



African Journal of Biological Sciences



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

Pratibha Chaudhary, Tarun Kumar, Archana Chaudhary, MS Ashawat, Vinay Pandit*
Department of Pharmaceutics, Laureate Institute of Pharmacy, Kathog, Jawalamukhi

Corresponding author

e-mail: vinay2121@gmail.com

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 to enhance 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 tablets will have promising utilities in management of diabetic patient with hypertension.

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

Article History

Volume 6, Issue 5, 2024

Received: 22 May 2024

Accepted: 03 Jun 2024

doi: 10.48047/AFJBS.6.5.2024.11085-11113

Introduction

Hypertension (defined as a blood pressure $\geq 140/90$ 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. It is 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, dipeptidyl diphosphatase (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 with a 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 antidiabetic drug was carried out. Cilnidipine a unique Ca^{2+} channel blocker because of its inhibitory action on the sympathetic N-type Ca^{2+} channels along with L-type Ca^{2+} channels. Cilnidipine 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. Hydroxypropyl methyl cellulose (HPMC K-4M), sodium carboxy methyl cellulose (Na CMC) and Carbopol 934-P was obtained from Sigma Chemicals, USA. Aspartame was obtained from Strides Arco Labs, Bangalore, India. Magnesium stearate and ethyl cellulose were supplied from Loba Chemie 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 quantity 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 5 mL 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 determined 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 (10 mg) 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]

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

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 Cilnidipine 100 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 $\mu\text{g/mL}$ 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 $\mu\text{g/mL}$ 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 $\mu\text{g/mL}$ 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 were transferred 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 were developed 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 spectrum was 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 buccal tablets. 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 performed for core powder blend.^[57]

Compression of Tablet by Direct Compression Method

Buccal tablets containing Pioglitazone and Cilnidipine were prepared by direct compression method. The ingredients of the core layer were weighed accurately and mixed by trituration in a glass mortar and pestle for 15 minutes. All the ingredients were screened through sieve no. 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 punch was 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 batch and individually weighed using digital balance (Citizon, Model No. CG 203). Hardness was measured using Monsanto hardness tester and the thickness was measured by using digital vernier calliper (International Biological Laboratories).

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 minutes at the end of test, tablets were dusted and re-weighed the 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 in a 100 mL volumetric flask, mass equivalent to one tablet was taken and volume was made to mark with phosphate buffer (pH 6.8). The flask was shaken for 24 hrs 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 buccal tablets was determined to evaluate the possible irritation effects on the 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 (W_0) and placed in a petridish containing 5 mL of phosphate buffer (pH 6.8) for 8 hours. After that, the tablets were taken out from the petridish and excess water was removed carefully by using filter paper and weighed again (W_t). The swelling index was calculated using the following formula.^[67, 68]

$$SI = (W_t - W_0) / W_0 \times 100$$

Where SI = Swelling index

W_t = Weight of tablets after time (t)

W_0 = Weight of tablet before placing in the Petri dish

Bioadhesive Strength

A modified physical balance was used for determining the bio adhesive strength. The left pan was removed. The buccal tablet was then stuck to glass stopper through its backing membrane using an adhesive (Feviquick). To left arm of balance the glass stopper along with the tablet was hanged. A clean glass mortar was placed below hanging glass stopper. The balance was so adjusted that right hand side was exactly 5 g heavier than the left. Fresh porcine buccal mucosa was obtained from a local slaughter house and used within 2 hrs of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues, washed with distilled water and then with phosphate buffer pH 6.8 at 37°C. The fresh porcine buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied with the mucosal side upwards using thread over the hollow cylinder, the cylinder was used because it was gave strength to the buccal mucosa and it was not float during the adhesion. The cylinder was then lowered into the glass beaker (250 mL) which was then filled with 200 mL phosphate buffer pH 6.8 kept 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 be tested for bioadhesion was then stuck with a little moisture. The 5 g weight on the right pan was removed. This lowered the tablet over the mucosa, with a force of 5 g. The balance was kept in this position for 3 minutes and then the weight was added slowly to the right hand pan until the tablet detached from the mucosal surface. The detachments force gave the bioadhesive strength of the buccal tablet in g. From the bioadhesive strength, force of adhesion and then the averages of three determinations were calculated: ^[69,70,71]

$$\text{Force of adhesion (F)} = [W \times g] / 1000$$

Where g is acceleration due to gravity (9.80665 m/sec²)

Residence Time

The *ex-vivo* residence time was determined using a locally modified USP disintegration apparatus. The disintegration medium was composed of 900 mL (pH 6.8) of phosphate buffer maintained at

