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DESIGN AND DEVELOPMENT OF BIOADHESIVEBUCCAL PATCHES OF AN ANTIDIABETIC DRUG

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ABSTRACT

The buccal region offers an attractive route of administration for systemic drug delivery. Glimepiride isa potent drug against Diabetes mellitus-II with a half life of 3-5 hours. Though Glimepiride has 100% oral absorption, due to high first pass metabolism its bioavailability is less. The recommended dosage is4 mg b.i.d leading to admistration of the drug twice a day. The present study is aimed to design sustained release mucoadhesivebuccal patch formulation of Glimepiride in order to by-pass GIT and release the drug for extended periods of time. Buccal patches were formulated using polymers Carbopol 934 P(CP 934 P), polyvinyl alcohol and Hydroxy Propyl Methyl Cellulose E 15 (HPMC E 15) in various proportions and combinations. The patches were prepared by solvent casting method. The designed patches were evaluated for thickness uniformity, folding endurance, weight uniformity, content uniformity, swelling behaviour, determination of mucoadhesive time and buccal mucosa sensitivity test. In vitro diffusion studies were conducted for 6 hours in phosphate buffer (pH 6.8) solution using dialysis membrane. Formulation containing maximum amount of swellable and hydrophilic polymer HPMC E 15 and CP 934 P, showed higher swelling index. This occurred due to more hydrophilic polymeric matrix composition which retarded the release of the drug. The diffusion followed zero order kinetic model (R^2 = 0.9995).

KEYWORDS: Glimepiride, Buccal, Carbopol, HPMC E 15, Diabetes.

INTRODUCTION

Among the various route of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, peroral administration of drug has advantages such as hepatic first pass metabolism and enzymatic degradation within the GI track, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosa are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of pre-systemic elimination within the GI tract and depending on the particular drug, a better enzymatic flora for drug administration.[1] The nasal cavity as a site for systemic drug delivery has been investigated by many research groups[2,3] and the route has already reached commercial status with several drugs including LHRH and calcitonin.[4]

However, the potential irritation and the irreversible damage to the ciliary action of the nasal cavity from chronic application of nasal dosage forms, as well as the large intra and inter-subject variability in mucus secretion in the nasal mucosa, could significantly affect drug absorption from this site. Even though the rectal, vaginal, and ocular mucosa all offer certain advantages, the poor patient acceptability associated with these sites renders them reserved for local applications than systemic drug administration.[5]

The oral cavity, on the other hand, is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply, it is robust and shows short recovery times after stress or damage[6], and the virtual lack of Langerhans cell makes the oral mucosa tolerant to potential allergens.[7] Furthermore, oral transmucosal drug delivery bypasses first pass effect and avoids pre-systemic elimination in the GI tract. These factors make the oral mucosal cavity a very attractive and feasible site for systemic drug delivery.

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularized, drug that are absorbed through the oral mucosa directly enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism in the liver. For some drugs, this result in rapied onset of action via a more comfortable and convenient delivery route than the intravenous route. Not all drugs, however can be administered through the oral mucosa because of the characteristics of the oral mucosa and

the physiochemical properties of the drug.[8] The oral cavity is viewed as a convenient and easily accessible site for the delivery of therapeutic agents. Absorption of drugs through oral cavity was noted as early as 1847 by Sobero, the discovers of Nitroglycerine, and systemic studies of oral cavity absorption were first reported by Walton and Lacey in 1935. Since then, substantial efforts has been focused.

Buccal delivery of drugs at first glance, seems to offer a combination of advantages of transdermal and peroral delivery. A buccal 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 the epidermis.

Conventional formulations for local oral delivery are principally lozenges, troches, mouth paints, mouthwashes, oral gels, pastes and suspensions.[8,9] Release of drug from these preparations involves initial burst of activity, subsequently declines to sub therapeutic level.

