A Review on Development and Evaluation of Mouth Dissolving Buccal Tablet for Antidiabetic Activity

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***Abstract*: Glimepiride is second generation new sulfonyl urea oral antidiabetic. Glimepiride is poorly soluble in acidic environment. The aim of this study was to design and optimize Glimepiride mucoadhesive buccal tablets for systemic delivery as an alternative route. Glimepiride containing mucoadhesive buccal tablets were developed by direct compression method. Four mucoadhesive polymers namely HPMC 100M, Xanthan gum, Chitosan and Guar gum were used for preparation of tablets which intended for prolong action. The prepared tablets were evaluated for different physical parameters and dissolution study was performed in pH 6.8 phosphate buffer solution for 12 hours. The compatibility study showed that the drug was compatible with polymers and other excipients. Tablet preformulation parameters were within the Pharmacopoeial limit. HPMC 100M showed above 95% release within 8 hours whereas HPMC 100M in combination with Gaur gum and Chitosan sustained the drug release over a period of 12 hours. The drug release from prepared tablets follows the Higuchi kinetic model, and the mechanism is found to be non-Fickian/anomalous according to Korsmeyer–Peppas model. The stability studies were carried out for 3 months and prepared tablets were found to be stable. Thus, the present study concluded that, Glimepiride buccal tablets containing combination of natural and synthetic polymer can be successfully prepared for the treatment of diabetes as well as for prolonged drug delivery.**

***Keywords*: Glimepiride, Direct compression, Buccal tablets, HPMC 100M, Chitosan, Xanthan gum, Gaur gum, and Higuchi kinetic model.**

INTRODUCTION

GENERAL INTRODUCTION:

- Drug delivery to human body is very important to reduce symptoms of any disease and to provide relief from discomforts caused by these diseases. To suppress disease and its symptoms drug has to be administrated to patient by two major routes i.e. oral and parenteral routes. However several studies have shown that both routes of drug administration are not effective in all cases.[1]
- Among all trans-mucosal sites, buccal cavity was found to be the convenient and easily accessible site for the local or systemic delivery of drugs. Because of its expanse of relatively immobile smooth muscle, abundant vascularization, direct access to the systemic circulation through the internal jugular vein that bypasses hepatic first pass metabolism, makes it highly promising for delivery of drugs exhibiting poor oral bioavailabilities. Facile removal of formulation, better patient acceptance and compliance are some other prominent meritorious advantages of buccal adhesive systems.[3]

MUCOADHESIVE DRUG DELIVERY SYSTEMS:[4-6]

- These may be defined as drug delivery systems, which utilize the property of bioadhesion of certain water soluble polymers which become adhesive on hydration. These represent potential sites for attachment of any bioadhesive system.
- The mucoadhesive drug delivery system includes the following:-
    1) Buccal drug delivery system.
    2) Oral delivery system.
    3) Vaginal delivery system.
    4) Rectal delivery system.
    5) Nasal delivery system.
    6) Ocular delivery system

Buccal mucosal structure and its suitability:[7-8]

Maxillary artery supplies blood and blood flow is faster and richer (2.4 ml/min/cm^2), thus facilitates passive diffusion of drug molecules across the mucosa.

The turnover time for the buccal epithelium has been estimated at 5-6 days.

Buccal mucosa composed of several layers of different cells as shown in figure. 1. Lining epithelium is the nonkeratinized stratified squamous epithelium that has thickness of approximately 500-600µm and surface area of 50.2cm^2. Basement membrane, lamina propria followed by the submucosa is present below the epithelial layer.

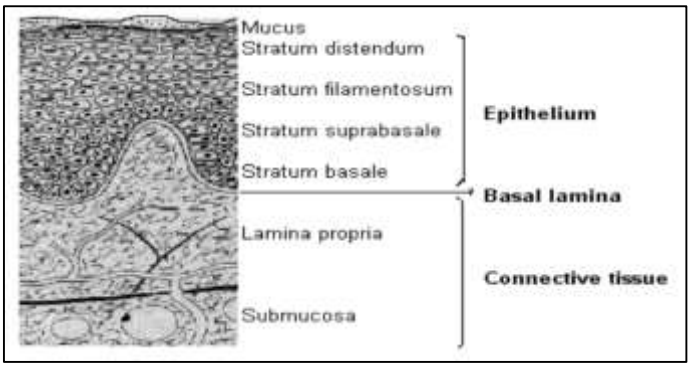


Figure 1: Cross-Section through buccal mucosa

Buccal drug delivery systems:[10-12]

The histological features of buccal mucosa make it a feasible site for sustained release delivery systems, which could maintain a steady release of drug in the systemic circulation.

Various delivery approaches have been developed to deliver drugs into the oral cavity for either local or systemic action.

These include mouthwashes, lozenges, gels, chewing gums, lollipops, films, patches, tablets and some specialized transmucosal devices.

Advantages of mucoadhesive buccal drug delivery system:[11-12]

- Ease of administration & termination of therapy is easy.
- Permits localization of drug to the oral cavity for prolonged period of time.
- Can be administered to unconscious patients.
- Drugs which show poor bioavailability can be administered conveniently.
- It offers passive system of drug absorption and does not require any activation.
- The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal route.

Limitations of Buccal Drug Administration:[11-12]

- Drugs which irritate the mucosa or have a bitter or unpleasant taste or cannot be administered by this route.
- Drugs contained in the swallowed saliva follows per oral route and advantages of buccal route are lost also eating and drinking may become restricted.
- Only those drugs which are absorbed by passive diffusion can be administered by this route.
- Sometimes they show unpredictable bioavailability. Relatively low permeability for most drugs e.g. some lipophilic drugs are best absorbed.

Types of formulation:[13]

- **Adhesive Gels**
- **Adhesive Patches**
- **Bioadhesive buccal tablets**

FACTORS INFLUENCING MUCOADHESION:[17-18]

Factors that can influence mucoadhesion can be categorized into:

- Polymer related factors
- Environment related factors
- Physiological variables

MUCOADHESIVE POLYMERS:[19,20]

- ❖ Polymer and its degradation product should be non-toxic, non-irritant and free from leachable impurities.
- ❖ Should have sensible spreadability, wettability, swellability, solubility and biodegradability properties.
- ❖ Should contain a considerable degree of flexibility so as to attain the specified web with the mucous secretion.
- ❖ Should adhere quickly to buccal tissue layer and may possess sufficient mechanical strength.
- ❖ Should demonstrate acceptable period of time.
- ❖ Should not aid in development of secondary infections such as dental caries.

A wide range of polymers has been investigated as mucoadhesive in order to enhance buccal drug absorption by increasing the contact with the buccal mucosa for prolonged periods and were enlisted in Tables 1 and 2.

Table 1: Mucoadhesive polymers in buccal drug delivery

SOURCE	EXAMPLES
Natural/Semi **-synthetic** **Synthetic**	Agarose, chitosan, Carrageenan, Hyaluronic acid, various gums (guar, hacka, xanthan, gellan, carragenan, pectin and sodium alginate), Cellulose derivates [CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, methyl-hydroxyethyl-cellulose] Poly(acrylic acid)-based polymers [CP, PC, PAA, polyacrylates, poly (methylvinylether-comethacrylic acid), poly (2-hydroxyethyl methacrylate), poly(acrylic acid-co-ethylhexylacrylate), poly(methacrylate), poly (alkylcyanoacrylate), poly (isohexylcyanoacrylate), poly (isobutylcyanoacrylate), copolymer of acrylic acid and PEG]. Others Poly(N-2-hydroxypropyl methacrylamide) (PHPMAm), PEG, polyoxyethylene, PVA, PVP, thiolated polymers, phospholipid polymers , polyvinyl alcohol.