37±1°C. The porcine buccal 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 test apparatus-II, employing paddle stirrer at 50 rpm and 200 ml of pH 6.8 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 is placed at the bottom of the dissolution vessel. Samples of 5 mL were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.45µm membrane 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**

The permeation study of buccal tablet was carried out on porcine buccal membrane using modified Franz diffusion cell with a diffusion area of 17.35 cm² and the acceptor compartment volume of 30 mL. A semi permeable membrane (porcine buccal mucosa membrane) was clamped between the donor and acceptor compartments. The water in the acceptor compartment was continuously stirred at 100 rpm using a magnetic stirrer and maintained at 37 ± 0.5°C. The buccal tablet was placed into the donor compartment and was wetted with 1ml of 7.4 pH phosphate buffer. The diffusion was carried out for 10 hrs. The amount of drug permeated through the membrane was determined by removing samples periodically and replaced with an equal volume of 7.4 pH

phosphate buffer. These aliquots after filtration were diluted suitably and analyzed spectrophotometrically at 219 nm and 236 nm or absorbed against similar treated blank.^[74, 75]

Stability of buccal tablets

Stability studies of buccal tablets were performed for best formulation in normal human saliva. The human saliva was collected and filtered through filter paper. Buccal tablets were immersed in separate petridish containing 5 mL of human saliva and placed in a temperature-controlled oven for 10 hrs $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. At predetermined time interval the buccal tablets were evaluated by observing change in colour, shape, collapse of the tablet and change in pH. The experiments were repeated in triplicate.^[76,77]

Result and Discussion

Preformulation Study

The results of Physical characterization, melting point, Solubility, Partition coefficient are 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	$105^{\circ}\text{C} \pm 0.02$	$188^{\circ}\text{C} \pm 0.05$
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 Cilnidipine, the determination of maximum absorption was done using methanol as solvent, using solution of 12 $\mu\text{g/mL}$ and 10 $\mu\text{g/mL}$ concentration, respectively. The spectrum for Pioglitazone and Cilnidipine was obtained at 219 nm and 236 nm, respectively.

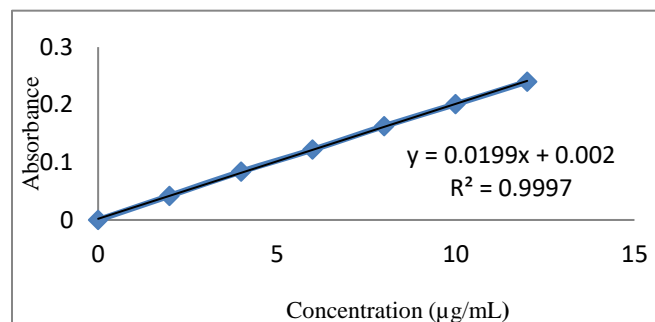
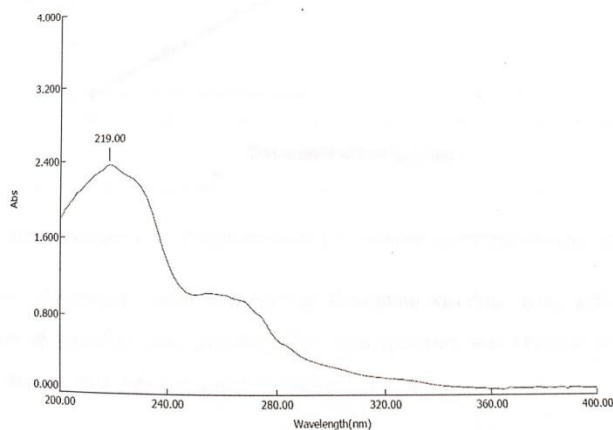


Figure 1: UV – visible spectrophotometer scan spectrum of Pioglitazone in Methanol and Calibration curve for Pioglitazone

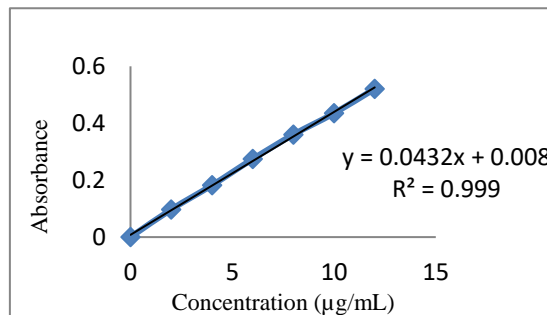
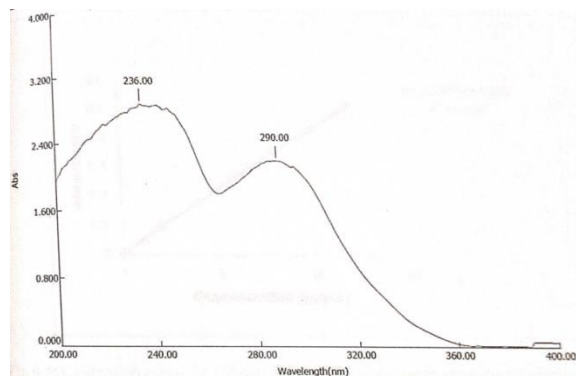