Bioadhesive drug delivery formulations were introduced in 1947 when gum tragacanth was mixed with dental adhesive powder to apply penicillin to the oral mucosa; this was eventually leads to Orabase.[10] Recently, considerable attention has been focused on the development of alternative drug delivery systems for proteins and peptide drugs. As the peroral administration has disadvantages such as the hepatic first pass metabolism and enzymatic degradation within the gastrointestinal tract, proteins and peptides are usually not suitable for peroral administration and therefore mostly delivered by parenteral route.[11] Nasal, ocular, vaginal, rectal and buccal mucosal membranes have been evaluated as potential alternative routes for peptide absorption. Buccal administration of drugs provides a convenient route of administration for both systemic and local drug actions.[12]

MATERIALS AND METHODS

Following drug substance, resin, excipients and chemicals were used for the formulation and evaluation studies.Glimepiride was gif sample of Orbicular Pharmaceutical Technology Pvt.

Ltd., Hyderabad, Carbapol 934 was a gift from Corel Pharma Chem., Ahmedabad. Hydroxy propyl methyl cellulose E15 (HPMC E15), Propylene Glycol were provided by Themis laboratory Mumbai, Polyvinyl alcohol, Dimethylsulphoxidewere purchased from Thomas baker Pvt. Ltd, Mumbai. All other chemicals were of analytical grade and were used without further purification.

METHODS

Solvent Evaporation Technique

Matrix type buccal patches containing Glimepiride were prepared by solvent evaporation technique, using different ratios of polyvinyl alcohol, Carbopol 934 and HPMC E 15. The polymers were weighed in requisite ratios by keeping the total polymer weight 2.50 gm. and allowed for swelling for about 2 hrs. In solvent mixture (1:1 ratio of dichloromethane, methanol). Propylene glycol was incorporated as plasticizer and DMSO as penetration enhancer. Then the drug solution was added to the polymeric solution, casted on to Petri plate of surface area about 70 cm^2, allowed for air drying overnight followed by vacuum drying for 8-10 hr. The entire sheet was cut into small patches with an area of 3.14 cm^2 i.e. with a diameter of 2 cm. About 6 patches were obtained from each sheet.

Table No. 1: Formulation of matrix type Buccal patches.

Batches	Glimepiride (mg)	HPMC E15 (mg)	PVA (mg)	PG (drops)	Carbopol 934 (mg)	Water (ml)
F1	4	20	100	2	100	15
F2	4	20	200	2	100	15
F3	4	20	300	2	100	15
F4	4	20	100	2	200	15
F5	4	20	200	2	200	15
F6	4	20	300	2	200	15
F7	4	20	100	2	300	15
F8	4	20	200	2	300	15
F9	4	20	300	2	300	15

RESULT AND DISCUSSION

A. Spectroscopic studies of Glimepiride

The UV spectrum of Glimepiride in phosphate buffer pH 7.4 showed maximum absorption at 220 nm. Hence drug used in the formulation was found to be pure according to USP specification. The UV spectrum of the Glimepiride in phosphate buffer is given in Figure 1.

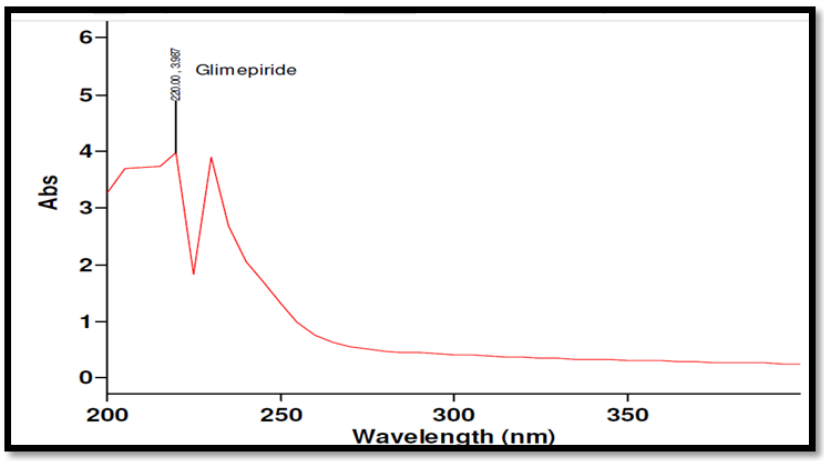


Fig No.1 Absorption spectrum of Glimepiride.

B. Standard calibration curve of Glimepiride

A standard curve was prepared by dissolving 10 mg of Glimepiride dissolved in required quantity of methanol and make up to 100ml with phosphate buffer pH 7.4 to get solutions in concentration range 2 to 16µg/ml.

