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DESIGN, DEVELOPMENT AND CHARACTERIZATION OF BIOADHESIVE BUCCAL PATCHES FOR BETTER THERAPEUTIC EFFICACY.

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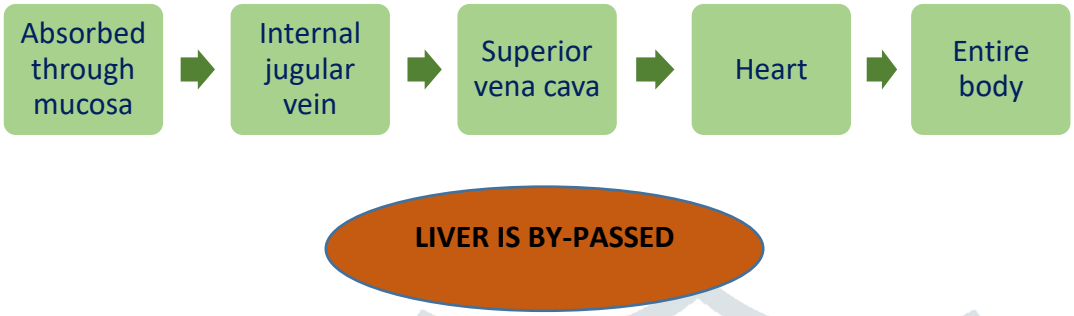
Abstract: The oral route is mayhap the one mostly preferred by patient and clinicians. Based on our current understandings of biochemical and physiological aspects of absorption and metabolism many drugs cannot be delivered effectively through conventional oral route, because after administration are subjected to pre-systemic clearance. Extensively in liver, which often leads to a lack of significant correlation between membrane permeability, absorption and bioavailability. Accordingly other absorptive mucosa are considered as potential sites for drug administration. The nasal cavity as a site for systemic drug delivery has been investigated by many research groups and route has already reached commercial states with several drugs including LHRH and calcitonin. Recent interest has been expressed on delivery of drug to or via mucus membrane by use of adhesive material several muco-adhesive formulations are available under development and drug delivery via buccal mucosa is a novel route facilitate direct entry of drug molecules into systemic circulation, avoiding first-pass metabolism and drug degradation in harsh gastrointestinal environment, which are often associated with oral administration.

Keywords: buccal patch, mucoadhession, etc

INTRODUCTION:

There are many ways to deliver drug into the body, in the company of the various routes of drug delivery, the oral route is mayhap the one mostly preferred by patient and clinicians. Based on our current understandings of biochemical and physiological aspects of absorption and metabolism many drugs cannot be delivered effectively through conventional oral route, because after administration are subjected to pre-systemic

clearance. Extensively in liver, which often leads to a lack of significant correlation between membrane permeability, absorption and bioavailability. Accordingly other absorptive mucosa are considered as potential sites for drug administration.[1] The nasal cavity as a site for systemic drug delivery has been investigated by many research groups[2,3] and route has already reached commercial states with several drugs including LHRH and calcitonin[4].



Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because oral mucosa is highly vascularized, drugs that are absorbed through oral mucosa directly enter the systemic circulation, bypassing gastrointestinal tract, and first pass metabolism in the liver.(5)

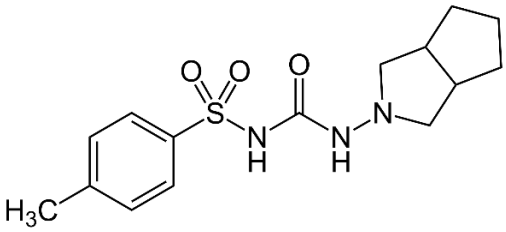
Buccal delivery at a first glimpse seems to offer a combination of advantages of transdermal and per oral delivery. A buccal delivery device offers the easy application and removal of transdermal delivery without the excellent barrier properties of the stratum corneum and with less immune activity than epidermis. Conventional formulations for local oral delivery are principally lozenges, troches, mouth paints mouthwashes, oral gels, pastes and suspensions[6,7]. Release of drug from these preparations involves initial burst of activity, subsequently declines to sub therapeutic level.

Bioadhesive drug delivery formulation were introduced in 1947. When gum tragacanth was mixed with dental adhesive powder to apply penicillin to oral mucosa; this was eventually leads to orabase[8]. Recently, consider able attention has been focused on development of alternative drug delivery systems for proteins and peptide drugs. As the peroral administration has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the gastrointestinal tract, proteins peptides are usually not suitable for perenteralroute[9]. Nasal, ocular,vaginal rectal and buccal mucosal membranes have been evaluated as potential alternative routes for peptide absorption buccal administration of drug provides a convenient route of administration for both systemic and local drug action[10].

DRUG PROFILE

Gliclazide

Structural formula



Chemical Name

N-(hexahydrocyclopenta[c]pyrrol-2(1H)-ylcarbamoyl)-4-methylbenzenesulfonamide

Molecular formula: C15H21N3O3S

Molecular weight: 323.41 g·mol−1

Melting point: 180 to 182 °C (356 to 360 °F)

PKA: 5.8

Bioavailability: 100% Protein binding>99.5%

Biological half-life: 10.4 hours

Solubility :

Gliclazide is freely soluble in ethanol, methanol and completely insoluble in water.

PHARMACOLOGY:

1. Pharmacokinetics and metabolism:

Absorption: Gliclazide is extensively absorbed from the gastrointestinal tract. Following oral administration of 3 mg/kg of gliclazide to four healthy subjects, the peak plasma levels (mean 5.0 µg/mL) were achieved between 4 to 6 hours. The absorption half-life in man is 1.3 hours.

Distribution: The mean apparent volume of distribution in 4 healthy subjects was 20 to 40% of bodyweight.