Figure 2: UV- visible spectrophotometer scan spectrum of Cilnidipine in methanol and Calibration curve for Cilnidipine

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-CH₃ (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 comparison 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 mixture and both the drugs are compatible and formation can be developed for the combination of Pioglitazone and Cilnidipine.

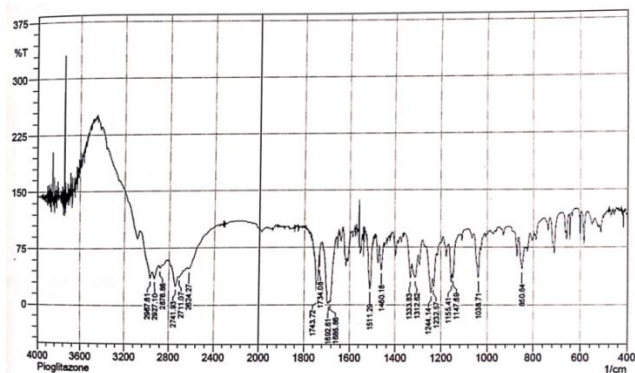


Figure 3: FT-IR spectrum of Pioglitazone

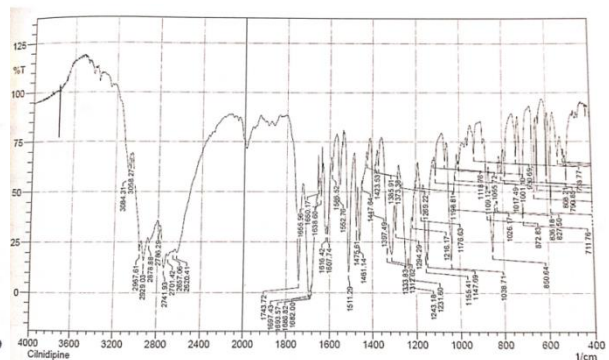


Figure 4: FT-IR spectrum of Cilnidipine

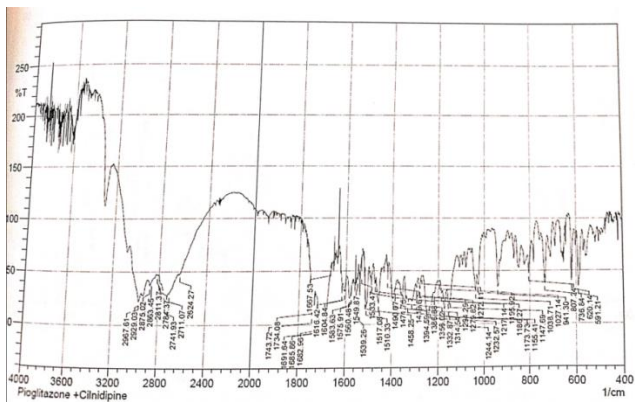


Figure 5: FT-IR spectrum of mixture of Pioglitazone and Cilnidipine

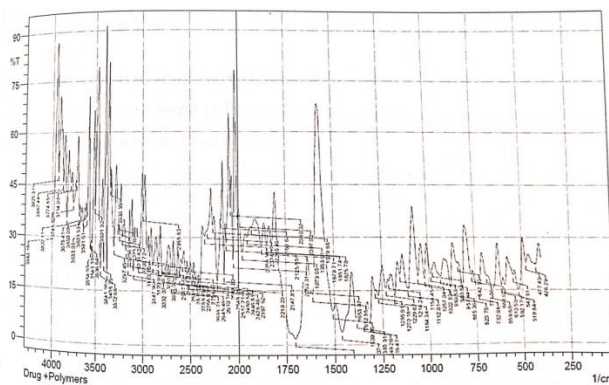


Figure 6: FT-IR spectrum of drugs and polymers

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 were prepared 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 formulation showed almost uniform mass, thickness and showed favorable 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 and 6.333 Kg/cm^2 , and the 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 good mechanical resistance of tablets.

