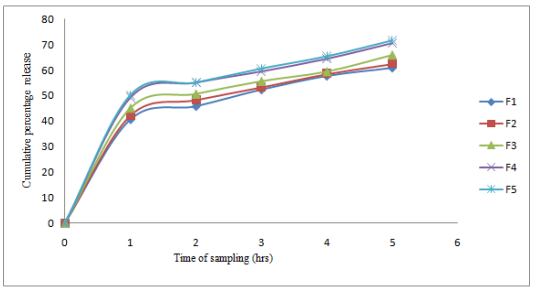

Figure 8: *Ex vivo* Cumulative percentage release of Pioglitazone

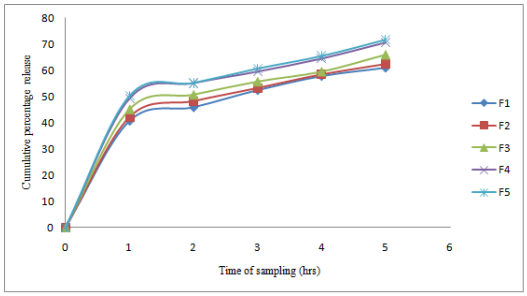

Figure 9: *Ex vivo*Cumulative percentage release of Cilnidipine

Stability of buccal tablets

The stability studies performed in normal human salivawould be more accurate to mimic the stability of the buccal tablet in oral cavity *in-vivo*. Based on theresults of *ex-vivo* mucoadhesion, *in-vitro* release studies, *ex-vivo* residence, formulation F5 was selected for stability study. Stabilitystudies in normal human saliva showed no change in the color of buccal tablets, which would have happened if drugwas stable in human saliva. Results reveal that the buccal tabletsare having sufficient stability in the human saliva. The thicknessand diameter of tablets slightly changed due to swelling of thepolymers in human saliva but buccal tablets did not collapse tillthe end of studies confirming that the device strength wassufficient.

Table 6: Stability data of F5 formulation in human saliva

Time	Color change	Thickness (mm)	Change diameter shape (mm^2)	Collapsing
0	No change	3.45 ± 0.04	10.80 ± 0.037	No change
1	No change	3.47 ± 0.05	10.81 ± 0.02	No change
2	No change	3.49 ± 0.02	10.19 ± 0.04	No change
3	No change	3.58 ± 0.04	10.26 ± 0.03	No change
4	No change	3.61 ± 0.05	10.35 ± 0.08	No change
5	No change	3.69 ± 0.04	10.42 ± 0.05	No change
6	No change	3.73 ± 0.06	10.51 ± 0.04	No change
7	No change	3.86 ± 0.09	10.59 ± 0.07	No change
8	No change	3.92 ± 0.04	10.62 ± 0.04	No change

*Result in mean ± SD, where n=3

CONCLUSION

Buccal tablets were manufactured direct compression method using different levels and combinations of the polymers HPMC K15 cps, K100. Solubility of Pioglitazone and Cilnidipine was determined595.0 ± 0.29 mg/mL for Pioglitazone and 519.0 ± 0.03 mg/mL for Cilnidipine in Methanol. The prepared buccal tablets physical characteristics were evaluated and they complied with the official pharmacopoeias limits.

The mucoadhesive strength were influenced by the nature and proportions of the mucoadhesive polymers used in the formulations. In all the formulations, as the mucoadhesive polymer mixture concentration increased, the mucoadhesive strength also increased. Buccal tablets formulated (F4 andF5) with a mixture of carbopol 934p, HPMCK15 cps, PEG 6000, lactose, magnesium stearate and ethyl cellulose showed comparatively higher bioadhesion than that of all other formulation. Very strong mucoadhesion could damage the epithelial lining of the buccal mucosa. Mucoadhesive strength exhibited by the formulation F4 and F5 tablets can be considered satisfactory for maintaining them in the oral cavity for 12hrs. The surface pH was determined in

order to investigate the possibility of any side effects, in the oral cavity. The surface pH of the buccal tablets depends on the nature and composition of mucoadhesive polymers. Surface pH of the all the formulation were found to be in the range of 6.1 to 6.3. This pH is near to the neutral, so the buccal tablet does not cause any irritation on the mucosa. The *ex-vivo* residence time was determined by using modified physical balance method. Formulations F4 to F5 showed higher Bioadhesive time when compared to the other formulations. As the concentration of the Carbopol 934p same in all formulation. The residence time also increased. This test reflects the mucoadhesive capacity of polymers used in formulations. The results revealed that themixture of carbopol 934p and HPMC containing formulations showed better bioadhesion than the mixture of all other muccoadhesive polymer in the formulations. Based on ex-*vivo*mucoadhesion, *ex-vivo* residence time and *in-vitro*release studies formulation F5 was selected for *ex-vivo* permeation study.

The *in-vitro* dissolution results revealed that the drug release was more than 95% within 4 hrs, suggesting high solubility of buccal tablet in methanol. The *ex-vivo* permeation study indicated the drug was highly permeable (≈40% within 1 hr). The polymer interaction contributed positively in two-way interactions and was negative in case of three-way interactions. The contribution of the individual polymers had shown negative effect. Therefore the formulation F4 and F5 had the optimum response values among all the formulations.

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