Protein binding: Using equilibrium dialysis, it was shown that the majority of the drug is protein bound. At a plasma concentration of about 8 µg/mL, 94.2% of the drug was protein bound and 5.8% was free.

Metabolism: Although more than 90% of unchanged gliclazide is found in plasma following administration, this is intensively metabolized with little of the unchanged compound (<1%) found in urine. Five principal metabolites have been found in urine, essentially oxidised and hydroxylated derivatives, the majority of which undergo glucuroconjugation.

Excretion: Gliclazide is essentially eliminated via the urine: 60 to 70% as against 10 to 20% via faeces.

Half-life: The mean elimination half-life is 10.4 h.

2. Pharmacodynamics:

Gliclazide acts primarily by enhancing the release of endogenous insulin. Residual function of beta-cells is therefore necessary for its action. Clinical studies demonstrate that the sulphonylureas are ineffective in completely pancreatectomized patients and in juvenile onset diabetic subjects. The mechanism of action is not fully understood. Sulphonylureas including gliclazide cause degranulation of the pancreatic beta-cells, a phenomenon associated with increased rate of insulin secretion[11].

Extrapancreatic effects of sulphonylureas have been reported and certain of these may potentiate the effects of secreted insulin. These effects include reduction in hepatic uptake of endogenous insulin and increased sensitivity of peripheral tissues to insulin. Sulphonylurea agents may stimulate hyperplasia of the beta-cells.

At normal therapeutic doses gliclazide has been shown in man to reduce platelet adhesiveness and aggregation. When these are close to normal at the inclusion time, no significant difference is observed.

Indications

Control of hyperglycemia in gliclazide responsive diabetes mellitus of stable, mild, non-ketosis prone, maturity onset or adult type which cannot be controlled by proper dietary management and exercise, or when insulin therapy is not appropriate.

Contraindications

- Known hypersensitivity or allergy to gliclazide, other sulfonylureas, sulfonamides, or to any of the excipients of this product.
- Unstable and/or insulin dependent diabetes mellitus, particularly juvenile diabetes, diabetic ketoacidosis, diabetic pre-coma and coma.
- During stress conditions such as serious infection, trauma or surgery.
- In the presence of severe hepatic impairment.
- In the presence of severe renal impairment.
- Treatment with miconazole via systemic route or oromucosal gel pregnancy and lactation.

Warnings

The use of gliclazide will not prevent the development of complications peculiar to diabetes mellitus.

Use of gliclazide must be considered as treatment in addition to proper dietary regimen and not as substitute for diet.

The efficacy of gliclazide, in reducing glucose to the desired level decreases over a long period of time in many patients: this may be due to progression in the severity of the diabetes, or to a reduced response to treatment. If a loss of adequate blood glucose- lowering response to GLICLAZIDE is detected, the drug should be discontinued.

Side Effects

Common side effects of Gliclazide

- stomach ache or indigestion.
- feeling sick (nausea)
- being sick (vomiting) or diarrhoea.
- constipation.

Serious side effects of Gliclazide

yellow skin or the whites of your eyes turn yellow - these can be signs of a liver problem.

paleness, prolonged bleeding, bruising, sore throat and fever - these can be signs of a blood disorder.

MATERIALS USED

The following material or the best possible laboratory reagents were used as

Sr. No.	Material Used
1	Gliclazide
2	HPMC K4M
3	Carbapol 934
4	Polyvinyl alcohol
5	Propylene Glycol
6	Dimethylsulphoxide

Formulation Table:

Batches	Gliclazide (mg)	HPMC K4M (mg)	PVA (mg)	PG (drops)	Carbopol 934 (mg)	Ethanol (ml)	Water (ml)
F1	40	33	50	2	40	10	15
F2	40	33	50	2	40	10	15
F3	40	33	50	2	40	10	15
F4	40	40	80	2	50	10	15
F5	40	40	80	2	50	10	15
F6	40	40	80	2	50	10	15
F7	40	30	50	2	60	10	15
F8	40	30	50	2	60	10	15
F9	40	30	50	2	60	10	15

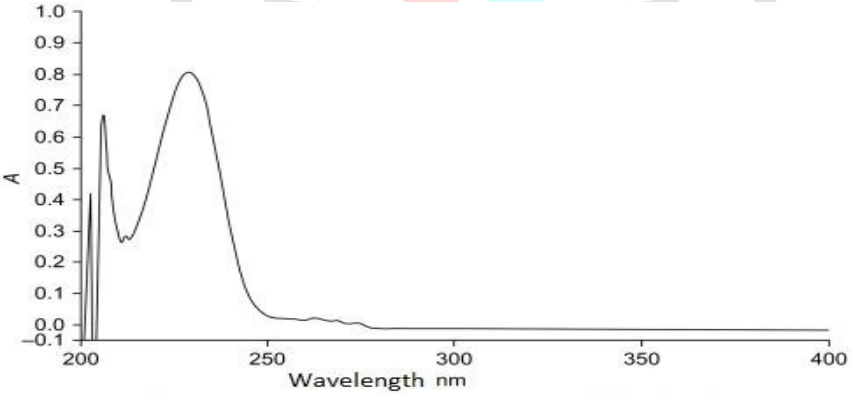
Result and discussion:

Spectroscopic studies:

A. **UV spectroscopy:**

Sr.No.	Concentration of drug (µg/ml)	Absorbance
1	0	0
2	2	0.0872
3	4	0.1280
4	6	0.1695
5	8	0.2061

The UV spectrum of Gliclazide in phosphate buffer pH 6.8 showed maximum absorption at 229.5 nm. Hence drug used in the formulation was found to be pure according to USP specification. The UV spectrum of the Gliclazide in phosphate buffer is given in figure below.