Table 4: Results of evaluation of tablets of different formulations

Parameter	Formulation code				
	F1	F2	F3	F4	F5
Hardness (Kg/cm²)	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 was determined in order to investigate the possibility of any side-effects, in the oral cavity as acidic or alkaline pH is bound to cause irritation to the buccal mucosa. Surface pH of all formulations was found to be almost in neutral pH and ranged between 6.03 and 6.71 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 time proceeds because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer get hydrated which results in and swelling and a gel barrier is formed at the outer surface. As the gelatinous layer progressively dissolves or disperses. The swelling behavior provides an idea regarding the moisture intake capacities of polymers and the differences in

swelling of the hydrophilic polymers may be due to the difference in resistance of the matrix network structure.

Bioadhesive Strength

The bioadhesion strength of buccal tablets. Adhesion occurs shortly after the beginning of swelling but the bond formed between mucosal layer and polymer not very strong. The adhesion will increase with the degree of hydration until a point where over-hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer/tissue interface. The formulation F5 showed maximum mucoadhesion strength. The mucoadhesive strength of the formulation F5 was found to be maximum of 0.0754 Newton. This may be due to fact that positive charges on surface of Carbopol 974-P could give rise to strong electrostatic interaction with mucous or negatively charged mucous membrane.

Residence Time

The formulation F5 showed maximum residence time. The residence time of buccal tablets ranged between 6.4- 9.2 hrs and noted this much time required for buccal 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 F5 were found to be highest percentage drug release. During the study it was 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 drug release 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 rate was found to be increased. This may be due to increased hydration (or) swelling characteristics of polymers with increased concentrations. From the overall data it was found that the formulation 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 was selected for *ex-vivo* permeation study. Pigs resemble that of humans more closely than any other animal in terms of structure and composition and therefore porcine buccal mucosa was selected for permeation studies. The results of drug permeation from buccal tablets through the porcine buccal mucosa revealed that Pioglitazone and Cilnidipine was released from the tablet and permeated through the porcine buccal membrane and could 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 4 hrs.

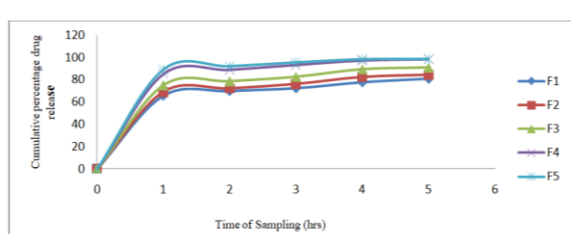


Figure 7: *In vitro* Cumulative percentage release of Pioglitazone

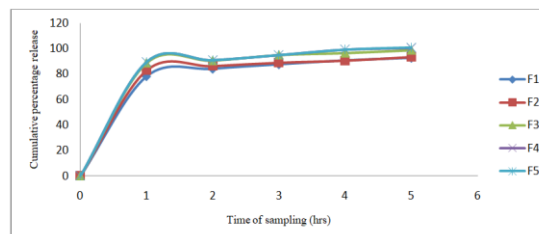


Figure 8: *In vitro* Cumulative percentage release of Cilnidipine

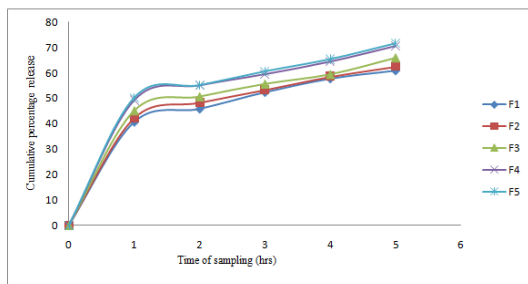


Figure 8: *Ex vivo* Cumulative percentage release of Pioglitazone

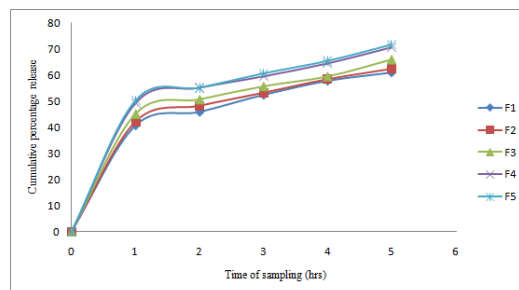


Figure 9: *Ex vivo* Cumulative percentage release of Cilnidipine

Stability of buccal tablets

The stability studies performed in normal human saliva would be more accurate to mimic the stability of the buccal tablet in oral cavity *in-vivo*. Based on the results of *ex-vivo* mucoadhesion, *in-vitro* release studies, *ex-vivo* residence, formulation F5 was selected for stability study. Stability studies in normal human saliva showed no change in the color of buccal tablets, which would have happened if drug was stable in human saliva. Results reveal that the buccal tablets are having sufficient stability in the human saliva. The thickness and diameter of tablets slightly changed due to swelling of the polymers in human saliva but buccal tablets did not collapse till the end of studies confirming that the device strength was sufficient.