Table 2: Other criteria for bioadhesive polymer classification

CRITERIA	CATEGORIES	EXAMPLES
Aqueous solubility	Water-soluble	CP, HEC, HPC (water 38.8°C), HPMC (cold water), PAA, sodium CMC, sodium alginate
Charge	Non-ionic Covalent Cationic/ Anionic	
Potential bioadhesive forces	Electrostatic interaction	Cyanoacrylate Acrylates [hydroxylated methacrylate, poly(methacrylic acid)], CP, PC, PVA, Chitosan

DIABETES MELLITUS:[21-23]

Definition:

The term diabetes is a clinical condition with ‘‘an increased blood sugar levels” with a gradual reduction in the levels of insulin. The cells of the body are starved due to inadequate secretion of insulin so that there is increase in blood glucose concentration with insulin resistance.

Prevalence:

The “World Health Organization recognizes three main forms” of diabetes mellitus: type- I formerly known as insulin dependent diabetes mellitus (IDDM)” type- II formerly known as non-insulin dependent diabetes (NIDDM)”

Epidemiology:

Type-I diabetes mellitus account for up to “10 % of all cases of diabetes and results from an autoimmune destruction of the pancreatic β-cells” type-II diabetes mellitus” is heterogeneous disorder of glucose metabolism.

Type-II diabetes mellitus occupy a major percentage of known cases of diabetes. Diabetes mellitus usually results from defects in insulin sensitivity and a relative defect in insulin secretion.

CLASSIFICATION OF DIABETES MELLITUS

Clinically diabetes has been classified into following types

1. Insulin dependent diabetes mellitus (IDDM).
2. Non-insulin dependent diabetes mellitus (NIDDM).

Common symptoms of both type 1 and type 2 diabetes include:

- ❖ Fatigue, constantly tired
- ❖ Unexplained weight loss
- ❖ Excessive thirst (polydipsia)
- ❖ Excessive urination (polyuria)
- ❖ Excessive eating (polyphagia)
- ❖ Poor wound healing
- ❖ Blurry vision

ORAL HYPOGLYCEMIC AGENTS USED IN DIABETES MELLITUS[23-24]

I. Sulfonyl ureas:

Glyburide,
Glimepiride
Glipizide

II. Biguanides

Metformin
Phenformin

III. Intestinal glucosidase inhibitors

Gliclazide
Repaglinide
sodium glymidine

Acarbose

IV. Aldose reductase inhibitor

Tolrestat
Alrestatin

V. Thiazolidinedione derivatives:

Pioglitazone
Englitazone
Troglitazone
Rosiglitazone

DIAGNOSIS OF DIABETES:[23-24]

1. Urine test
2. Fasting blood glucose level
3. Insulin assay
4. Oral glucose tolerance test
5. Glycated hemoglobin (HbA1c) test

OBJECTIVES

NEED FOR THE STUDY

The drug shows low, pH dependent solubility. In acidic and neutral aqueous media, glimepiride exhibits very poor solubility at 37°C (<0.004 mg/mL). In media with pH > 7, the solubility of drug is slightly increased to 0.02 mg/mL.
The combinations of polymers were preferred because it could offer acceptable adhesion and biocompatibility properties.

Hence this research was aimed at formulating glimepiride buccal tablets for oral administration as potential emergency to prevent hyperglycemia coma using direct compression technique.

OBJECTIVES OF THE STUDY

The main objective of the present investigation was to prepare muco-adhesive buccal tablets of glimepiride using different natural and synthetic polymers to reduce dosing frequency and to improve the bioavailability.
The objective was obtained by following plan of work.

- ✓ Determination of melting point of glimepiride.
- ✓ Determination of λ_{max} of glimepiride.
- ✓ Determination of calibration curve of glimepiride.
- ✓ Selection of different types of polymers and excipients.
- ✓ Determination of drug-excipients compatibility study by using FTIR Spectroscopy.
- ✓ Preparation of mucoadhesive buccal tablets containing glimepiride by direct compression technique.
- ✓ Evaluation of powder mixtures for pre-compression parameters such as angle of repose, bulk density, tapped density, Carr's index and Haunser's ratio.
- ✓ Evaluation of tablet formulation for post-compression parameters such as weight variation, thickness, hardness, friability, drug content, swelling index, *in-vitro* drug release and *in-vitro* release kinetics studies.
- ✓ To carry out short term stability studies at 25ºC/60% RH and 40ºC/75%RH, as per ICH guideline.

4. MATERIALS AND METHOD

4.1. MATERIALS

Table 3: List of chemicals

SI. No	Materials	Company name
1.	Glimepiride	Yarrow Chem Products, Mumbai
2.	HPMC 100M	Yarrow Chem Products, Mumbai
3.	Guar gum	Loba Chemie Pvt. Ltd., India
4.	Xanthan gum	Loba Chemie Pvt. Ltd., India
5.	Chitosan	Yarrow Chem Products, Mumbai
6.	Aspartame	Loba Chemie Pvt. Ltd., India
7.	Lactose	Loba Chemie Pvt. Ltd., India
8.	Magnesium stearate	S.D fine Chem limited, Mumbai
9.	Talc	Yarrow Chem Products, Mumbai

4.2 EQUIPMENTS

Table 4: List of the Equipments/Apparatus

Sl. No	Equipment	Model/Company
1.	Electronic analytical balances	Acculab Sartorius group
2.	UV-Visible spectrophotometer	Spectrophotometer UV-1800
3.	Fourier transform infrared spectrophotometer	Bruker spectrophotometer
4.	PH meter	Techno scientific products
5.	Multi tablet Punching machine	Lab Press, Ahmadabad
6.	Roche Friabilator	PSM Industries, Bengalore
7.	Hardness tester	Monsanto hardness tester
8.	Electrical weighing balance	Shimadzu, Japan
9.	Dissolution test apparatus	Lab India (DT-50)
10.	Stability chamber	Labtop, Sky Lab Instruments.

DRUG PROFILE:

GLIMEPIRIDE:[53-55]

Glimepiride is a medium- to long-acting "third generation" sulfonylurea anti-diabetic drug. The primary mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells.

Molecular Formula: $C_{24}H_{34}N_4O_5S$

Chemical Structure:

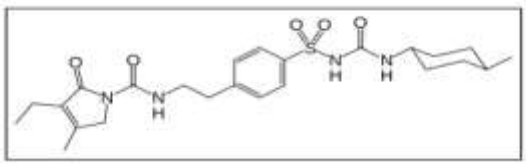


Figure 2: Molecular structure of Glimepiride

- **Chemical name:** 3-ethyl-4-methyl-N-(4-[N-((1r,4r)-4 methylcyclohexylcarbamoyl) sulfamoyl] phenethyl)-2-oxo-2,5-dihydro-1H-pyrrole-1-carboxamide.
- **Molecular weight:** 490.6g/mol.
- **Appearance:** White crystalline Solid.
- **Melting point:** 212-214 °C.
- **Solubility:** Practically insoluble in methanol and water, slightly soluble in ethanol and sparingly soluble in methylene chloride.

❖ **Pharmacology:**

- **Therapeutic Category:** Anti-diabetic drug. Mechanism of action: Like all sulfonylureas, glimepiride acts as an insulin secretagogue. It lowers blood sugar by stimulating the release of insulin by pancreatic beta cells and by inducing increased activity of intracellular insulin receptors. Glibenclamide (glyburide) is associated with an incidence of hypoglycemia of up to 20–30%, compared to 2% to 4% with glimepiride. Furthermore, glibenclamide diminishes the glucagon secretion in reaction to hypoglycemia, whereas glimepiride does not suppress this counter-regulatory reaction.
- **Pharmacokinetics:** With glimepiride, GI absorption is complete, with no interference of meals. It is metabolized by oxidative biotransformation, and 60% is excreted in the urine, the remaining being excreted in the feces.
- **Use and Indications:** Glimepiride is indicated to treat type 2 diabetes mellitus; its mode of action is to increase insulin production by the pancreas. It is not used for type 1 diabetes because the pancreas is no longer able to produce insulin.
- **Toxicity:** Side effects from taking glimepiride include gastrointestinal tract (GI) disturbance, and rarely thrombocytopenia, leukopenia, hemolytic anemia, and occasionally allergic reactions occur.