Table No. 2: Standard calibration curve of Glimepiride.

Sr.No.	Concentration of drug in µg/ml	Absorbance
1	0	0
2	2	0.1655
3	4	0.3469
4	6	0.4973
5	8	0.6482
6	10	0.8230
7	12	0.9808

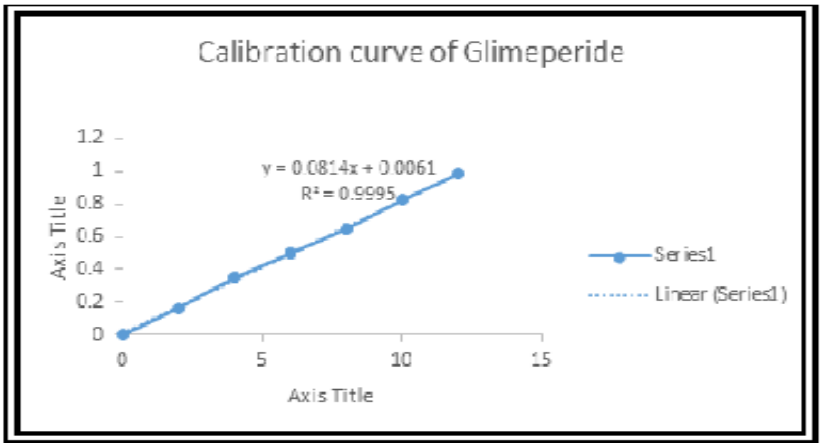


Figure no.2 Calibration curve of Glimepiride.