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 determined 595.0 ± 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 and F5) 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 12 hrs. 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 the mixture of carbopol 934p and HPMC containing formulations showed better bioadhesion than the mixture of all other mucoadhesive 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 ($\approx 40\%$ 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.

REFERENCES

1. Anwer Z, Sharma P.K , Garg V.K, Kumar N, Kumari A. Hypertension management in diabetic patients. European Review for Medical and Pharmacological Science 2011; 15: 1256-1263.
2. Geldsetzer P, Jennifer MG, Theilmann M, Awasthi A, Vollmer S, Jaacks LM. Diabetes and Hypertension in India. A nationally representative study of 1.3 million adults. JAMA Intern Med. 2018;178 (3):363-372. doi:10.1001/jamainternmed.2017.8094.
3. Darshan S Khangura, M.D, Muhammad Waqar Salam, Stephan A Brietzke, M.D, James R Sowers, M.D. Hypertension in Diabetes. NCBI Bookshelf A service Library Of Medicine, National Institute of Health.
4. SheteMukeshMadhukarCilnidipine: Next Generation Calcium Channel Blocker. Journal Of The Association Of Physicians Of India, Vol. 64, April 2016.

5. Strongman H, Korhonen P, Williams R, et al. Pioglitazone and risk of mortality in patients with type 2 diabetes: results from a European multidatabase cohort study. *BMJ Open Diab Res Care* 2017;5:e000364. doi:10.1136/bmjdr-2016-000364.
6. Iswariya V. T, Hari Om Prakash Rao A., Buccal Tablets a Comprehensive Review *European Journal Of Pharmaceutical And Medical Research*.ISSN 3294-3211,ejpmr, 2016,3(8), 252-262
7. Ohishi Mitsuru. Hypertension with Diabetes Mellitus: Physiology and Pathology. *Hypertension Research* 41, 389-393 (2018).
8. HeringDagmara, TrzebskiAndrzej, Narkiewicz Krzysztof. Recent advances in the pathophysiology of arterial hypertension: potential implicationsfor clinical pract *Advances in pathophysiology of arterial hypertension*. *Pol Arch Intern Med*. 2017; 127 (3): 195-204doi:10.20 452/pamw.3971.
9. VasilisTsimihodimos, Clicerio Gonzalez-Villalpando, James B. Meigs, EleFerrannini. Hypertension and Diabetes Mellitus Coprediction and Time Trajectories. *Hypertension*. 2018;71:422-428. DOI: 10.1161/Hypertensionaha.117.10546.
10. Okur Mehmet Evren, KarantasIoannis D., SiafakaPanoraia I. Diabetes Mellitus: A Review on Pathophysiology, Current Status of Oral Medications and Future Perspectives.*ActaPharmaceuticaScientia*. Vol. 55 No. 1, 2017, DOI: 10.23893/1307-2080.APS.0555, pp.61-82.
11. John Waugh, Gillian M. Keating, Greg L. Plosker, Stephanie Easthopeand Dean M. Robinson. Pioglitazone A Review of its Use in Type 2 Diabetes Mellitus. *Adis Drug Evaluation, Drugs* 2006; 66 (1): 85-109;0012-6667/06/0001-0085/\$44.95/0.
12. RanpiseNisharani, JamkarPreeti, LangoteHarshada. Do Fixed Dose Combinations Play an Important Role in the Management of Coexistent. *Indian Journal of Pharmaceutical Education and Research* | Vol 49 | Issue 3| Jul-Sep, 2015.pp 190-199.
13. Shashank R. Joshi, Diabetes Care in India. *Annals of Global Health* 2015 I cahn School of Medicine at Mount Sina I, VOL .81 , NO. 6 , 2015 ISSN 2214 -9996.