EXPERIMENTAL WORK:

Preparation of mucoadhesive buccal tablets of Glimepiride:

- ❖ Direct compression method has been employed to prepare buccal tablets of Glimepiride using HPMC 100M, Gaur gum, Xanthan gum, and Chitosan as polymers.
- ❖ Tablet ingredients were screened through a 0.150-mm sieve before mixing to achieve a uniform particle size distribution.
- ❖ Then, 4 mg of Glimepiride and required amounts of polymer and Lactose were weighed carefully and mixed with a cubic mixer for 15 minutes.
- ❖ Magnesium stearate and talc were added to the powder mixture and blended for an additional 3 minutes.
- ❖ Buccal tablets were compressed by using a single-punch tablet machine (Lab Press India) equipped with 7-mm round flat punch set.
- ❖ Tablet weight was kept constant at 100 mg, and the thickness of tablets was adjusted to 3 mm.
- ❖ Tablets were stored in an airtight container away from the light for further studies. The compositions of all formulations are given in Table 5.[59-60]

POST-COMPRESSION EVALUATION STUDIES:[63-64]

Evaluations of Glimepiride mucoadhesive buccal tablets:

Compressed tablets were subjected to various evaluation studies, which included thickness, hard ness, drug content uniformity, weight variation, friability, swelling index, mucoadhesive strength, *in-vitro* drug release studies, release kinetics studies and stability studies.

Determination of weight variation:

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug.

The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average.

The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the table 9.

Table 9: Limit of weight variation

Sl. No.	Average weight of tablet (mg)	Maximum % difference allowed
1.	130 or less	10
2.	130-324	7.5
3.	324<	5

Thickness of Tablets:

Thickness of the tablet is important for uniformity of tablet size. Thickness of each tablet was measured using Vernier Caliper. The average thickness of the tablet was calculated. The test passed if none of the individual thickness value deviated by ± 5% of the average value.

Hardness Test:

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness tester. The tablet was placed vertically between the jaws of the tester. The two jaws placed under tension by spring and screw guage. By turning the screw, the load was increased and at collapse the applied pressure from the spring was measured in Kg/cm^2.

Determination of Friability:

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients.

Method:20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator dusted off the fines and again weighed and the weight was recorded.Percentage friability was calculated by using the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \times 100$$

A maximum loss of weight (from a single test or from the average of the three tests) not greater than 1.0 % is acceptable for most tablets.

Drug content estimation:

20 tablets were weighed from each batch and average weight is calculated. All tablets were crushed and powder equivalent to 10 mg drug was dissolved in 6.8 pH phosphate buffer and the volume was made up to 100 ml with same solvent. From the stock solution, 1ml solution was taken in 10 ml volumetric flask and the volume was made with 6.8 pH phosphate buffer. Solution was filtered and absorbance was measured spectrophotometrically at 227 nm against 6.8 pH phosphate buffer as a blank. Amount of drug present in a tablet was calculated.

Swelling studies:

For the determination of swelling index (SI), tablets were weighed and fixed onto 2×2 cm glass slides, which were then immersed in Petri dishes containing 10 ml of PBS (pH 6.8) medium. Temperature was kept constant at 37°C±0.5°C during the study. After predetermined times, tablets were removed, and the excess surface water was wiped with filter papers. Swollen tablets were carefully reweighed, and SI was calculated.

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

Where W_t is the swollen tablet weight at a given time, W_0 is the tablet weight obtained initially. All experiments were performed in triplicate.[65]

In-vitrodrug release studies:

In-vitro drug release studies were determined by *in-vitro* dissolution test. The *in-vitro* dissolution studies were performed using the USP-II (Paddle) dissolution apparatus using 900 ml of 6.8 pH phosphate buffer at a temperature of 37 ± 0.5ºC at 50 rpm. 5 ml of sample was collected up to 12 hours and the same volume of fresh media was replenished. The drug content in the samples was estimated using UV visible spectrophotometer at 227 nm.Percentage cumulative drug release was calculated and graph was obtained by plotting cumulative percentage drug release VS time.[67-68]

Table 10: Detailsof *in-vitro*dissolution test

Dissolution test apparatus	USP type II
Speed	50 rpm
Stirrer	Paddle type
Volume of medium	900 ml
Volume withdrawn	5 ml
Medium used	6.8 pH phosphate buffer
Temperature	37±0.5ºC
Duration	12 hours

Determination of release kinetic studies:[69]

a) Zero order kinetics:

When the data is plotted as cumulative % drug release versus time, if the plot is linear then the data obeys zero- order release Kinetics, with a slope equal to K^0.

Zero order release would be predicted by the following equation:-

$$A_t = A_0 - K_0 t$$

Where,

A_t= Drug release at time 't'.

A_0= Initial drug concentration.

K_0=Zero-order rate constant (hr^{-1}).

b) First order Kinetics:

When the data is plotted as log cumulative % drug remaining versus time yields a straight line, indicating that the release follows first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with the slope values.

First order release would be predicted by the following equation:-

$$\text{Log } C = \log C_0 - K_t / 2.303$$

Where,

C = Amount of drug remained at time 't'.

C_0 = Initial concentration of drug.

K = First-order rate constant (hr^{-1}).

Stability studies:[70]

Stability studies are done to understand how to design a product and its packaging such that product has appropriate physical, chemical and microbiological properties during a defined shelf life when stored and used.

Storage conditions:

The optimized batches of Glimepiride mucoadhesive buccal tablets were subjected for three month stability studyas per ICH guidelines.The selected formulationswere placed in a wide mouth glass bottles, mouth of the bottle was tightlyclosed and packed in aluminum foils.In the present study, stability studies were carried out at 25ºC/60% and 40ºC/75% RH for a specific period of 3 months for the selected formulations. Prepared tablets were evaluated for drug content and *in-vitro* drug release profile.

Table 12: Storage conditions as per ICH guidelines

Study	Storage conditions	Minimum period of time
Long term	25ºC ±2 ºC/60%RH±5%RH	12 Months
	30 ºC±2 ºC/65%RH±5%RH	
Intermediate	30 ºC±2 ºC/65%RH±5%RH	6 Months
Accelerated	40 ºC±2 ºC/67%RH±5%RH	6 Months

5. RESULTS AND DISCUSSION

The primary aim of oral controlled drug delivery system is to deliver drugs for longer period of time to achieve better bioavailability, which should be predictable and reproducible. But this is difficult due to number of physiological problems such as fluctuation in the gastric emptying process, narrow absorption window and stability problem in the intestine. These include bioadhesive or mucoadhesive systems, swelling and expanding systems, floating systems and other delayed gastric emptying devices.

Bioadhesion may be defining as the state in which two materials, at least one of which is biological in nature, are held together for extended period by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucous membrane the phenomenon is referred to as mucoadhesion. Bioadhesive formulations use polymers as the adhesive component. These polymers are often water soluble and when used in a dry form, they attract water from the mucosal surface and this water transfer leads to strong interaction. These polymers also form viscous layers when hydrated with water, which increases the retention time over the mucosal surfaces leads to adhesive interactions.

Glimepiride (a BCS class II drug) is a second generation sulfonylurea oral anti-diabetic drug having high permeability and low solubility. Hence the aim of the current investigation was to design mucoadhesive tablets for buccal delivery of Glimepiride with a unidirectional drug flow, thus improving its therapeutic efficiency, tolerability and patient compliance.

PRE-FORMULATION STUDIES:

Melting Point Determination:

Melting point of pure drug Glimepiride was found to be 212.5±5°C and it is within the range specified in the official limits (212-214°C), which complied with official standards, indicating purity of the drug sample.

Determination of absorption maximum (λ_{max})

The λ_{max} of the Glimepiridewas found to be 227 nm in 0.1M NaOH. The graph of absorption maximum (λ_{max}) is showed in figure 3.