a. FT-IR Spectra of Glimepiride

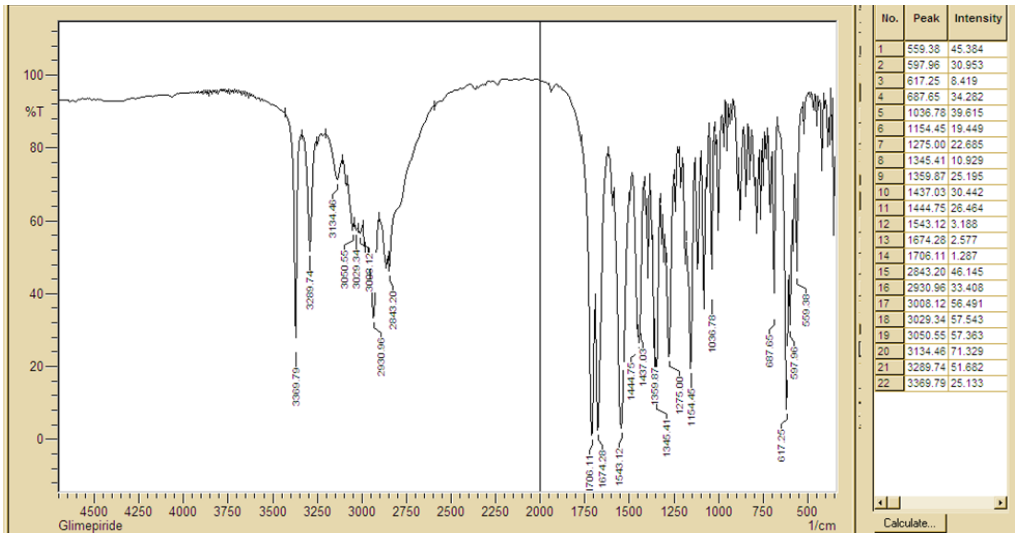


Figure 3: FT-IR Spectra of Glimepiride

B. FT-IR spectra of HPMC E15.

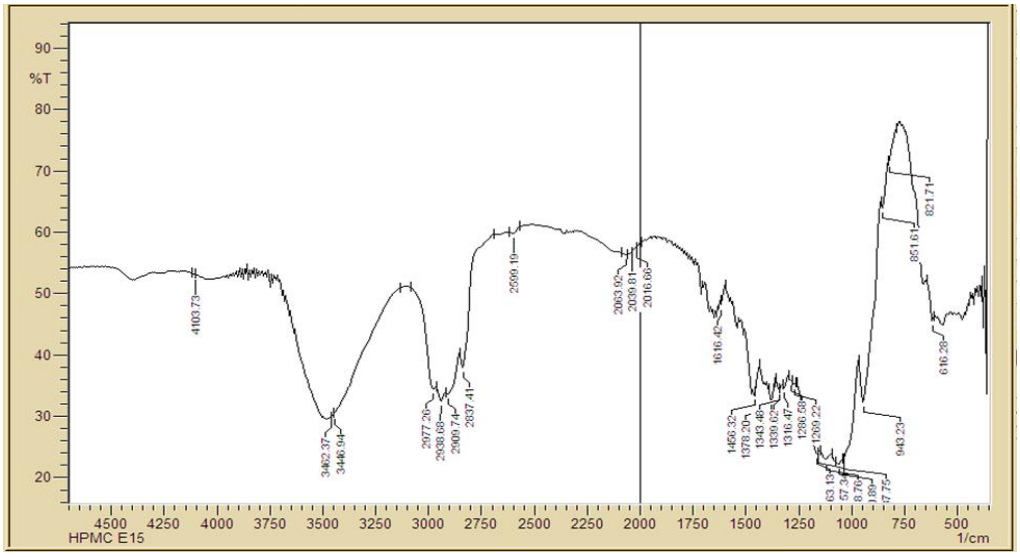


Figure 4: FT-IR spectra of HPMC E15.

C.FT-IR spectra of carbopol 934

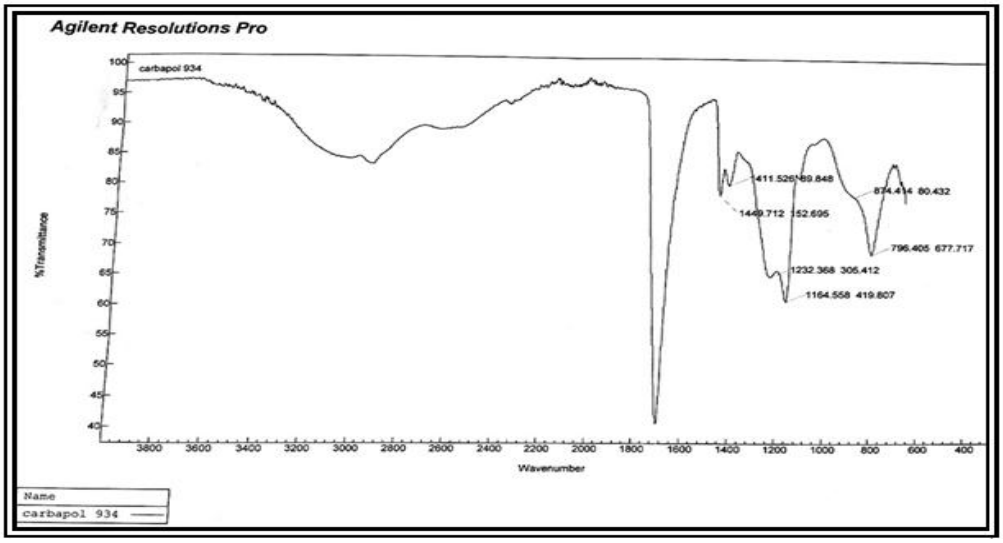


Figure no. 5. FT-IR spectra of carbopol 934.

Compatibility studies between Drug, HPMC E15, Carbopol 934.