14. Yazdanpanah Leila, ShahbazianHajjesh, NazariIraj, Hamid Reza Arti. Incidence and risk factors of Diabetic foot cohort (ADFC Study)- two year follow up study, International Journal of Endocrinology; Vol. 2018, Article ID 7631659, 9 pages.
15. Subramanian Savitha, MD, Hirsch Irl B., MD. Personalized Diabetes Management: Moving from Algorithmic to Individualized Therapy. Diabetes Spectrum Volume 27, Number 2, 2014.pp. 87-91.
16. Akilew Awoke, Tadesse Awoke, ShitayeAlemu and BerihunMegabiaw. Prevalence and associated factors of hypertension among adults in Gondar, Northwest Ethiopia: acommunity based cross-sectional study. BMC Cardiovascular Disorders 2012, 12:113, <http://www.biomedcentral.com/1471-2261/12/113>.
17. PrajapatiDhara, KediaGeeta.Prevalence of diabetes and its risk factors: a cross-sectional study in Ahmedabad, Gujarat.International Journal of Medical Science and Public Health; 2016; Vol .5; Issue 03.pp. 425-429.
18. Vaz N.C, Ferreira A.M., Kulkarni M.S, Vaz, F.S. Prevalence of diabetes mellitus in a rural population of Goa, India. The National Medical Journal Of India Vol. 24, N0.1, 2011.
pp.16-18.
20. KaurSukhraj, MahajanMridula, Bal B.S, Prevalence of Insulin Resistance In Siblings Of Type 2 Diabetes of North West Punjabi Population. Journal Of Clinical and Diagnostic Research, JClinDiagn Res. 2014 Aug; 8(8); CC14-CC18;doi: 10.7860/JCDR/2014/ 10198.4701.
21. Bavry AA, Khaliq A, Gong Y, Handberg EM, Cooper-DeHoff RM, Pepine CJ. Harmful effects of NSAIDs among patients with hypertension and coronary artery disease.The American Journal of Medicine. 2011 July; 124(7): p. 614-620.
22. PiriyaPrasarth S, Sriamornsak P. Effect of source variation on drug release from HPMC tablets: Linear regression modeling for prediction of drug release. International Journal of Pharmaceutics. 2011 June 15; 411(1-2): p. 36-42.
23. Goswami SD, Goyal S, Goyal D, Sharma R, Mehta N, PK, et al. Formulation and evaluation of Mucoadhesive tablets of Famotidine. Journal of Pharmaceutical and Biomedical Sciences. 2011; 12(13): p. 1-3.

24. Palem C.R., Gannu Ramesh Development of bioadhesive buccal tablets for Felodipine and Pioglitazone in combined dosage form: in vitro, ex vivo and in vivo characterization. *Journal Drug Delivery* Vol. 18, 2011-Issue 5. pp. 344-352.
25. Sharma Avinash, Grover Neelam, Kaushik Shayam, Bhardwaj Rajiv, Sankhyan Naveen. Prevalence of Hypertension Among School children in Shimla. *Indian Pediatrics*, Vol. 47 October 17, 2010. pp 873-876.
26. Mohammadi-Samani S, Bahri-Najafi R, Yousefi G. Formulation and in vitro evaluation of Prednisolone buccoadhesive tablets. *IIFarmaco*. 2005 April; 60(4): p. 339-344.
27. Narendra C, Srinath M S, Prakash Rao B. Development of three layered buccal compact containing Metoprolol tartrate by statistical optimization technique. *International Journal of Pharmaceutics*. 2005 November 4; 304(1-2): p. 102-114.
28. Abdul Hamid Zargar, Abdul Ahad Wani, Bashir Ahmad Laway, Shariq Rashid Masoodi, Arshad Iqbal Wani, Mir Iftikhar Bashir, Farooq Ahmad Dar. Prevalence of diabetes mellitus and other abnormalities of glucose tolerance in young adults aged 20–40 years in North India (Kashmir Valley). Article in *Diabetes research and clinical practice* · October 2008 DOI: 10.1016/j.diabres.2008.08.006 · Source: PubMed. *Diabetes research and clinical practice* 82 (2008) 276 – 281.
29. Contreras F, Rivera M, Vasquez J, Parte MA De la, Velasco M. Diabetes and Hypertension Physiopathology and therapeutics. *Journal of Human Hypertension* (2000) 14, Suppl 1, S26- S31. pp 1-7.
30. <http://en.wikipedia.org/wiki/pioglitazone>.
31. <http://en.wikipedia.org/wiki/cilnidipine>.
32. Rowe RC, Sheskey PJ, Quinn ME. *Handbook of pharmaceutical excipients*. 6th ed. London: Pharmaceutical Press; 2009. 94-730 p.
33. Lachman L, Lieberman HA, Kanig JL. *The theory and practice of industrial pharmacy*. 3rd ed. Bombay: Varghese Publishing House; 1986. 293-345 p.
34. <http://en.wikipedia.org/wiki/pioglitazone>.
35. <http://en.wikipedia.org/wiki/cilnidipine>.