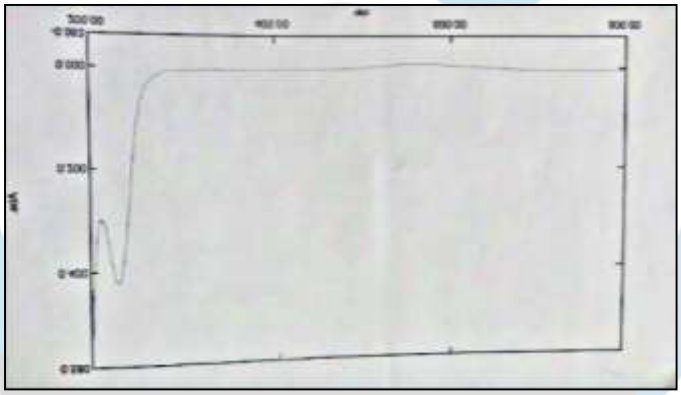


Figure 3: UV spectrum of Glimepiride in 0.1M NaOH

Calibration curve of Glimepiride:

The absorbance was measured in a UV spectrophotometer at 227 nm in 0.1M NaOH. The linear plot between concentrations versus absorbance showed that Beer-Lambert's law was obeyed in concentration range of 2-10 µg/ml in 0.1M NaOH (figure 4). The methods have shown good reproducibility. Correlation coefficient (r^2)values were found to be 0.998 in 0.1M NaOH, which indicate linearity. The data of calibration curve of Glimepiride is showed in table 12.

Table 12: Spectrophotometric data of Glimepiride in 0.1M NaOH

Sl. no	Concentration (µg/ml)	Absorbance at 227 nm			Average	Standard deviation (±SD)
		Trial 1	Trial 2	Trial 3		
1	0	0.000	0.000	0.000	0.000	0.000
2	2	0.147	0.149	0.150	0.149	0.0029
3	4	0.315	0.319	0.307	0.314	0.0061
4	6	0.491	0.489	0.492	0.492	0.0073
5	8	0.642	0.637	0.640	0.638	0.0018
6	10	0.842	0.838	0.849	0.840	0.0044

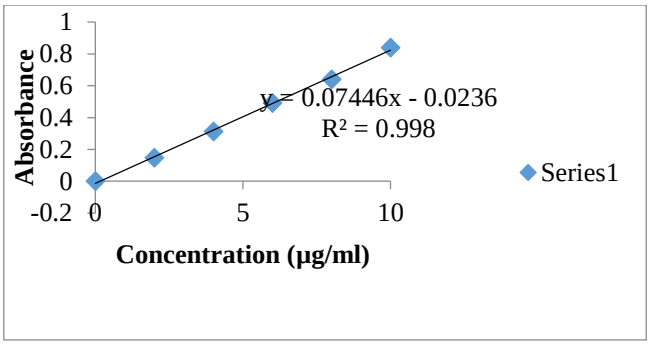


Figure 4: Calibration curve of Glimepiride in 0.1M NaOH

Fourier transformed infrared (FTIR) spectroscopy:

Table 14: Results of FTIR spectrum of Glimepiride

Functional group	Observed peaks cm^{-1}				
	Glimepiride	Drug + HPMC	Drug + Chitosan	Drug + Xanthan gum	Drug + Gaur gum
N-H stretching	3406.40	3464.27	3448.84	3437.26	3330.53
Carbonyl group	1776.60	1645.33	1666.91	1651.12	1641.71
C-N stretching	1379.19	1377.22	1375.29	1379.15	1352.19
S=O stretching	1197.83	1122.61	1174.69	1155.40	1109.47

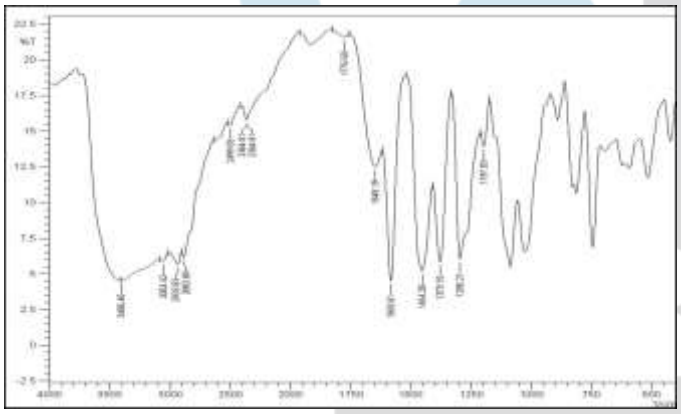


Figure 6: Infrared spectrum of Glimepiride and HPMC 100M

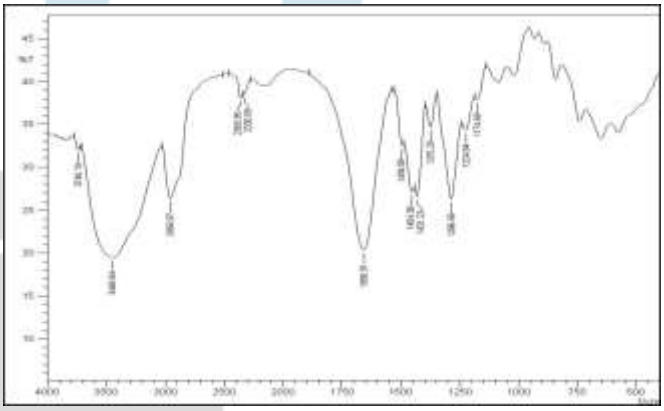


Figure 7: Infrared spectrum of Glimepiride and Chitosan

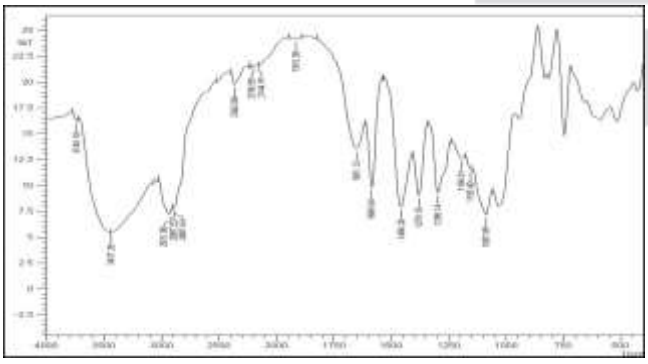


Figure 8: Infrared spectrum of Glimepiride and Xanthan gum

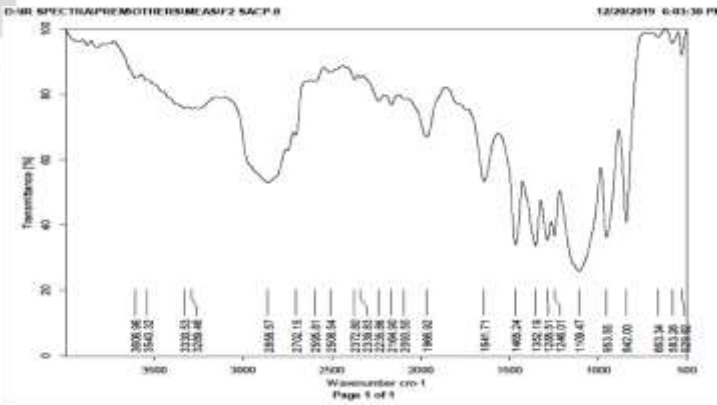


Figure 9: Infrared spectrum of Glimepiride and gaur gum

Evaluation Parameters:

Pre-compression evaluation studies:

Table 15: Results of pre-compression parameters

Formulation	Bulk Density (gm/c^3)	Tapped Density (gm/c^3)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (^{O})
F1	0.228±0.013	0.417±0.027	12.15±0.39	1.18±0.0024	19.79□0.40
F2	0.275±0.022	0.443±0.090	11.42±0.35	1.16± 0.0062	27.31□0.35
F3	0.342±0.063	0.434±0.068	10.52±0.37	1.18±0.0048	28.92□0.61
F4	0.318±0.024	0.412±0.043	13.31±0.65	1.16±0.0049	25.31□0.27
F5	0.332±0.048	0.437±0.063	13.49±0.63	1.24±0.0022	29.77□0.54
F6	0.276±0.049	0.417±0.047	12.12±0.57	1.19±0.0025	23.08□0.69
F7	0.270±0.067	0.424±0.069	10.94±0.83	1.20±0.0074	27.83±0.36
F8	0.318±0.038	0.432±0.052	13.34±0.57	1.19±0.0042	19.51□0.22
F9	0.342±0.090	0.430±0.044	12.53±0.42	1.24±0.0075	19.75□0.92
F10	0.329±0.088	0.443±0.029	11.31±0.30	1.27±0.0043	26.90±0.34
F11	0.290±0.042	0.440±0.037	12.94±0.54	1.25 ±0.0049	23.47□0.14
F12	0.341±0.094	0.424±0.038	13.12±0.25	1.21±0.0021	28.35□0.82

Post-compression evaluation studies:

The prepared tablets were evaluated for different organoleptic features of the tablets like colour, odour, diameter and thickness. A part from the organoleptic features, it was also carried out for physical characteristics like hardness of the tablets, its percentage of friability, hardness, drug content, weight variation, drug release, drug release kinetics and stability study. Quality control test for Glimepiride mucoadhesive buccal tablets were performed as follows.

Organoleptic properties of tablets:

Table 16: Organoleptic properties of prepared mucoadhesive buccal tablets

Formulation	Colour	Odour	Shape
F1	White colour	odourless	Concave, round
F2	White colour	odourless	Concave, round
F3	White colour	odourless	Concave, round
F4	White colour	odourless	Concave, round
F5	White colour	odourless	Concave, round
F6	White colour	odourless	Concave, round
F7	White colour	odourless	Concave, round
F8	White colour	odourless	Concave, round
F9	White colour	odourless	Concave, round
F10	White colour	odourless	Concave, round
F11	White colour	odourless	Concave, round
F12	White colour	odourless	Concave, round

Determination of tablets thickness:

Tablets thickness was measured by using Vernier callipers. The average thickness was found in the range of 2.98-3.21 mm, which was within the allowed limit of deviation i.e. 5% of the standard value. The results of thickness were reported in table 17.

Determination of tablet hardness:

The resistance of tablets against shipping or breaking under the condition of storage, transportation, and handling before administration depends on its hardness. The hardness of tablets of each batch was measured by Monsanto hardness tester. The hardness was measured in terms of Kg/cm^2. Hardness was found in the range of 4.27 to 4.69 kg/cm^2. This ensures good handling characteristics of all batches of prepared tablets (table 17).

Determination of Friability:

Throughout pharmaceutical industry, friability testing has become an accepted technology and the instrument used in to perform this process is called Friabilator or Friability Tester. Friability of prepared tablets was determined by using Roche friabilator.

Another measure of a tablet's strength is friability. Glimepiride mucoadhesive buccal tablets were evaluated for percentage friability and the results are reported in table 17. The percentage friability of prepared tablet was in the range of 0.26 % to 0.68 %. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. Results of friability test were also has been found within limit (i.e. less than 1%). The results of friability signify that the tablets were mechanically stable in nature. It can withstand rigors of shipping and handling.

Weight variation test for tablets:

The weight variation study was performed on 20 individuals on randomly selected samples from each batch; the weight uniformity results of prepared matrix tablets indicate no significant difference in the weight of individual tablet from average value and the

variation was found within the limit. As the powder material was free-flowing, tablets obtained were uniform in weight due to uniform die fill with acceptable variation as per IP standards. The weight of the tablets was found in the range of 98.51 to 102.48 mg and results were dissipated in table 17. All the formulated tablets pass weight variation test as the % weight variation was within the IP limits (<7.5%). The weights of all batches of tablet formulations were found to be uniform with low standard deviation values.

Drug content estimation:

The assay of Glimepiride mucoadhesive buccal tablets were found in the range of 98.89-102.05 %w/w. The acceptable limit of Glimepiride content as per I.P. is 90 to 110%. The results revealed that the assay of Glimepiride was within the acceptable limits and confirms uniform distribution of drug in powder mixture. The results were reported in table 17.

Table 17: Results of post-compression parameters

Surface pH:

Formulation	Thickness (mm)± SD	Weight variation (mg)± SD	Hardness (kg/cm^2) ± SD	Friability (%) ± SD	Drug content (%) ± SD
F1	3.20 ±0.040	99.80±0.43	4.38±0.062	0.28±0.013	99.90±0.046
F2	3.11±0.028	100.11±0.45	4.65±0.014	0.49±0.055	100.11±0.049
F3	2.98±0.042	100.45±0.32	4.50±0.046	0.43±0.086	100.50±0.061
F4	2.99±0.073	98.51±0.94	4.42±0.040	0.26±0.018	101.86±0.035
F5	3.16±0.044	102.48±0.32	4.27±0.026	0.63±0.035	98.89±0.034
F6	3.18±0.082	99.88±0.55	4.58±0.046	0.57±0.079	99.68±0.090
F7	3.19±0.050	98.89±0.40	4.69±0.080	0.68±0.021	101.20±0.046
F8	3.20±0.063	100.60±0.29	4.60±0.032	0.26±0.044	99.18±0.062
F9	3.21±0.076	98.92±0.35	4.63±0.037	0.39±0.050	98.89±0.063
F10	3.09 ±0.072	102.08±0.23	4.51±0.082	0.47±0.054	100.62±0.072
F11	3.18±0.037	99.69±0.58	4.38±0.022	0.60±0.035	99.92±0.034
F12	3.04±0.059	100.18±0.25	4.47±0.037	0.62±0.059	99.94±0.050

The surface pH of the buccal tablets was determined in order to investigate the possibility of any irritation effects *in-vivo*, as acidic or alkaline pH may cause irritation to the buccal mucosa. Surface pH of the buccal tablet formulation was found in the range of 6.80-7.14 (near to neutral pH). It was inferred that neutral pH of the formulation does not cause any irritation to the mucosa. Results are showed in table 18.

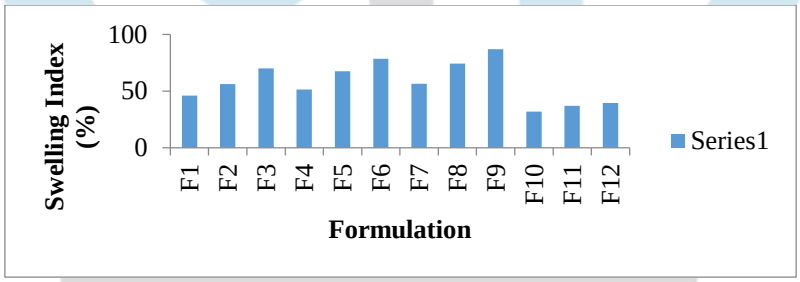


Figure 10: The comparison of percentage swelling Index

Table 18: results of percentage swelling index of buccal tablets (F1-F12)

Formulation	Swelling index (%)	Surface pH
F1	45.94±1.32	6.94±0.22
F2	56.26±1.90	6.80±0.10
F3	70.02±2.59	7.60±0.51
F4	51.35±1.52	7.13±0.27
F5	67.41±2.08	6.91±0.32
F6	78.42±3.67	7.12±0.67
F7	56.43±2.23	6.83±0.44
F8	74.18±3.44	7.18±0.80
F9	87.09±3.75	7.11±0.42
F10	31.77±2.03	6.87±0.28
F11	36.93±2.11	6.90±0.13
F12	39.56±2.68	7.10±0.52

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

In-vitro drug release study of Glimepiride mucoadhesive buccal tablet was performed using USP type-II dissolution test apparatus. The dissolution test was carried out using pH 6.8 phosphate buffer as dissolution medium and experiment was carried out for 12 hours. In this study, HPMC 100M was used as primary release retardant and Xanthan gum, Chitosan and guar gum as

secondary release retardant. The release of Glimepiride from mucoadhesive buccal tablet was analyzed by plotting the cumulative percent drug release against time.