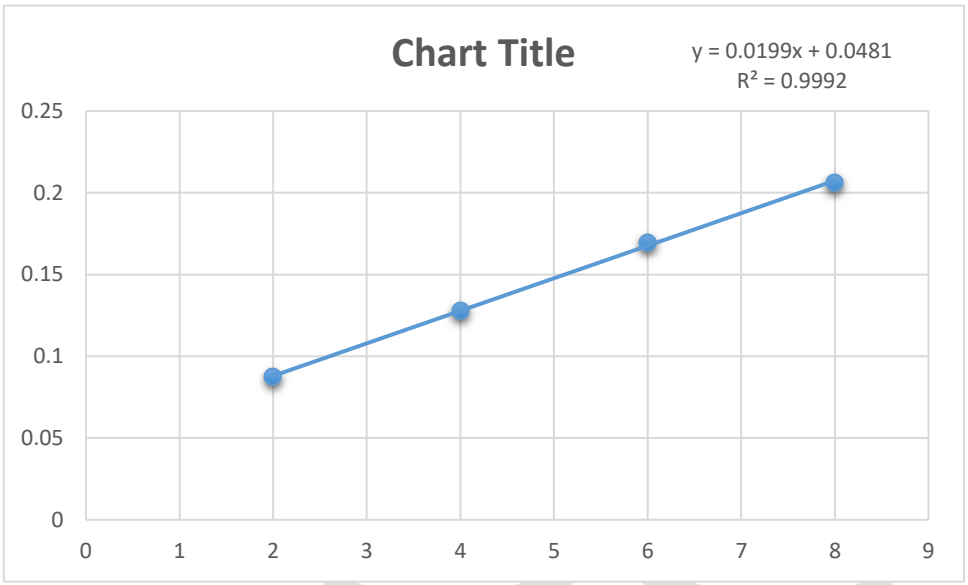


UV absorption spectrum of Gliclazide

B. Standard calibration curve of Gliclazide:

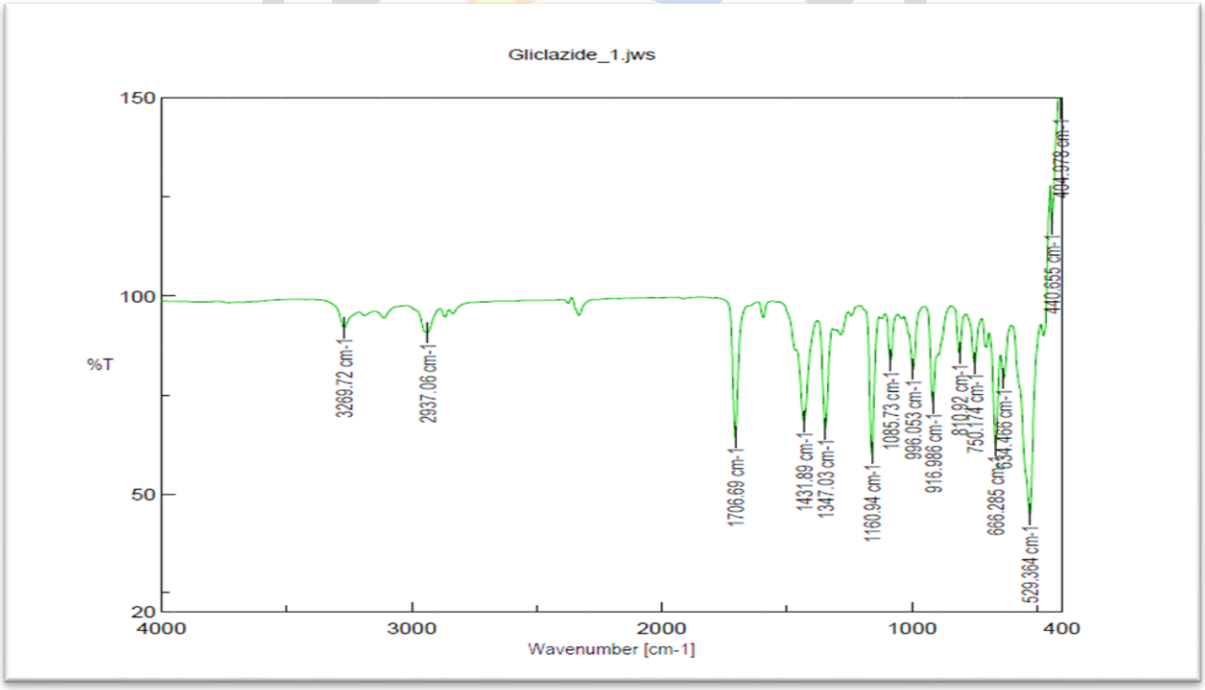
A standard curve was prepared by dissolving 10 mg of Gliclazide dissolved in required quantity of methanol and make up 100 ml with phosphate buffer pH 7.4 to get solutions in concentration range 2 to 8 µg/ml. The absorbance of these solutions were determined spectrophotometrically at 220 nm. The absorbance values were noted as shown in table 4 and figure shows standard calibration curves with slope 0.0814 and regression value of 0.9995. The curve was found to be linear in the range 2 to 8 µg/ml at 229.5 nm.