36. Indian pharmacopoeia. Ghaziabad: The Indian Pharmacopoeia Commission; 2007.
37. Ashford M. Assessment of biopharmaceutical properties. In: Aulton ME. Aulton's pharmaceuticals the design and manufacture of medicines. 3rd ed. London: Harcourt Publishers Limited. 2007. p. 304-322.
38. Connors KA, Amidon GL, Stella VJ. Chemical stability of pharmaceutical: A handbook for pharmacists, New York: Wiley- interscience Publications; 1986.
39. NaveedSafila, Ashraf Zehra, MukhtarTasleem. Assay of Pioglitazone HCL by using UV Visible spectrophotometer. British Journal of Research. www.britishjr.org.ISSN:2394-3718.
40. Singh Vijay Vikram, Chaudhary Hema B, Tiwari Richa. Method development of Pioglitazone by UV Spectrophotometer. International Journal Of Drug Development and Research.
41. Sharma Y. R, Introduction to UV Visible spectroscopy. Elementary organic spectroscopy 4th edition. S. Chand publisher; 1980; p. 68-192
42. Pavia D.L, Gary M.L, James A, George S. Ultraviolet spectroscopy, Introduction to spectroscopy, 4th edition Cengage learning; 2009, p. 381-417.
43. Chaudhari P.P, Bhalariao A.V. Method validation for spectrophotometer estimation of Cilnidipine. International Journal Of Pharmacy And Pharmaceutical Sciences.Vol4, Suppl 5, 96-98.
44. Sidhdhaparamital, Patel Biraju, Parmar Ashok, Vekariya Hitesh, Patel Piyush. Development and validation of spectrophotometric method for simultaneous determination of Cilnidipine and OlmesartanMedoximil in tablet dosage form.Research Article Pharmaceutical Sciences, IJPBS/ Volume 4/ Issue 2/ APR-JUN/ 2014/ 97-101.
45. Pavia DL, Lampman GM, Kriz GS. Introduction to spectroscopy. 3rd ed. United States: Thomson Learning Inc. 2001. p.13-84.
46. Farouk Faten, Moussa BA, Azzazy H.M.E. Fourier transform infrared spectroscopy for in process inspection, counterfeit detection and quality control of anti- diabetic drugs. Spectroscopy 26 (2011) 297-309, DOI 10.3233/SPE-2011-0531,IOS Press .p.297-309.
47. ChowdaryAppana, Suravarapu N.L.R, MeddalaSwathi. Formulation and Characterization of Pioglitazone Hydrochloride nanoparticles.www.wjpps.com, Vol 4, Issue 04, 2015.

48. Patel Ashish, Panchal Arti, Patel Viral, Nagar Akhil. FTIR spectroscopic method for quantitative analysis of Cilnidipine in tablet dosage form. *International Journal Of Pharma Sciences and Research*, ISSN :0975-9492, Vol. 6 No.7 Jul 2015.
49. Mali Bhakti, Moharil S.N, MhasalVaibhav, Narkhede M.B. Drug excipient interaction study of Tramadol HCL with polymers. *World Journal Of Pharmaceutical Research*, ISSN 2277-7105 Volume 6, Issue 13, 848-861.
50. Validation of analytical procedures: text and methodology Q2(R1). ICH Harmonised Tripartite Guideline. 2005; 1-13.
51. Indian pharmacopoeia. Ghaziabad: The Indian Pharmacopoeia Commission; 2007; 1: 136-188 p.
52. Harris DC. Quantitative chemical analysis. 8th ed. New York: WH Freeman and Company; 2010. 96-116 p.
53. Davidson AG. Ultraviolet-visible absorption spectrophotometry. In: Beckett AH, Stenlake JB. *Practical pharmaceutical chemistry - part two*. 4th ed. New York: CBS Publishers and Distributors; 2005. p. 275-337.
54. Bolton S, Bon C. *Pharmaceutical statistics practical and clinical application*. 5th ed. New York: Informa Healthcare; 2009. p. 13-127.
55. Shabir GA. Step-by-step analytical methods validation and protocol in the quality system compliance industry. *Inst Valid Technol*. 1-14.
56. ViswanadhanPrasanthVasantha, PadoleAnand, Abraham Abin, Mathew S.T. Buccal Tablets of Lisinopril by Direct compression Method for Buccal Drug Delivery, *Intl. R. J. of Pharmaceuticals* (2012), Vol. 02, Issue 02, pp. 30-38 ISSN 2048- 4143.
57. Merck Research Laboratories. *The merk index*; 2006 p.1428.
58. Sinko PJ. *Martin's physical pharmacy and pharmaceutical sciences*. 5th ed. New Delhi: Wilkins Kluver Health Pvt Ltd; 2007. p. 533-560.
59. Mohamed EA, Hammid SNA. Formulation and evaluation Pioglitazone tablets. *Int. J. PharmSci*.2013; 2(2):339-346.