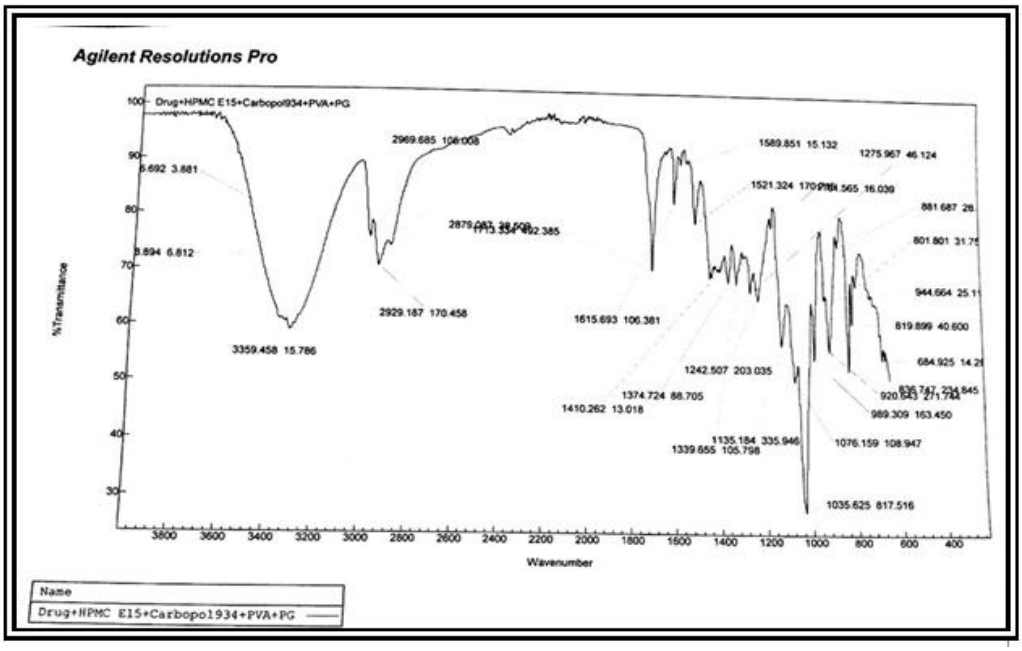


Figure no.6 FT-IR mixture of Glimepiride, HPMC E15, Carbopol 934.

Evaluation of Buccal Patches

1. Physiochemical evaluation

Table no.3 Physical appearance.

Formulation	Flexibility	Smoothness	Transparency
F1	Flexible	Smooth	Opaque
F2	Flexible	Smooth	Opaque
F3	Flexible	Smooth	Opaque

F4	Flexible	Smooth	Opaque
F5	Flexible	Smooth	Opaque
F6	Flexible	Smooth	Opaque
F7	Flexible	Smooth	Opaque
F8	Flexible	Smooth	Opaque
F9	Flexible	Smooth	Opaque

2. Surface pH Determination

Table no.4 Surface pH

Formulation	Surface pH
F1	6.6 ± 0.06
F2	6.47 ± 0.06
F3	6.53 ± 0.06
F4	6.43 ± 0.06
F5	6.63 ± 0.06
F6	6.63 ± 0.06
F7	6.33 ± 0.06
F8	6.17 ± 0.06
F9	6.27± 0.15

3. Weight Uniformity and Thickness.

Table no. 5: Weight uniformity and thickness.

Formulation	Weight uniformity	Thickness
F1	42.3±1	0.11±0.006
F2	40.0±0.00	0.12±0.006
F3	41±0.00	0.11±0.006
F4	41.3±0.58	0.13±0.006
F5	42.3±0.58	0.13±0.006
F6	41.3±0.58	0.13±0.006
F7	43.7±0.58	0.14±0.006
F8	42.5±0.6	0.13±0.006
F9	42.7±0.6	0.14±0.006

4. Drug Content Uniformity

The percentage drug content was determined using the standard calibration curve and the same procedure was repeated for three patches of each formulation. The drug content uniformity was found to be in the range of 98.96% - 100.43%. Results are shown in Table 6. As the drug content values of same formulation did not show a significant difference, it can be concluded that the drug was uniformly dispersed in buccal patches.

5. Folding Endurance

Folding endurance of patches was determined manually by repeatedly folding a film at the same place until it breaks. The number of folding required to break or crack a patch was

taken as the folding endurance. The prepared Glimepiride patches has sufficient flexibility and good mechanical strength. The folding endurance was found to be increased with increasing concentration of PVA and decreasing concentration of Carbapol 934. All the patches showed good value of folding endurance (more than 200 was considered to be good) and the formulations F7 - F9 showed folding endurance values more than 300 (Table 6). This confirms that there will be no breakage of patch till its use.

Table no.6 Content uniformity and folding endurance.

Formulation	Content uniformity	Folding endurance
F1	100.43±0.85	232±2
F2	99.47±0.12	256±2.4
F3	99.12±0.14	261±2.5
F4	99.12±0.18	263±2.6
F5	99.41±0.44	282±1.7
F6	99.81±0.06	275±3.06
F7	99.82±0.05	318±2.6
F8	99.71±0.47	332±2
F9	98.96±0.7	326±4.2

6. Ex-vivo Permeation study

Thisstudy of Glimepiride can carried out by using the goat buccal mucosa was performed using a Franz diffusion cell with 8 ml 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^{o}±0.5^{o}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.