Standard Calibration Curve of Gliclazide:

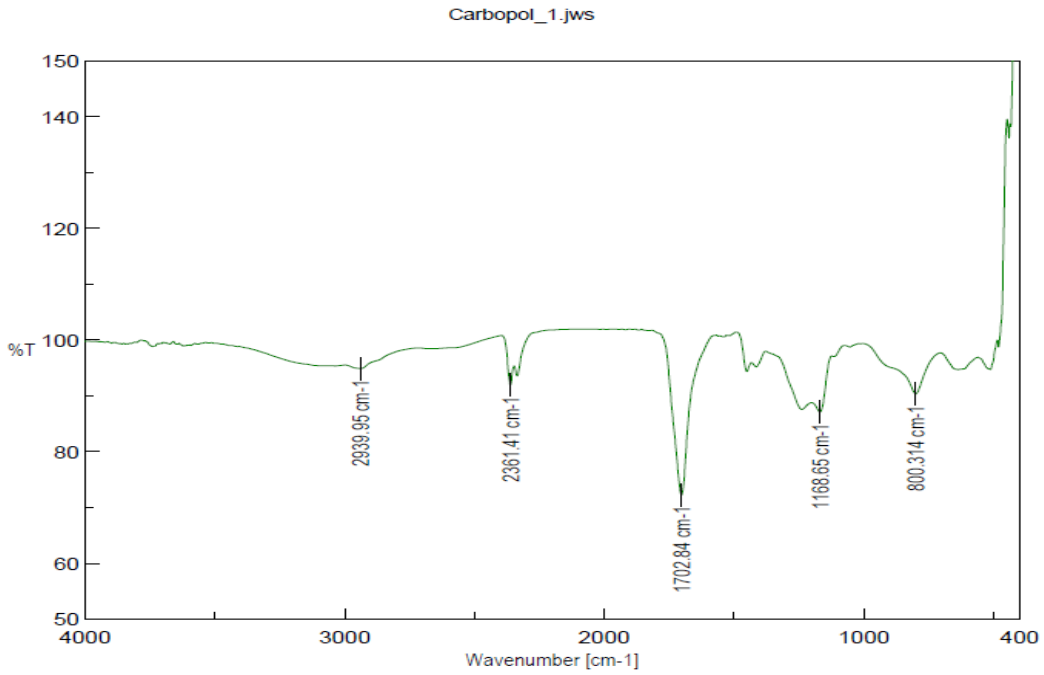


Calibration curve of Gliclazide

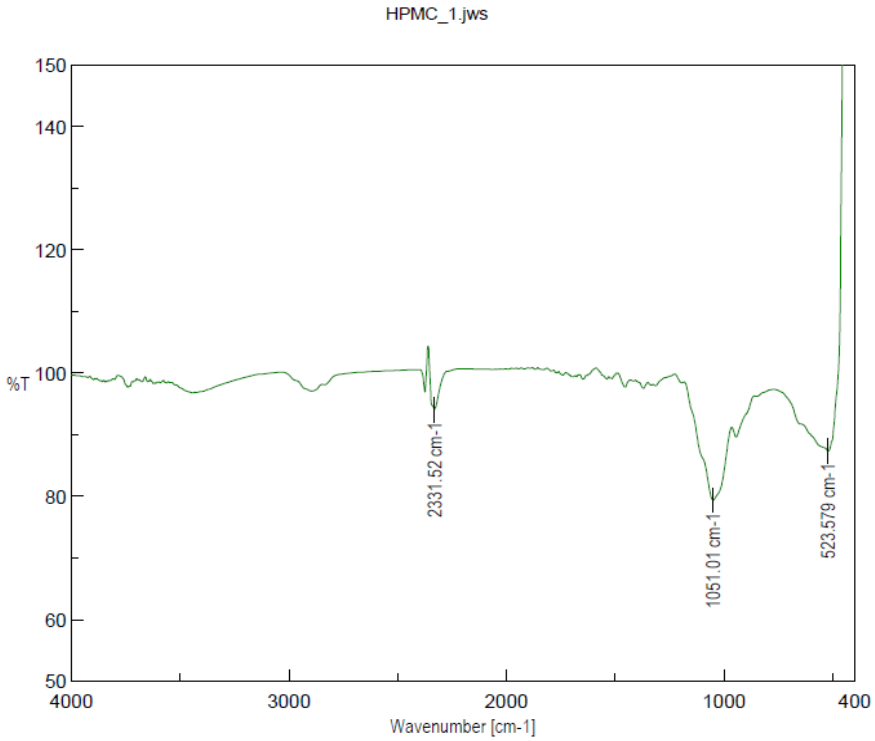
A. FT-IR Spectra of Gliclazide



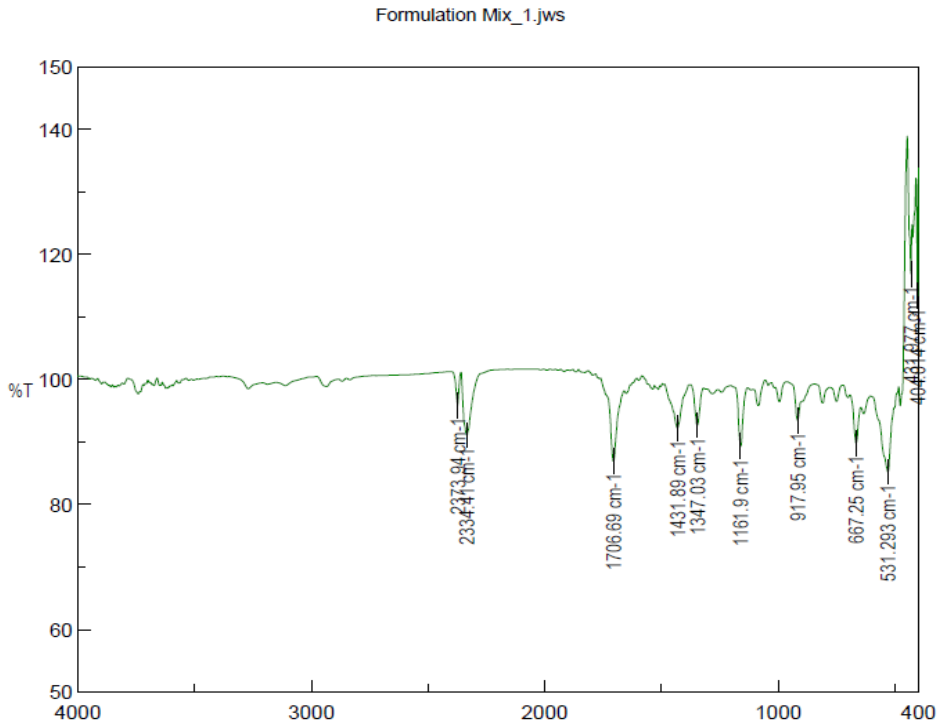
B. FT-IR Spectra of Carbapol



C. FT-IR Spectra of HPMC K4M



D. compatibility studies between drug and HPMC K4M, Carbapol, PVA, and PG



Evaluation of Buccal Patches:

Physicochemical Evaluations

Formulation	Flexibility	Smoothness	Transparancy
F1	✓	✓	Opaque
F2	✓	✓	Opaque
F3	✓	✓	Opaque
F4	✓	✓	Opaque
F5	✓	✓	Opaque
F6	✓	✓	Opaque
F7	✓	✓	Opaque
F8	✓	✓	Opaque
F9	✓	✓	Opaque

Physical Appearance

Surface pH Determination:

The surface pH was determined by the method similar to that used by Bottenberg *et al*., A combined glass electrode was used for this purpose. The patches were allowed to swell by keeping them in contact with 1 ml of distilled water (pH 6.8±0.1) for 2 h at room temperature, and pH was noted down by bringing the electrode in contact with the surface of the patch, allowing it to equilibrate for 1 minute. The surface pH of the patches 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, hence attempt was made to keep the surface pH of the patch close to the neutral pH.

Formulations	Surface pH
F1	6.2 ± 0.06
F2	6.3 ± 0.06
F3	6.47 ± 0.06
F4	6.63± 0.06
F5	6.42 ± 0.06
F6	6.45 ± 0.06
F7	6.33 ± 0.06
F8	6.27 ± 0.06
F9	6.17 ± 0.06

Surface pH

Weight uniformity and thickness:

Weight variation values (mg) of different Gliclazide patches werefound to be in the range of 157.6-169.1 mg. The average thickness of all the bio-adhesive patches ranged from 0.6 to 0.58 mm. Thus therewas proportional gain in weight of patches with that of increasein the thickness of patches. The thickness and weight uniformityvalues were uniform for the patches within the respective group offormulation type. This shows that the patches cast were uniform.

Formulation	Weight Uniformity	Thickness
F1	157.61 ± 0.59	0.14 ± 0.006
F2	159.62 ± 0.08	0.13 ± 0.006

F3	161.64 ± 0.01	0.14 ± 0.006
F4	163.61 ± 0.01	0.13 ± 0.006
F5	163.26 ± 0.01	0.13 ± 0.006
F6	158.61 ± 0.09	0.13 ± 0.006
F7	157.26 ± 0.00	0.11 ± 0.006
F8	157.83 ± 0.09	0.12 ± 0.006
F9	157.63 ± 0.09	0.11 ± 0.006

Drug content uniformity:

The percentage drug content was determined by UV spectrophotometer at 229.5 nm method using thestandard calibration curve and the same procedure was repeatedfor three patches of each formulation. The drug content uniformity of superior batch was found to be in the range of 97.93% - 99.99%. As the drug content values of same formulation did not show a significant difference, it can be concluded that the drug was uniformlydispersed in buccal patches.

Folding endurance:

Folding endurance of patches was determined by repeatedly folding a film at the same place until it breaks**.** The number of folding required to break or crack a patch wastaken as the folding endurance. The folding endurance was found to be increased with an increasing concentration of PVA and decreasing concentration of carbapol. Allthe patches showed good value of folding endurance (more than200 was considered to be good value). This confirms that there will be no breakage of patchtill its use.

Formulation	Content uniformity	Folding endurance
F1	97.92±0.9	190.87±5
F2	95.98±0.9	197.87±0.9
F3	95.97±0.92	195.87±5
F4	98.98±0.21	193.87±0.32
F5	99.96±0.43	192.87±0.12
F6	98.95±0.42	199.87±0.5
F7	96.92±0.98	199.87±0.1
F8	99.91±0.87	198.87±0.9

F9	98.81±0.1	197.87±0.3

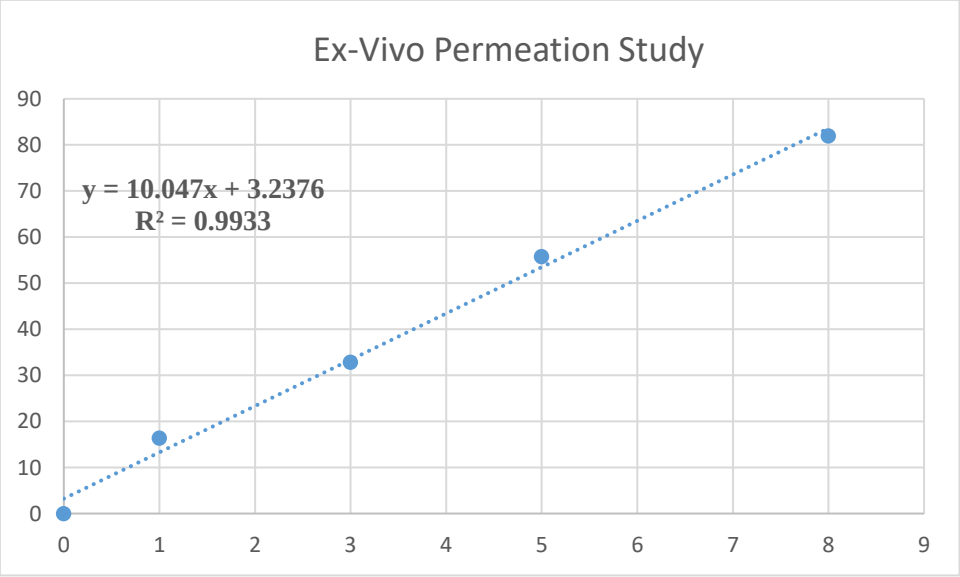
Table.no.5**Content uniformity and folding endurance**

