Research Paper Available online www.ijrpsonline.com ISSN: 2249–3522

International Journal of Research in Pharmacy and Science

# Design and Characterisation of Mucoadhesive Buccal Patch of Glimepride

**Patel Naveen[1*], L Aparna[1], S Uma[1], Patil Swaraj[2]**

[1]KLE College of Pharmacy, Rajajinagar-2nd block, Bangalore-10, Karnataka, India
[2]School of Pharmacy DAVV, Indore, Madhya Pradesh 452017

**ABSTRACT:**
The buccal region offers an attractive route of administration for systemic drug delivery. Glimepiride is a potent drug against Diabetes mellitus-II with a half life of 3-5 hours. Though Glimepride has 100% oral absorption, due to high first pass metabolism its bioavailability is less. The recommended dosage is 4 mg b.i.d leading to admistration of the drug twice a day. The present study is aimed to design sustained release mucoadhesive buccal patch formulation of Glimepride 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), Ethyl Cellulose (EC) and Hydroxy Propyl Methyl Cellulose(HPMC) in various proportions and combinations. Tween 80 was used as permeation enhancer and glycerine as plasticizer. The patches were prepared by solvent casting method. The designed patches were evaluated for thickness uniformity, folding endurance, weight uniformity, content uniformity and swelling behaviour. *In vitro* diffusion studies were conducted for 24 hours in phosphate buffer (pH 6.6) solution using dialysis membrane. Formulation containing maximum amount of swellable and hydrophilic polymer HPMC K100M and CP 934 P, showed higher swelling index and could sustain for 24 hours. This occurred due to more hydrophilic polymeric matrix composition which retarded the release of the drug. The diffusion followed zero order kinetic model.( $R^2$ = 0.9778)

**KEY WORDS:** Glimepiride, Buccal, Carbopol, HPMC K100M, Diabetes mellitus-II

***Corresponding author:**
**Naveen Patel**
KLE College of Pharmacy,
Rajajinagar-2nd block,
Bangalore-10, Karnataka, India
Phone No: +91-9880703240
Email: naveen.patel5@gmail.com

# INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to other conventional methods of systemic drug administration, since buccal mucosa is relatively permeable with rich blood supply and acts as an excellent site for the absorption of drugs[1,2]. The administration of drugs via buccal route facilitates a direct entry of drug molecules into the systemic circulation, avoiding the first-pass metabolism and drug degradation in the harsh gastrointestinal environment, which are often associated with oral administration [3–5]. The buccal cavity is easily accessible for self medication, and hence it is safe and well accepted by patients. Also buccal patches can be very easily administered and even removed from the application site, terminating the input of drug whenever desired.

Over the last two decades mucoadhesion has become of interest for its potential for localized drug delivery, by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining a formulation an intimate contact with the absorption site (e.g. buccal cavity)[6]. Bioadhesion is defined as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred to as mucoadhesion[7]. Recently Jasti *et.al*[8], Johnston *et.al*[9], Semalty *et.al*[10] have reviewed the use of mucoadhesive polymers in buccal drug delivery and highlighted the use of novel mucoadhesive polymers. Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels, have recently been developed. However, buccal patch offer greater flexibility and comfort than adhesive tablets. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva[11]. Buccal route of drug delivery provides direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability[12]. Other advantages include excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action[13].

Glimepride is the first III generation sulfonyl urea against Diabetes mellitus-II. Though Glimepride has 100% oral absorption, due to high first pass metabolism it has a low and variable bioavailability. The drug is given in 4mg twice a day and hence there is less patient compliance. The physicochemical properties of glimepride i.e., slight water solubility, low molecular weight (490.62), high first pass

metabolism and its suitable elimination half-life (t1/2=5 h) , make it a suitable candidate for administration by buccal route.

As Glimepride has first pass metabolism, buccal patches were designed with an objective to increase its bioavailability. Sustained release formulation was developed with polymers CP 934 P(Carbopol 934 P), HPMC (Hydroxy propyl methyl cellulose), EC(Ethyl cellulose) in various proportions which released the drug over an extended period of 24 hours giving an advantage of once a day dosing. Tween 80 was used as permeation enhancer and glycerine as plasticizer.