Figure 11 shows the *in-vitro* dissolution profiles of Glimepiride mucoadhesive buccal tablet.

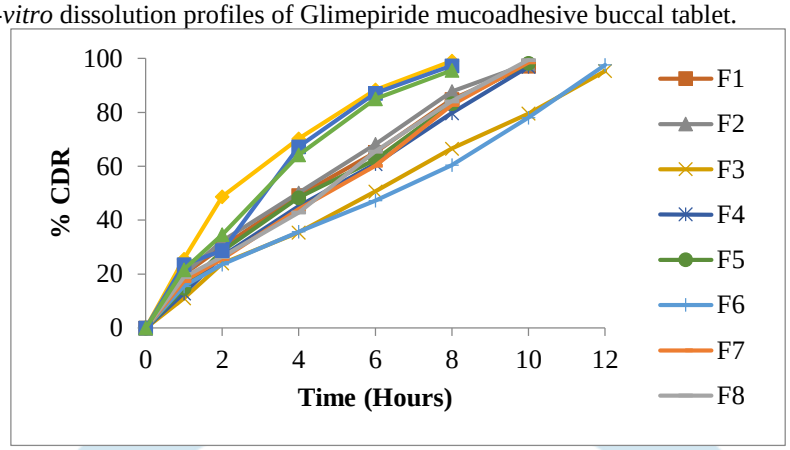


Figure 11: Comparative dissolution profile of buccal tablets F1 to F12

Table 19: *In-vitro* drug release profile of Glimepiride buccal tablets

Time (Hour)	Cumulative percentage Drug Release (%CDR)											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	16.45	19.87	20.05	11.04	12.87	14.71	15.47	17.43	18.89	25.55	23.55	21.67
2	28.55	30.17	32.28	23.96	26.65	28.61	23.55	25.64	26.43	48.72	28.72	34.66
4	48.14	49.15	50.14	35.43	45.16	48.39	35.72	44.17	42.88	70.26	67.26	64.22
6	62.16	65.19	68.16	50.65	60.88	62.43	47.26	60.22	65.48	88.32	87.11	85.02
8	82.77	84.86	87.78	66.53	79.75	83.22	60.45	82.79	84.15	99.04	97.31	95.58
10	96.36	97.22	98.01	79.54	96.94	98.25	78.08	98.58	99.44	--	--	--
12	--	--	--	95.38	--	--	97.63	--	--	--	--	--

Release kinetic studies:

The drug release data was further subjected to the various models to get the information about the drug release kinetics. The release data was treated with zero order, first order, Higuchi model and Korsmeyer-Peppas model.

Table 20: Release exponent values and release rate constant

Batch	Zero order	First order	Higuchi's plots	Korsmeyer-Peppas plots		Best fit Model	Drug release mechanism
	R^2	R^2	R^2	R^2	n		
F1	0.853	0.970	0.994	0.816	0.695	Higuchi model	non-Fickian
F2	0.880	0.916	0.984	0.848	0.678	Higuchi model	non-Fickian
F3	0.874	0.985	0.990	0.866	0.680	Higuchi model	non-Fickian
F4	0.881	0.956	0.989	0.834	0.805	Higuchi model	non-Fickian
F5	0.858	0.940	0.994	0.856	0.768	Higuchi model	non-Fickian
F6	0.853	0.948	0.988	0.883	0.673	Higuchi model	non-Fickian
F7	0.851	0.953	0.990	0.837	0.715	Higuchi model	non-Fickian
F8	0.878	0.919	0.993	0.868	0.774	Higuchi model	non-Fickian
F9	0.880	0.955	0.992	0.864	0.694	Higuchi model	non-Fickian
F10	0.872	0.940	0.987	0.850	0.682	Higuchi model	non-Fickian
F11	0.837	0.982	0.990	0.825	0.791	Higuchi model	non-Fickian
F12	0.828	0.976	0.991	0.887	0.764	Higuchi model	non-Fickian

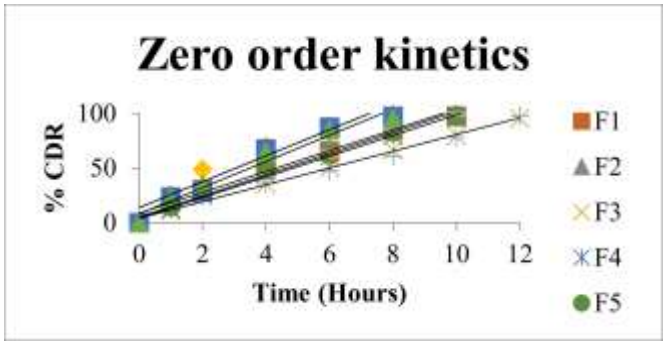


Figure 14: Comparative Higuchi release profile

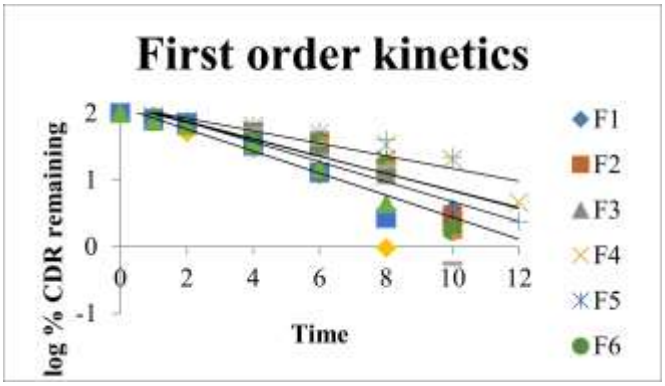
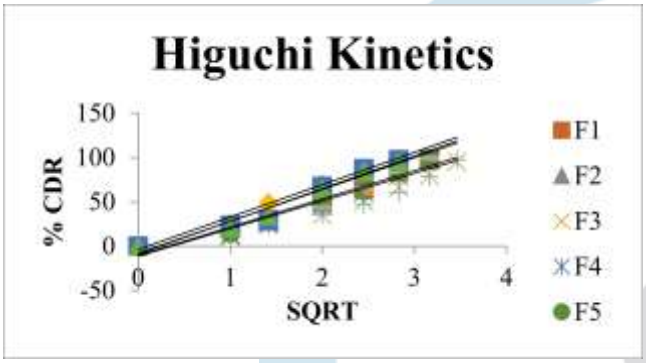
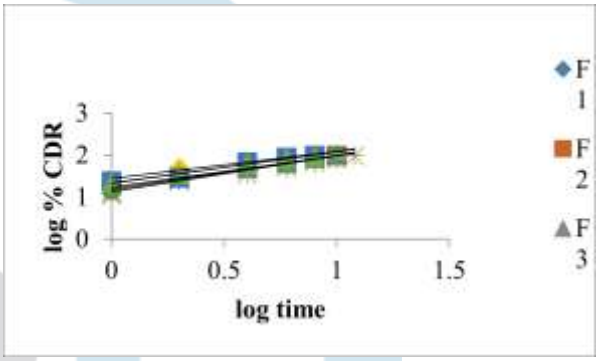


Figure 15: Comparative Korsemeyer/Peppas release profile





Stability studies:

Based on the results of *in-vitro* drug release behaviour formulation F4 and F7 were selected as optimized formulation. Short term stability study was conducted for optimized formulation for the period of three months. Stability study was performed for three month at two different storage conditions i.e. 25ºC/60% RH and 40ºC/75% RH.