Ex-vivo Permeation study:

The in vitro study of Gliclazide permeation through the goat buccal mucosa was performed using a Franz diffusion cell with 8ml capacity. Freshly obtained goat buccal mucosa was mounted between the donor and receptor compartments so that the smooth surface of the mucosa faced the donor compartment. The patch was placed on the mucosa and the compartments clamped together. The donor compartment was filled with 1 ml of simulated saliva pH 6.8. The receptor compartment (8 ml capacity) contained isotonic phosphate buffer pH 6.8. The hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 100 rpm and maintaining the temperature at 37^0 $\pm 0.5^0$ C. One ml sample was withdrawn at predetermined time intervals and analyzed for drug content at 220 nm. The graph of % drug permeated v/s time was plotted and flux, permeability coefficient was determined.

Time (hour)	Ex-vivo permeation study
0	0
1	16.356
3	32.877
5	55.775
8	81.978

Table no. 6 Ex-vivo permeation study



Ex-vivo Study

Measurement of mechanical property:

Tensile strength:

Thetensile strength was found to be in the range of 10.12 to 15.68 kg/mm^2. As the concentration of hydrophilic polymer carbopol 934 was increased the tensile strength was found to be increased. All film showed 100% flatness.

Formulation	Tensile strength (N/mm^2)
F1	15.68
F2	12.74
F3	13.45
F4	11.98
F5	10.95
F6	12.14
F7	11.24
F8	12.10
F9	10.39

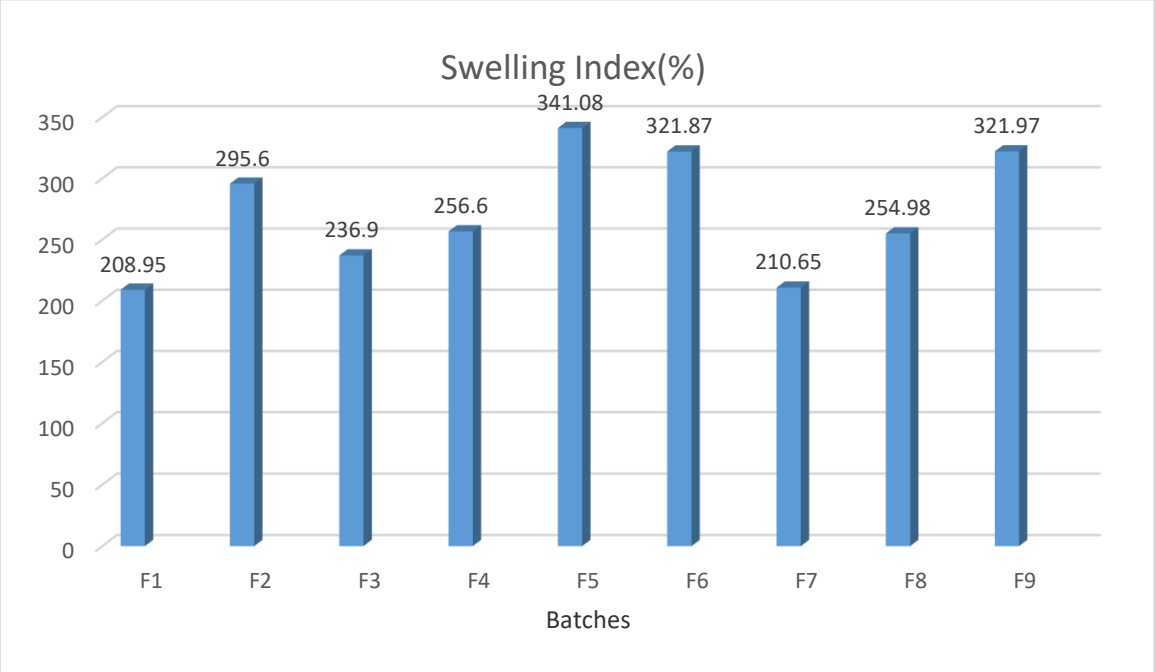
Table no. 7 Tensile strength

Swelling Index:

Thedegree of swellingof bio-adhesive polymer is an important factor affecting bioadhesion. All the patches showed maximum increase in swelling after 1 h. Figure below shows the comparative swelling index of different formulation of Gliclazide buccal patches. The formulated patches F1-F9 showed increase in the swelling index which indicates that as the concentration of the PVA increases the swelling of the patch increases.

Formulation	% Swelling Index
F1	208.95
F2	295.6
F3	236.9
F4	256.6
F5	341.08

F6	321.87
F7	210.65
F8	254.98
F9	321.97



Bar Graph Showing % swelling index of gliclazide buccal patches after 1 hour

Ex vivo Bioadhesion Time:

ThisEx-vivo bio-adhesion time was performed after application of the patches on freshly cut goat buccal mucosa. Within 15 min of slaughter, buccal mucosa was isolated and immediately immersed in an ice-cold phosphate buffer saline pH 6.8. It was kept immersed for 10 min, with aeration to maintain viability. The goat buccal tissues were then fixed on internal side of a beaker with cyanoacrylate glue. Each patch was divided in portions of 3.14 cm^2 and cut; a side of each patch was wetted with 50 ml of PBS pH 6.8 and was pasted to the goat buccal tissue by applying the light force with the finger tip for 30 sec. The beaker was filled with 200 ml of the PBS pH 6.8, was kept at 37 ± 0.5^0C and was aerated. After a 2 min, a 50 rpm stirring rate was applied to stimulate the buccal cavity environment and the patch adhesion was monitored for 300 min. Time required for the patch to detach from the goat buccal mucosa or its complete erosion from the mucosa was recorded as the muco-adhesion time.