CP 934 P and HPMC are release-retardant mucoadhesive polymers with high swellability and hydrophilicity. Anionic polyelectrolytes like HPMC have been extensively used for designing mucoadhesive delivery systems due to their ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer. [14,15] EC is a hydrophobic polymer with high mechanical strength. So, they will provide delayed release of drug from buccal patches for long time. Glycerine is used as an additive that increases the plasticity or fluidity of the formulation. Tween 80 modifes the solvent nature of stratum corneum, thus improving drug partitioning into skin and also increases diffusitivity of the drug into skin.

## MATERIALS AND METHODS

The following chemicals were obtained from different sources and used as received. Glimepride was a kind gift sample from Astra Zeneca, Bangalore. CP 934 P, EC, HPMC, Tween 80 and glycerine were obtained from S.D Fine chemicals, Mumbai. All other chemicals and reagents used were of analytical grade. Double-distilled water was used throughout.

### FORMULATION OF BUCCAL PATCH OF GLIMEPRIDE:

A series of buccal patches composed of different proportions and combinations of HPMC, CP 934 P and EC were dissolved/dispersed in 10 ml of water in a beaker and allowed to swell by keeping it aside for 5 minutes. Glycerine was incorporated as a plasticizer at a concentration of 15% w/w of dry weight of polymers (61.2 mg approximately equals 2 drops).Tween 80(1 drop) was added to the polymer solution as permeation enhancer. Glimepride 8 mg was dispersed in 5 ml water in another beaker. The drug solution was added to the polymer solution and was mixed thoroughly with the help of a magnetic stirrer. A clean petridish was placed over a flat surface. The whole solution was poured into the petridish and kept for 24 hours. Inverted funnel was placed over to avoid sudden evaporation. After

drying, the films were observed and checked for possible imperfections upon their removal from the petridish.

Patches with any imperfections, entrapped air, differing in thickness, or weight (or) content uniformity were excluded from further studies.

**Table 1: shows the quantities of different ingredients in the formulation.**

| Code | Glimepride (mg) | HPMC (mg) | CP 934P (mg) | EC (mg) | Tween 80 | Glycerine | Water (ml) |
|---|---|---|---|---|---|---|---|
| **F1** | 8 | 400 | - | - | 1 drop | 2 drops | 15 |
| **F2** | 8 | 300 | 50 | 50 | 1 drop | 2 drops | 15 |
| **F3** | 8 | 200 | 100 | 100 | 1 drop | 2 drops | 15 |
| **F4** | 8 | 100 | 200 | 100 | 1 drop | 2 drops | 15 |
| **F5** | 8 | - | 400 | - | 1 drop | 2 drops | 15 |
| **F6** | 8 | 50 | 300 | 50 | 1 drop | 2 drops | 15 |
| **F7** | 8 | - | - | 400 | 1 drop | 2 drops | 15 |
| **F8** | 8 | 50 | 50 | 300 | 1 drop | 2 drops | 15 |
| **F9** | 8 | 100 | 100 | 200 | 1 drop | 2 drops | 15 |

**EXPERIMENTAL METHODS:**

**PREPARATION OF STANDARD CALIBRATION CURVE OF GLIMEPRIDE:**

Standard curve of Glimepride was prepared with a known concentration of drug in between 2-10 µg/ml using UV spectrophotometer (Shimadzu) at λmax 231 nm.

**EVALUATION OF THE PREPARED FORMULATION:**

**A) THICKNESS UNIFORMITY:**

The thickness of each patch was measured at 5 different positions of the patch and the average was calculated.

**B) DRUG CONTENT UNIFORMITY:**

A patch of size 1×1 $cm^2$ was cut and placed in a beaker.10 ml of 6.6 pH phosphate buffer solution was added. The absorbance of the solution was measured against the corresponding blank solution at λ max 231 nm.