Table 21: Results of stability studies for formulation F4

Storage period	Stored at 25ºC/60% RH		Stored at 40ºC/75% RH	
	Formulation F4		Formulation F4	
	% Drug content	% CDR	% Drug content	% CDR
Initial	101.86±0.035	95.38	101.86±0.035	95.38
1 month	101.80±0.061	95.31	101.64±0.063	95.24
2 month	101.41±0.090	95.25	101.32±0.094	95.10
3 month	101.23±0.084	95.19	101.10±0.044	95.04

Table 22: Results of stability studies for formulation F7

Storage period	Stored at 25ºC/60% RH		Stored at 40ºC/75% RH	
	Formulation F7		Formulation F7	
	% Drug content	% CDR	% Drug content	% CDR
Initial	101.20±0.046	97.83	101.20±0.046	97.83
1 month	101.12±0.038	97.68	101.14±0.039	97.62
2 month	101.07±0.051	97.38	100.84±0.055	97.27
3 month	101.02±0.093	97.22	100.57±0.042	97.16

6. CONCLUSION

Diabetes is a group of metabolic diseases characterized by an elevation of blood glucose levels over a prolonged period by a relative or absolute deficiency of insulin. Symptoms of high blood glucose level include increased hunger (polyphagia), thirst (polydipsia) and frequent urination (polyuria).

Glimepiride is an oral antidiabetic agent used along with exercise, diet, and sometimes with other medications to treat type 2 diabetes. For this research study glimepiride was choosen, because it is most commonly prescribed oral antidiabetic agent, widely available in Indian market, drug of choice for the physician.

Mucoadhesive buccal delivery of drugs is considered as an alternative to oral administration, especially for drugs which suffer from first-pass metabolism.

The following conclusions can be drawn from the result obtained.

- FTIR studies revealed that there was no interaction between drug and excipients. All the excipients used were compatible with the Glimepiride.
- Pre-compression studies showed that Glimepiride physical mixture showed good flow property.
- The powder blends were compressed into tablet and evaluated for post-compression parameters like weight variation, thickness, hardness, percentage friability and drug content. All formulation batches showed acceptable results.
- The surface pH of buccal tablets was found in the range of salivary pH, suggested prepared buccal tablets could be used without risk of mucosal irritation.
- The *in-vitro* drug release was carried out using USP Type-II dissolution apparatus in 6.8 pH phosphate buffer for a period of 12 hours. Drug release was retarded with increasing in polymer concentration.
- Among all batches, formulation F4 and F7 showed sustained the drug release behaviour for the period of 12 hours.

Therefore, development of bioadhesive buccal drug delivery of Glimepiride tablets was one of the alternative routes of administration to avoid first-pass effect and provide prolonged release. A combination of HPMC 100M with Chitosan and Gaur gum results in sustained buccal drug delivery. Hence, mucoadhesive buccal delivery of Glimepiride could be considered as a successful surrogate to bypass the hepatic metabolism and attain prolonged release, leading to reduced demand of repeated administration and enhanced patient compliance.

FUTURE SCOPE OF THE STUDY:

- Present work can be extended to the *in-vivo* pharmacokinetics studies.
- The formulation of mucoadhesive buccal drug delivery system can be tried with different grades of HPMC.
- *The work can be extended to the* in-vivo *studies to conclude* in-vitro *and* in-vivo *correlation.*

8. BIBLIOGRAPHY

1. Jin JF, Zhu LL, Chen M. The optimal choice of medication administration route regarding intravenous, intramuscular, and subcutaneous injection. Patient Prefer Adherence. 2015;9:923-42.
2. Wen H, Jung H, Li X. Drug delivery approaches in addressing clinical pharmacology-related issues: Opportunities and challenges. AAPS J. 2015;17(6):1327-40.
3. Yajaman S, Ketousetuo K, Bandyopadhyay AK. Buccal bioadhesive drug delivery-A promising option for orally less efficient drugs. J Contr Rel. 2006;114(1):15-40.
4. Shaikh R, Raj Singh TR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci. 2011;3(1):89-100.
5. McBain JW, Hopkins DG. On adhesives and adhesive action. J Phys Chem. 1925;29:188-204.
6. imenez-Castellanos MR, Zia H, Rhodes CT. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm. 1993;19:143-94.
7. Gilhotra RM, Ikram M, Srivastava S, Gilhotra N. A clinical perspective on mucoadhesive buccal drug delivery systems. J Biomed Res. 2014;28(2):81-97.
8. Nicolazzo JA, Reed BL, Finnin BC. Buccal penetration enhancers--how do they really work? J Control Release. 2005; 105(1-2):1-15.
9. Chien YW: Mucosal drug delivery: potential routes for non-invasive systemic administration. In: Y.W. Chien (Ed.). Novel drug delivery systems. Marcel Decker, New York, 1992: 197-228.
10. Chinna Reddy P, Chaitanya KS, Madhusudan Rao Y. A review on bioadhesive buccal drug delivery systems: current status of formulation and evaluation methods. Daru. 2011;19(6):385-403.
11. Shojaei AH, Chang RK, Guo X. Systemic drug delivery via the buccal mucosal route. J Pharm Technol. 2001;25(6):70-81.
12. Gandhi RB, Robinson JR. Oral cavity as a site for bioadhesive drug delivery. Adv. Drug Deliv Rev. 1994;13:43-74.
13. Rossi S, Sandri G, Caramella CM. Buccal drug delivery: A challenge already won? Drug Discov Today Technol. 2005; 2(1):59-65.
14. Longer MA, Robinson JR. Fundamental aspects of bioadhesion. Pharmacy Int. 1986;7:114-7.
15. McBain JW, Hopkins DG. On adhesives and adhesive action. J Phys Chem. 1925;29:188-204.
16. Jimenez-Castellanos MR, Zia H, Rhodes CT. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm. 1993;19:143-94.
17. Peppas NA, Little MD, Huang Y. Bioadhesive Controlled Release Systems. In: Wise DL, editor. Handbook of pharmaceutical controlled release technology. New York: Marcel Dekker; 2000. pp. 255–69.
18. Ahuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems. Drug Dev Ind Pharm. 1997;23:489-515.
19. Asane GS, Nirmal SA, Rasal KB, Naik AA, Mahadik MS, Rao YM. Polymers for mucoadhesive drug delivery system: a current status. Drug Dev Ind Pharm. 2008 Nov;34(11):1246-66.
20. Laffleur F. Mucoadhesive polymers for buccal drug delivery. Drug Dev Ind Pharm. 2014;40(5):591-8.
21. Kharroubi AT, Darwish HM. Diabetes mellitus: The epidemic of the century. World J Diabetes. 2015;6(6):850-67.
22. American Diabetes Association. Diagnosis and classification of diabetes mellitus [published correction appears in Diabetes Care. 2010 Apr;33(4):e57].
23. Schuster DP, Duvuuri V. Diabetes mellitus. Clin Podiatr Med Surg. 2002;19(1):79-107.
24. Lubbos H, Miller JL, Rose LI. Oral hypoglycemic agents in type II diabetes mellitus. Am Fam Physician. 1995;52(7):2075-8.
25. Khanna R, Agarwal SP, Ahuja A. Preparation and evaluation of bioerodible buccal tablets containing clotrimazole. Int J Pharm. 1996;138:67-73.
26. Ikinci G, Senel S, Wilson CG, Sumnu M. Development of buccal bioadhesive nicotine tablet formulation for smoking cessation. Int J Pharm. 2004;277:173-8.