Table no.7 Ex-vivo permeation study.

Time(hr)	Ex-vivo permeation study
0	0
1	10.6
2	22.56530984
3	37.2235723
4	51.06470231

5	68.20018226
6	82.49696233

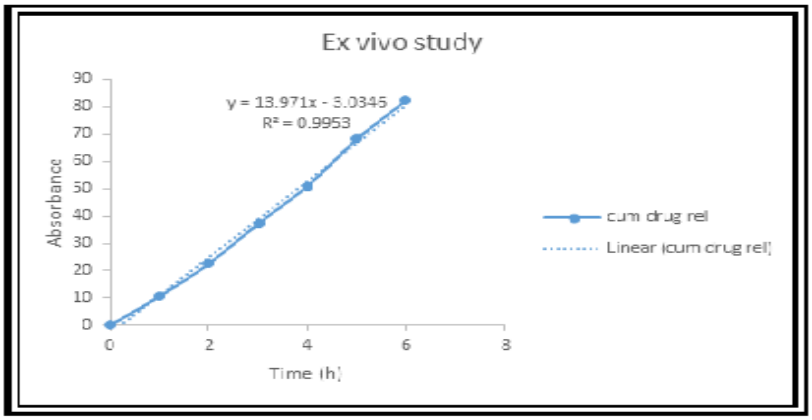


Figure no.7*ex –vivo* study.

7. Measurement of mechanical property

Tensile strength

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

Table no 8: Tensile strength.

Formulation	Tensile strength (N/mm^2)
F1	10.12
F2	11.13
F3	12.14
F4	10.56
F5	11.86
F6	11.57
F7	13.16
F8	12.87
F9	15.68

8. Swelling Index

The degree of swelling of bioadhesive polymer is an important factor affecting bioadhesion. All the patches showed maximum increase in swelling after 1 h. Fig.16 below shows the comparative swelling index of different formulations of Glimepiridebuccal 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.

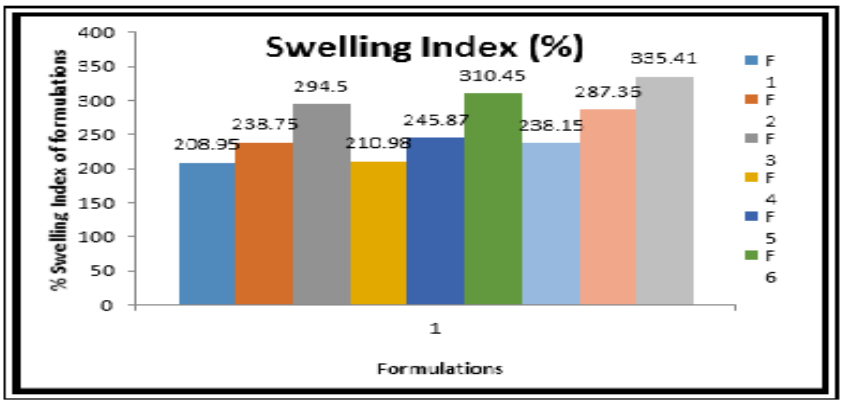


Fig No8: Bar graph showing % swelling index of Glimepiride buccal patches after 1 hr.

9. *Ex vivo* Bioadhesion Time

Table no.9 *Ex vivo* Bioadhesion Time.

Formulation	Bioadhesion Time (min)
F1	256
F2	267
F3	269
F4	286
F5	292
F6	282
F7	291
F8	290
F9	283

10. *In vitro*buccal permeation study

Table no.10 Calculation table for permeation study of F3 is optimize batch

Time (hr)	Cumulative %drug Diffuse
0	0
1	22.41
2	38.95048603
3	56.4626367
4	73.05437424
5	88.19866343
6	98.05285541