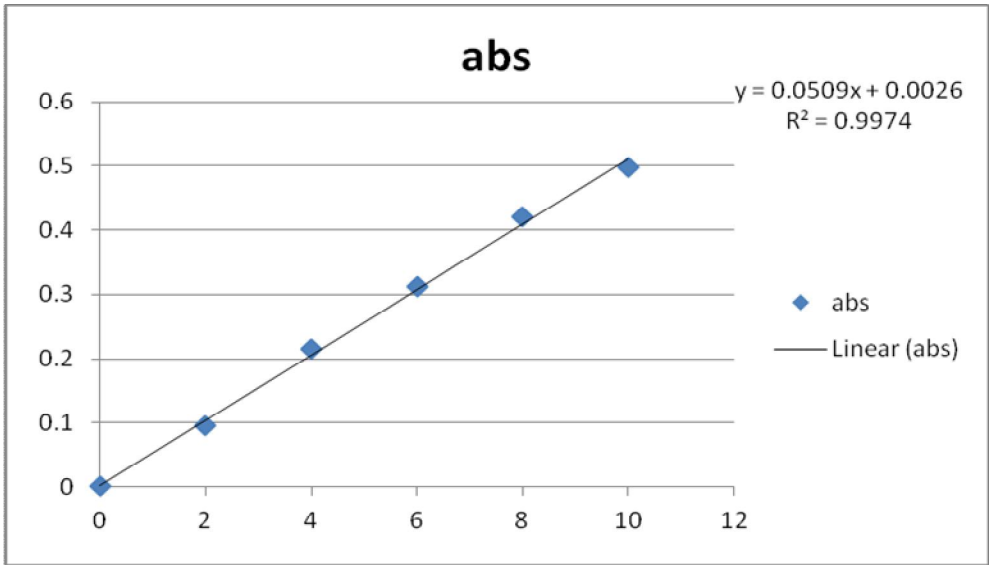


**Figure 1: Standard plot of Glimepride in 6.6 pH at 231 nm**

**C) WEIGHT UNIFORMITY:**

Patches sizes of 1x1 $cm^2$ were cut. The weights of 5 patches were taken and the weight variation was calculated.

**D) SWELLING STUDIES OF THE PATCHES:**

A drug-loaded patch of 1x1 $cm^2$ was weighed. It was kept in a petridish and 50 ml of phosphate buffer, pH 6.6 was added. After every 5 min it was weighed upto 30 min. The difference in the weighs was calculated.

$$\%S = \frac{X_t}{X_o} \times 100$$

where $X_t$ is the weight or area of the swollen patch after time t and $X_o$ is the original patch weight or area at zero.

**E) FOLDING ENDURANCE:**

Folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded upto 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance.

**F) IN-VITRO DIFFUSION STUDIES:**

Diffusion studies were carried out for the prepared patches by Franz diffusion cell with 6.6 pH phosphate buffer using dialysis membrane for a period of 24 hours. The donor chamber was exposed to air and receiver chamber had 6.6 pH Phosphate buffer with dialysis membrane in between. 1ml of solution from receiver chamber was withdrawn every 1 hour for 24 hours, and the aliquot of 1 ml was replaced. The withdrawn solution was analysed by UV at 231 nm.

**G) DETERMINATION OF RESIDENCE TIME:**

The in-vitro residence time was determined using a locally modified USP disintegration apparatus based on the disintegration apparatus applied by Nakamura *et.al*[16]. Disintegration medium was composed of 800 ml isotonic phosphate buffer pH 6.6 maintained at $37^0$C. A segment of rat buccal mucosa, 3 cm long, was glued to the surface of a glass slab, vertically attached to the apparatus. The mucoadhesive patch was brought hydrated into contact with the mucosal membrane. The glass slab was vertically fixed to the disintegration apparatus and allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the patch from the mucosal surface was recorded.

**RESULTS AND DISCUSSION:**

The main goal of the present investigation efforts was to

develop and evaluate new buccal patches using polymers like EC, HPMC, and CP 934 P in various combinations and proportions. Table no.2 gives information about various physicomechanical properties.

**Appearance**

The patches from all the batches were translucent and flexible without any sign of crack. The diameter of the patches was 7.6 cm and the area was of 45.34 $cm^2$

**Thickness**

All the patches have uniform thickness throughout. Average thickness is given in Table no.2. and ranged from 0.43 to 0.54 mm, the thinnest being of F3 and thickest of F9.

**Drug content uniformity**

The drug content (%) in all formulations varied between the range 96.04±0.11% to 98.94±0.05%. This indicates that the drug dispersed uniformly throughout the polymeric film.

**Weight variation**

The weight variation of these formulated buccal patches was in between 16 to 24 mg of 1 $cm^2$ patch area.