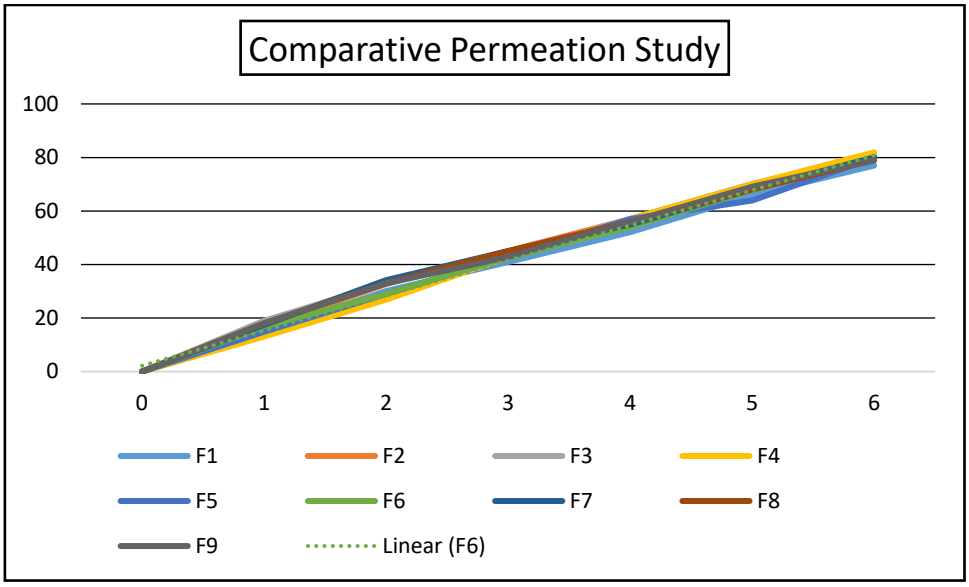
Formulation	Bio-adhesion Time (min)
F1	256
F2	234
F3	237
F4	290
F5	286
F6	249
F7	298
F8	276
F9	287

Table. No. 8 Bio-adhesion Time

Comparative study of F1–F9 batches

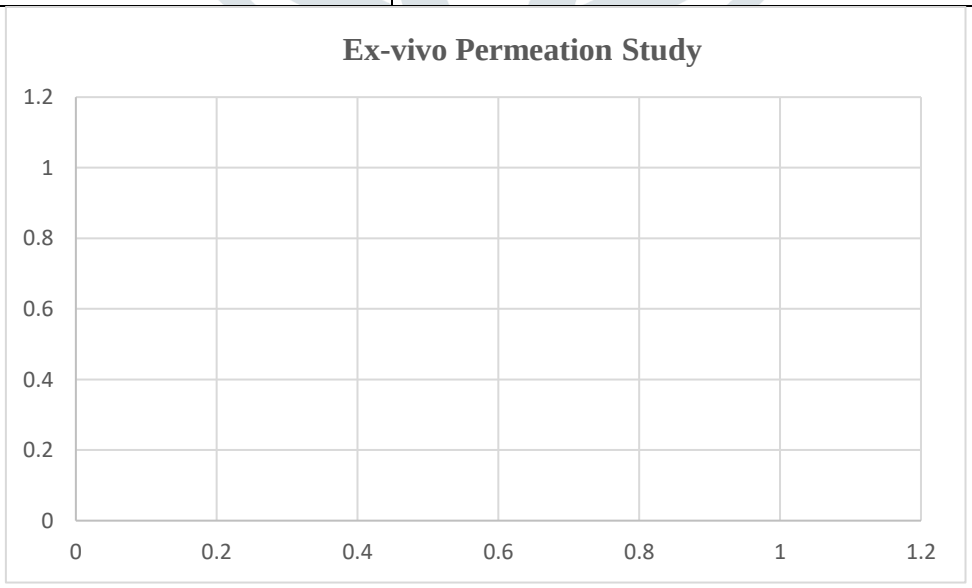
	0	1	2	3	4	5	6
F1	0	15.03	30.06	40.98	52.09	65.98	76.98
F2	0	16.87	32.76	44.98	56.98	69.986	79.87
F3	0	18.98	32.98	43.68	56.98	69.986	80.65
F4	0	13.089	26.87	42.87	56.98	69.986	81.89
F5	0	14.87	28.98	42.87	56.98	63.87	79.98
F6	0	16.87	28.98	42.87	53.98	67.88	79.98
F7	0	17.34	34.19	44.98	54.98	68.09	80
F8	0	18.04	32.98	44.98	55.87	68.09	78.98
F9	0	18.04	32.98	42.87	55.87	69.09	78.98

Table.no. 9 Comparative PermeationStudy



Ex-vivo Permeation Study:

Time(hour)	Ex-vivo Permeation Study
0	0
1	11.2
2	23.67543
3	38.08643
4	52.76532
5	69.12754
6	82.97533



Ex-vivo Permeation Study

Accelerated Stability Studies:

Stability was carried out on optimized buccal patch formulation for three months. It was found that formulation remained stable at temperature of 40^0C ± 2^0C and relative humidity of 75%± 5 as per ICH guidelines. The results obtained are shown in Table. The results shown that there was no change in physical appearance of buccal patches. Drug content showed no marked change after three months. These results concluded that buccal patches were chemically and physically stable at different temperature and humidity conditions for three months.