27. Desai KGH, Pramod TM. Preparation and evaluation of a novel buccal adhesive system. AAPS Pharm Sci Tech. 2004;5(3):1-9.
28. Darwis MK, Elmeshad AN. Buccal mucoadhesive tablet of flubiprofen: characterization and optimization. Drug Discov Ther. 2009;3(4):181-9.
29. Vaidya VM, Manwar JV, Sakarkar DM. Design and *in-vitro* evaluation of mucoadhesive buccal tablets of terbutaline sulphate. Int J Pharm Tech Res. 2009;1(3):588-97.
30. Chandira M, Debojit C, Jayakar B. Formulation, design and development of buccoadhesive tablets of Verapamil hydrochloride. Int J Pharm Tech Res. 2009;1(4):1663-77.
31. Miyazaki S, Nakayama A, Oda M, Takada M, Attwood D. Drug release from oral mucosa adhesive tablets of chitosan and sodium alginate. Int J Pharm. 1995;118(1995):257-63.
32. Yamsani VV, Gunna R, Kolli C, Bhanoji E, Yamsuni MR. Development and *in-vitro* evaluation of buccoadhesive carvedilol tablets. Acta Pharm. 2007;57(2007):185-97.
33. Minghetti P, Colombo A, Montanari L, Gueta GM, Gombos F. Buccoadhesive slow-release tablets of acitretin: Design and *in-vivo* evaluation. Int J Pharm. 1998;169(1998):195-202.
34. Noha AN, Fatma AI, Nabila AB, Lobna MM. Mucoadhesive delivery systems. II. Formulation and *In-vitro/In-vivo* evaluation of buccal mucoadhesive tablets containing water-soluble drugs. Drug Dev Ind Pharm. 2004; 30: 995-1004.
35. Shaila L, Subramanian G, Pandey S, Udupa N. Design, evaluation and pharmacokinetic study of mucoadhesive buccal tablets of nicotine for smoking cessation. Indian J Pharm Sci. 2006;1(2):829-31.
36. Ramana MV, Nagda C, Himaja M. Design and evaluation of mucoadhesive buccal drug delivery systems containing Metoprolol Tartrate. Indian J Pharm Sci. 2007;69:515-8.
37. Simpson DM, Messina J, Xie F, Hale M. Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: A multi-center, randomized, double-blind, placebo-controlled study. Clin Thera. 2007; 29: 588-601.
38. Madgulkar A, Kadam S, Pokharkar Varsha. Development of trilayered mucoadhesive tablet of Itraconazole with zero-order release. Asian. J. Pharm. Jan. 2008: 57-60.
39. Hirlekar RS, Kadam VJ. Design of buccal drug delivery system for a poorly soluble drug. Asian J Pharm Clin Res. 2009;2(3):49-53.
40. Semalty M, Semalty A, Kumar G. Formulation and characterization of mucoadhesive buccal films of glipizide. Indian J Pharm Sci. 2008;70:43-8.
41. Sahni J, Raj S, Ahmad FJ, Khar RK. Design and *in-vitro* characterization of buccoadhesive drug delivery system of insulin. Indian J Pharm Sci. 2008;70:61-65.
42. Llabot JM, Manzo RH, Allemandi DA. Double-layered mucoadhesive tablets containing nystatin. AAPS Pharm Sci Tech. 2002;3:1-6.
43. Narendra C, Srinath MS and Prakash Rao B. Development of three layered buccal compact containing Metoprolol tartrate by statistical optimization technique. Int J Pharm. 2005:304:102-14.
44. Tuncer D, Bilgen E, Omer O. A sustained release dosage form of acyclovir for buccal application: An experimental study in dogs. J Drug Targ. 2006;14:35-44.
45. Langoth N, Kahlbacher H, Schuh M, Kurka P. Thiolated chitosan: Design and *in-vivo* evaluation of mucoadhesive buccal peptide drug delivery system. Pharm Res. 2006;23(3): 573-9.
46. Nozaki Y, Ohta M, Chien YW. Transmucosal controlled systemic delivery of Isosorbide dinitrate: *in vivo/in-vitro* correlation. J Control Rel. 1997;43:105-14.
47. Collins AE, Deasy PB. Bioadhesive lozenge for the improved delivery of Cetylpyridinium chloride. J Pharm Sci. 1990;79(2)116-20.
48. Bouckaert S and Remon JP. *In-vitro* bioadhesion of a buccal miconazole slow release tablet. J Pharm Pharmacol 1993; 45: 504- 7.
49. Derle D, Joshi O, Pawar A, Patel J, Jagadale A. Formulation and evaluation of buccoadhesive bi-layer tablet of propranolol hydrochloride. Int J Pharm Pharma Sci. 2009;1(1):1-8.
50. Sonar GS, Jain DK, More DM. Preparation and *in-vitro* evaluation of bilayer and floating bioadhesive tablets of Rosiglitazone Maleate. Asian J Pharm Sci. 2007;2(4):161-9.
51. Celik B. Risperidone mucoadhesive buccal tablets: formulation design, optimization and evaluation. Drug Des Devel Ther. 2017;11:3355-65.
52. Shirsand S, Suresh S, Keshavshetti G, Swamy P, Reddy PV. Formulation and optimization of mucoadhesive bilayer buccal tablets of atenolol using simplex design method. Int J Pharm Investig. 2012;2(1):34-41.
53. Basit A, Riaz M, Fawwad A. Glimepiride: evidence-based facts, trends, and observations (GIFTS). Vasc Health Risk Manag. 2012;8:463-72.
54. Langtry HD, Balfour JA. Glimepiride. A review of its use in the management of type 2 diabetes mellitus. Drugs. 1998;55(4):563-84.

55. Massi-Benedetti M. Glimepiride in type 2 diabetes mellitus: a review of the worldwide therapeutic experience. Clin Ther. 2003;25(3):799-816.
56. Wade A, Weller PJ. Hand book of Pharmaceutical excipients. 2nd edn. London: The Pharmaceutical Press;1994:78-81.
57. Altinoz S, Tekeli D. Analysis of glimepiride by using derivative UV spectrophotometric method. J Pharm Biomed Anal. 2001;24(3):507-15.
58. Sogias IA, Williams AC, Khutoryanskiy VV. Chitosan-based mucoadhesive tablets for oral delivery of ibuprofen. Int J Pharm. 2012; 436(1-2):602-10.
59. Celik B. Risperidone mucoadhesive buccal tablets: formulation design, optimization and evaluation. Drug Des Devel Ther. 2017;11:3355-65.
60. Celik B, Ozdemir S, Barla Demirkoz A, Uner M. Optimization of piribedil mucoadhesive tablets for efficient therapy of Parkinson's disease: physical characterization and *ex-vivo* drug permeation through buccal mucosa. Drug Dev Ind Pharm. 2017; 43(11):1836-45.
61. Hausner HH. Friction conditions in a mass of metal powder. Int J Powder Metall. 1967;3:7-13.
62. Carr RL. Evaluating flow properties of solids. Chem Eng. 1965;72:163-8.
63. Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive delivery systems. I. Evaluation of mucoadhesive polymers for buccal tablet formulation. Drug Dev Ind Pharm. 2004;30(9):985-93.
64. Abdelkader H, Abdalla OY, Salem H. Formulation of controlled-release baclofen matrix tablets: Influence of some hydrophilic polymers on the release rate and *in-vitro* evaluation. AAPS Pharm Sci Tech. 2007;8(4):E100.
65. Shanker G, Kumar CK, Gonugunta CS, Kumar BV, Veerareddy PR. Formulation and evaluation of bioadhesive buccal drug delivery of tizanidine hydrochloride tablets. AAPS Pharm Sci Tech. 2009;10(2):530-9.
66. Gupta A, Garg S, Khar RK. Measurement of bioadhesive strength of mucoadhesive buccal tablet: Design of an *in-vitro* assembly. Indian Drugs 1993;30:152-6.
67. Nagpal M, Rajera R, Nagpal K, Rakha P, Singh S, Mishra D. Dissolution enhancement of glimepiride using modified gum karaya as a carrier. Int J Pharm Investig. 2012;2(1):42-7.
68. Kesavan K, Nath G, Pandit JK. Sodium alginate based mucoadhesive system for Gatifloxacin and its *in-vitro* antibacterial activity. Sci Pharm. 2010;78(4):941-57.
69. Hixson AW, Crowell JH. Dependence of reaction velocity upon surface and agitation. Ind Eng Chem. 1931;23(8):923-31.