**Folding endurance**

Films did not show any cracks even after folding for more than 300 times.

**Table 2: Physiochemical characteristics of bucal patches**

| Formuation | Thickness(mm) | Drug content uniformity(%) | Weight variation(mg) | Folding endurance |
|---|---|---|---|---|
| F1 | 0.44 | 96.65±0.08 | 17 | <300 |
| F2 | 0.45 | 98.94±0.05 | 16 | <300 |
| F3 | 0.43 | 96.01±0.12 | 18 | <300 |
| F4 | 0.46 | 97.73±0.05 | 13 | <300 |
| F5 | 0.47 | 96.04±0.11 | 20 | <300 |
| F6 | 0.53 | 98.56±0.04 | 18 | <300 |
| F7 | 0.53 | 98.00±0.09 | 15 | <300 |
| F8 | 0.51 | 97.94±0.11 | 22 | <300 |
| F9 | 0.54 | 99.24±0.12 | 24 | <300 |

**Swelling index**

Swelling index was found to be highest in F5 containing 400 mg of CP 934 P. F1 containing 400 mg of HPMC showed swelling index of 148.9 followed by F4 (swelling index-145.63)containing HPMC:CP 934 P:EC in ratio 1:2:1 and F3 (swelling index-135)containing HPMC:CP 934 P:EC in the ratio 2:1:1. Carbopol was concluded to be the hydrophilic polymer with a more tendency to swell followed by

HPMC. Patches of EC being least hydrophilic showed less tendency to swell.(F7 showed 80.44 had 400 mg of EC and no HPMC and CP 934 P).

**Table 3: Swelling index upto 1 hour of different formulations**

| Formulation | % weight increase after 30 min | % area increase after 60 min |
|---|---|---|
| F1 | 148.9 | 110.5 |
| F2 | 120.54 | 84.9 |
| F3 | 135 | 110.5 |
| F4 | 145.63 | 120.4 |
| F5 | 160.5 | 129.88 |
| F6 | 115 | 90.8 |
| F7 | 80.44 | 60.9 |
| F8 | 99.4 | 88.7 |
| F9 | 110.78 | 70.6 |

**In-vitro diffusion studies**

F5 containg more amount of CP 934 P and showing highest swelling index could retard the release of the drug upto 24 hours showing 99% at the end of 24 hours. It was concluded to be the best formulation in terms of cumulative release.

It was followed by F1 showing second highest swelling index and could retard the release of the drug upto 24 hours showing 98% release after 24 hours.

It was followed by F4, F3, F2, F6 showing 96%, 95%, 94% and 94% release respectively after 24 hours.

F7 having only EC and no amount of hydrophilic polymers HPMC and CP 934 P had least swelling index and could retard the drug only upto 18 hours giving 97% release.

F8 and F9 could retard the drug only upto 20 hours, as they had less amount of hydrophilic swellable polymers HPMC and CP 934 P and more amount of EC.