Parameter	0 day	30 days	60 days	90 days
Appearance	**No change**	**No change**	**No change**	**No change**
% Swelling Index	**No change**	**No change**	**Slightly change**	**Change**
% Drug Release	**No change**	**No change**	**Slightly change**	**Change**
Folding Endurance	**No change**	**Slightly change**	**Slightly change**	**Change**

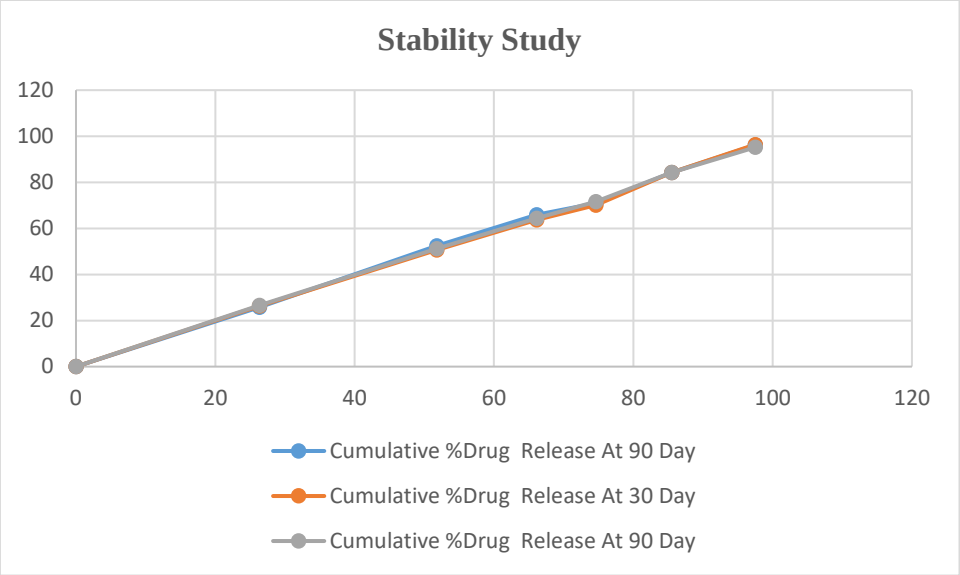
Accelerated Stability Study

Stability studies for drug diffusion of batch F1

Batch F1 is selected as optimized batch and further studied for stability study at 40^0C and 75% RH for 90 days.

Time	Cumulative %Drug Release At 0 Day	Cumulative %Drug Release At 30 Day	Cumulative %Drug Release At 60 Day	Cumulative %Drug Release At 90 Day
0	0	0	0	0
1	26.33	26.34	25.765	26.654
2	51.795	50.653	52.456	51.2621
3	66.15	63.65	65.876	64.44
4	74.64	70.12	70.982	71.57
5	85.529	84.21	84.34	84.2432

Table no. 10. Stability Study



CONCLUSION

The present study was aimed to developed buccal patches of Gliclazide. Before formulation of patches, pre-formulation studies were performed such as organoleptic characteristics, solubility study and drug polymer interaction study by FT-IR. In all above study the result was found to be desirable and there is no incompatibility between drug and polymers.

Gliclazide had shown it significant peaks at 3369.79 (N-H), 2930.96 (C-H), 2843.20 (O-H), 1444.75, 1543.12 (N=O), 1154.45 (C-N) and 1036.78 (C-O). The spectra of the physical mixture with all other excipients such as HPMC K4M, Carbopol 934, PVA, PG had shown all the principle peaks of Gliclazide drug, from which we can suggest the stable nature of drug during the process. FTIR spectrum of pure Drug, HPMC K4M, Carbopol 934, PG, and PVA showed that there was no major shifting, loss of appearance of functional peaks between the spectra of drug and excipients. Thus, the drug is compatible with the excipients.

Then 9 batches of matrix buccal patches of Gliclazide containing varying concentration of polymer by solvent casting method were developed and evaluated for their physical parameter such as weight uniformity, swelling index, folding endurance, thickness, % Drug release, Determination of muco-adhesion, diffusion study.

Diffusion studies of buccal patches were performed using Franz type of diffusion cell. The goat buccal membrane was used as a permeation barrier and phosphate buffer solution having pH 6.8 was used as a diffusion media. The diffusion study was conducted for 6 hrs. Batch F8 was found to show linear release of 99.91% up to 6 hrs. And followed zero order release kinetics. Based on the comparative study, the batch F8 was found to be superior in all respects among the other batches and then it was selected as an optimized batch.

This optimised batch was subjected for stability studies that were carried out at temperature 40^0C and 75% Relative humidity for 90 days and the swelling index was found to be 254.98 % and folding endurance was also found in the range of 198.87±0.9.

Drug permeation studies of batch F8 were also carried out and the percent drug diffusion was found to decrease from 98.05 to 93.21%.

Finally, it was observed that the formulated buccal patches of Gliclazide showed folding endurance, swelling index, % drug release. The polymers carbopol 934 and polyvinyl alcohol can be used to develop matrix type buccal patches.

As the concentrations of hydrophilic polymers were increased folding endurance as well as swelling index were also increased, increased folding endurance as well as swelling index shows the good film consistency. From drug diffusion studies, it was concluded, Polyvinyl alcohol concentration increased and carbopol when decreased into primary layer *In-vitro* diffusion rates were increased. Batch F8 was the optimised formulation showing uniform thickness, good % swelling index, % release and good folding endurance.

The formulation F8 showed linear zero order release for 6 hours with cumulative % drug diffused of 98.05 from 2 cm^2 patches of batch F8. This present work concludes that buccal patches shows promising effect in pharmaceutical field.

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