60. PrasanthVasantha Viswanadhan¹, AnandPadole, Abin Abraham¹ and Sam Thomarayil Mathew. Buccal tablets of Lisinopril by direct compression method for buccal drug delivery, Intl. R. J. of Pharmaceuticals (2012), Vol. 02, Issue 02, pp. 30-38 ISSN 2048-4143.
61. Prashant, A.B., Taware, G.V., Hariprasanna, R.C., and Najmuddin, M. (2011) Development and evaluation of mucoadhesive buccal tablets of loratadine. Journal of Pharmacy Research, 4, pp. 2699-2702.
62. Ashform M. Assessment of biopharmaceutical properties. In: Aulton ME. Aulton's pharmaceutics the design and manufacturing of medicines. 3rd ed. Churchill Livindstones. P.304-322.
63. Lachman L, Lieberman HA, Kang JL. The theory and practical of industrial pharmacy. 3rd ed. Varghese Publishing House. 2008:p. 171- 382.
64. Indian pharmacopoeia. Ghaziabad: The Indian Pharmacopoeia Commission; 2007; 1: 136-188 p.
65. Venkateswarlu K, Jami KP. Formulation development and in vitro evaluation of mouth dissolving tablets of Pioglitazone hydrochloride; Pharma Tutor.2016;4(12); 37-42.
66. Rawat PK, Mote PB, Singh S. Fast dissolving tablets of Pioglitazone hydrochloride by use of various superdisintegrants. IJARPB: 2013; 3(2):74-79.
67. Rawat PK, Mote PB, Singh S. Fast dissolving tablets of Pioglitazone hydrochloride by use of various superdisintegrants. IJARPB: 2013; 3(2):74-79.
68. BiswalBiswajit, KarnaNabin, BhavsarBhavesh . Formulation and Evaluation of Repaglinide Buccal Tablet: Ex Vivo Bioadhesion Study and Ex Vivo Permeability Study. Journal of Applied Pharmaceutical Science Vol. 4 (05), pp. 096-103, May, 2014.
69. Lindgren S, Janzon L. Dysphagia: prevalence of swallowing complaints and clinical finding. Med. Clin. North Am. 1993; 77: 3-5.
70. S.Velmurugan, B.Deepika, K Nagaraju, SundarVinushitha. Formulation and in-vitro evaluation of buccal tablets of Piroxicam. International Journal Of Pharm Tech Research, CODEN (USA): IJPRIF, ISSN :0974-4304, Vol.2, No.3, pp 1958-1968.

71. KashappaGoud H. Desai and T.M. Pramod Kumar, Preparation and Evaluation of a Novel Buccal Adhesive System, AAPS Pharm Sci Tech.,2004;5(3): 1-9.
72. Bhavin Patel, Piyush Patel, Ashok Bhosale and ShrawareeHardikar,Evaluation of Tamarind Seed Polysaccharide (TSP) as a mucoadhesive and sustained release component of nifedipinebuccoadhesive tablet & Comparison with HPMC and Na CMC, Inter. J. PharmTech Research.,2009;1(3): 404- 410.
73. Pulakkumarmetia,Amalkumarbandyopanyay,Invitro evaluation of novel mucoahesivebuccal tablets of oxytocin preparation with diospyrospergrina fruits mucilages,The pharmaceutical society of japan.,2008;128 (14) :603-609.
74. SolimanMohammadi-Samani, Rahim Bahri- Najafi, GolamhoseinYousefi; Formulation and in vitro evaluation of prednisolone buccoadhesive tablets; Il Farmaco.,2005;60:339–344.
75. Vamshi Vishnu Yamsani, Ramesh Gannu, Chandrasekhar Kolli, M. E. BhanojiRao and Madhusudan Rao Y, Development and in-vitro evaluation of buccoadhesivecarvedilol tablets, Acta Pharm., 2007; 57: 185-197.
76. Pulakkumarmetia,Amalkumarbandyopanyay,Invitro evaluation of novel mucoahesivebuccal tablets of oxytocin preparation with diospyrospergrina fruits mucilages. The pharmaceutical society of japan.,2008;128 (14) :603-609.
77. T.M. Pramodkumar, H.G.Shivakumar; Novel core in cup buccoadhesive systems and films of terbutalinesulphate- development and in- vitro evaluation; Asian J. Pharma. Sci., 2006; 1(3-4): 175- 187.
78. Han-Gon Choi, Chong-Kook Kim,Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva;J. Control. Rel., 2000; 68: 397– 404.