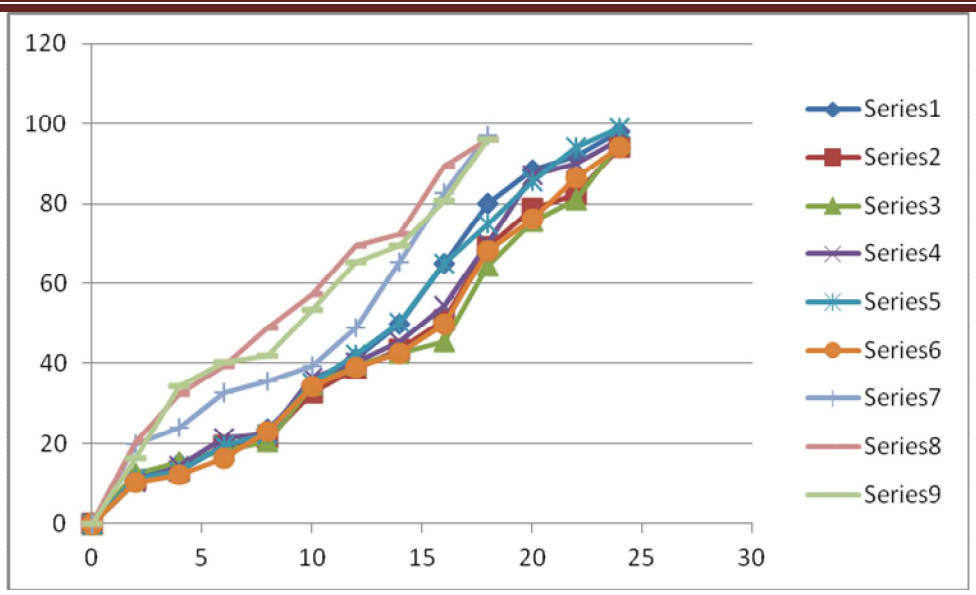


**Figure 2: % diffusion vs. time(mins) of different formulations**

**Determination of residence time**

F5 containing highest amount of CP 934 P showed highest residence time and was concluded to be the best formulation followed by F1 containing highest amount of HPMC.

This was followed by F4, F3 and F2 containing various combinations of these polymers HPMC: CP 934 P: EC.

F7, F8 and F9 showed lesser residence times as they contained fewer amounts of CP 934 P and HPMC and more amount of EC.

It was concluded that CP 934 P and HPMC have more mucoadhesive strengths than EC.

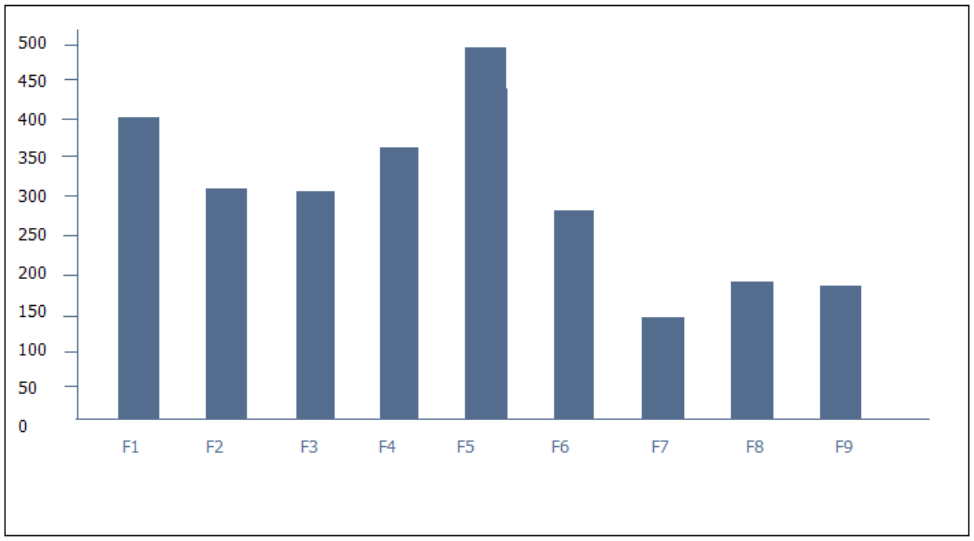


**Figure 3: In-vitro residence time of different formulations**

In order to predict and correlate the release behavior of Glimepride from different patches, it is necessary to fit into a suitable mathematical model. The in vitro release data from buccal patches were evaluated kinetically using various mathematical models like zero-order, first-order, Higuchi, and Koresmeyer–Peppas model equations.

*Zero-Order Kinetics.* $F=K_o t$, where F represents the fraction of drug released in time t, and $K_o$ is the zero-order release constant.

*First-Order Kinetics*. $\ln (1-F)=-K_1 t$, where F represents the fraction of drug released in time t, and $K_1$ is the first-order release constant.

*Higuchi Model.* $F=K_H t^{1/2}$, where F represents the fraction of drug released in time t, and $K_H$ is the Higuchi dissolution constant.

*Koresmeyer–Peppas Model.* $F=K_p t^n$, where F represents the fraction of drug released in time t, $K_p$ is the Koresmeyer–Peppas release rate constant, and n is the diffusion exponent.

The results of curve fitting into these above-mentioned mathematical models indicates the drug release behaviour from these formulated buccal patches.(Table 4).