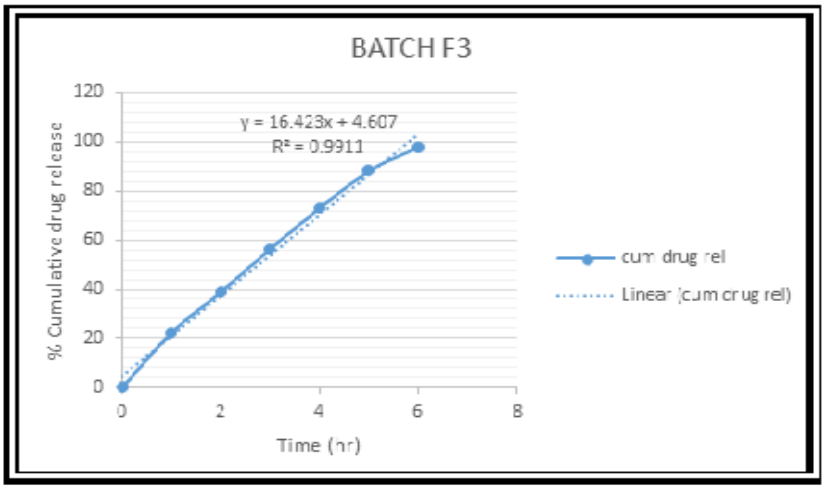


Figure no 9: permeation study of F3 batch.

11. Comparative study of F1-F9 batches

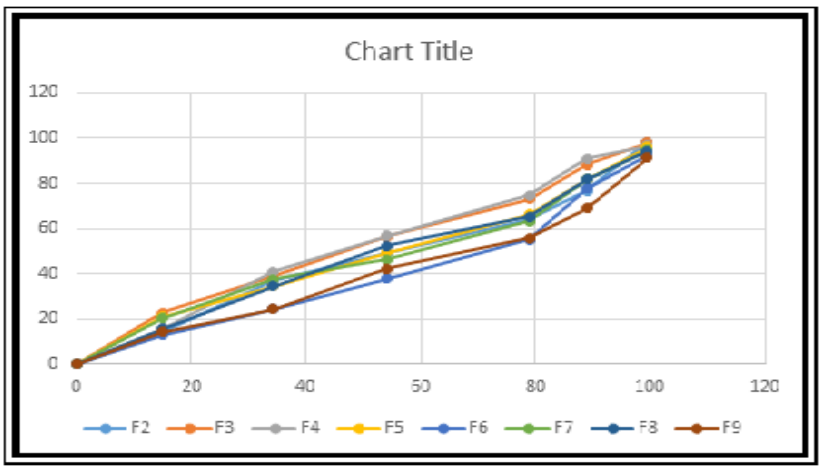


Figure no 10: Comparative permeation study.

The medicated film shows drug diffusion through Franz diffusion type of diffusion cell. The relationship can be established as**F1>F2>F3>F4>F5>F7>F8>F9>F6.**

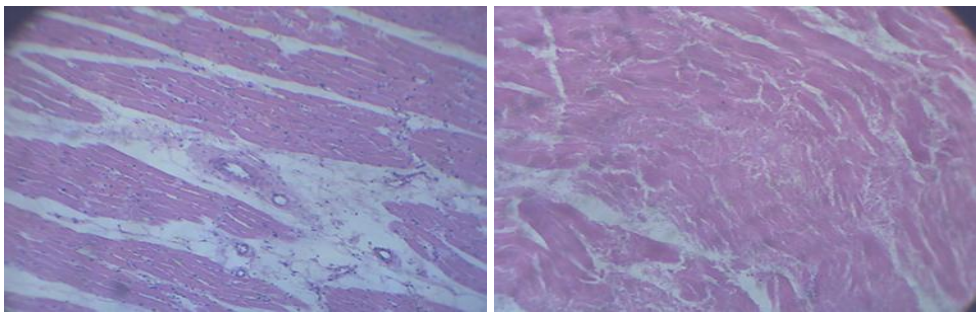
From diffusion study the Formulation F1 exhibited greatest 99.46 percentages of drug release values. In the present study it was observed that as the concentrations of hydrophilic polymer (Carbopol) decreased in the formulations, the drug release rate increased substantially, however with a very nominal decrease in formulation f3. The addition of hydrophilic component to an insoluble film former tends to enhance the release rates.

From the diffusion study of all the batches, batch F1 showed maximum drug release in 6 hours with linearity and follow zero order kinetic release. But F3 batch passes the folding

endurance and swelling index test, and also shows 98% drug release, Therefore batch F3 selected as optimised batch and further studies for accelerated stability studies.

12. Histopathological Study

The final optimized formulation F3 was subjected to buccal mucosa sensitivity test. The sections of control and sample mucosa (treated with final optimized formulation) observed under digital microscope are shown in Fig. 11,12. The histopathological evaluation of sections showed that cellular membrane was intact and there was no damage to the epithelial layer. Cell necrosis was not observed and hence it can be concluded that, formulated batch F3 is safe for buccal administration through bio adhesive patches.



a) Control **b) sample**

Figure no.11,12: Histopathological evaluation of sections of goatbuccal mucosa. (a) control (b) sample buccal mucosa.

13. 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 40ºC ± 2ºC 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.

Table no. 11: Accelerated Stability Study.

Parameters	0 day	30 days	60 days	90 days
Appearance	No change	No change	No change	No change
% Swelling index	291.5	285.4	270.06	225.3
% Drug release	98.052	97.64	93.32	94.21
Folding endurance	261	255	251	240

Stability studies for drug diffusion of batch F3

Batch F3 is selected as optimized batch and further studied for stability study at 40^0C and 75% RH for 90 days.

Table No.12: Stability study of drug permeation batch F3.

Time	Cumulative% drug release at 0 days	Cumulative %drug release after 30 days	Cumulative % drug release after 60 days	Cumulative % drug release after 90 days
0	0	0	0	0
1	26.33	26.33	25.61	26.42
2	50.79586877	51.60236938	51.33049818	51.26215067
3	65.15188335	64.54434994	64.16919806	63.44319563
4	73.64976	71.77248	70.76554	70.5723
5	84.52976	84.4212	83.345	83.2432
6	97.5421	96.4378	96.237	95.2221

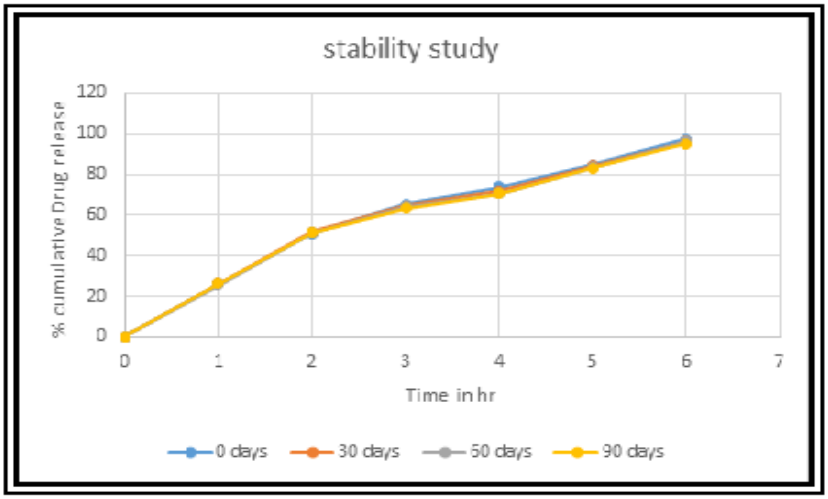


Figure 13: Comparative stability studies for drug permeation of batc F3.

CONCLUSION

The present study was aimed to developed buccal patches of Glimepiride. Before formulation of patches, preformulation 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.

Then 9 batches of matrix buccal patches of Glimepiride 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 mucoadhesion, diffusion study. The diffusion study was conducted

for 6 hrs. Batch F3 was found to show linear release of 98.05% up to 6 hrs. And followed zero order release kinetics. Based on the comparative study, the batch F3 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 decrease from 294.5 to 225.3% and folding endurance was also decreased from 261 to 240. Finally it was observed that the formulated buccal patches of Glimepiride 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. The formulation F3 showed linear zero order release for 6 hours with cumulative % drug diffused of 98.05 from 2 cm^2 patches of batch F3.This present work concludes that buccal patches shows promising effect in pharmaceutical field.

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Ltd., Hyderabad,Carbapol 934 was a gift from Corel Pharma Chem Authors also thank Principle Dr. P.S Kawtikwar Sudhakarao naik Institute of Pharmacy pusad, yavtmal for support and providing necessary facilities to carry out this work.

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