When the release rate of optimized formulation F5 and ITS respective correlation coefficients were compared, it was found to follow zero order kinetics.( $R^2 = 0.9778$)

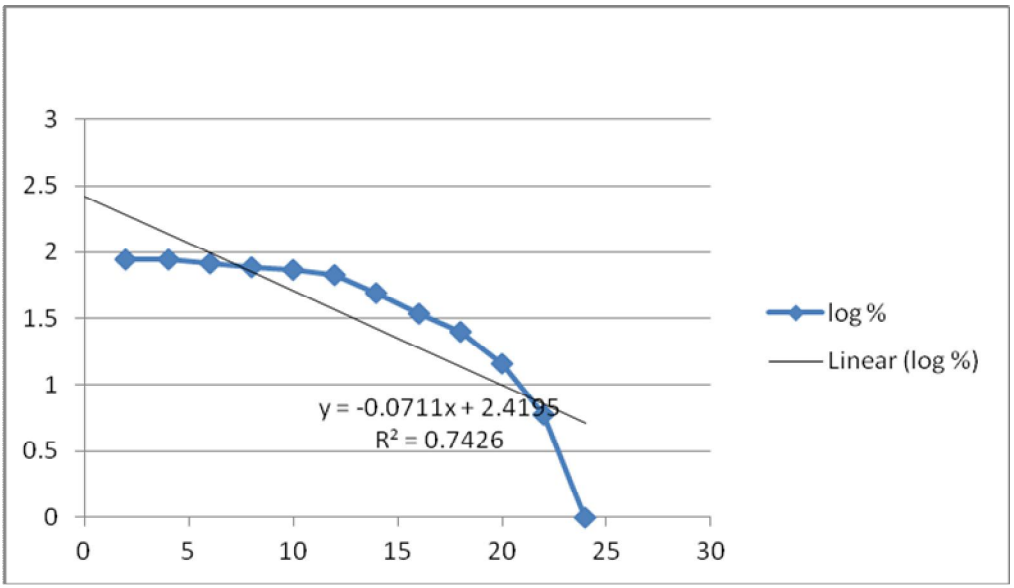


**Figure 4: First order : Time(hrs) vs. Log %Remanining to be diffused. $R^2 = 0.7426$**

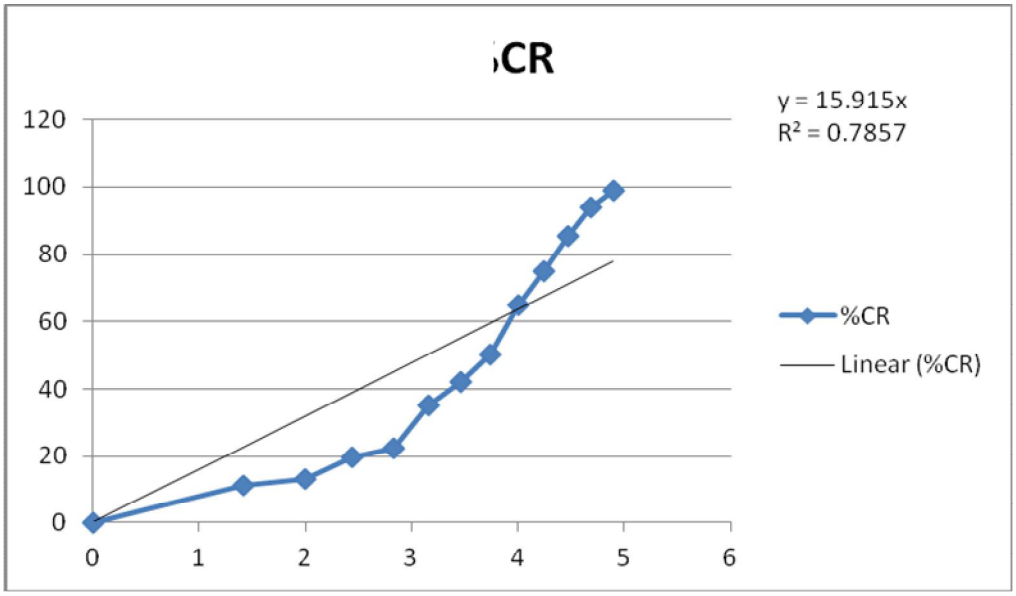


**Figure 5: Higuchi model: Square root of time in hours vs. % diffusion. $R^2$=0.7857**

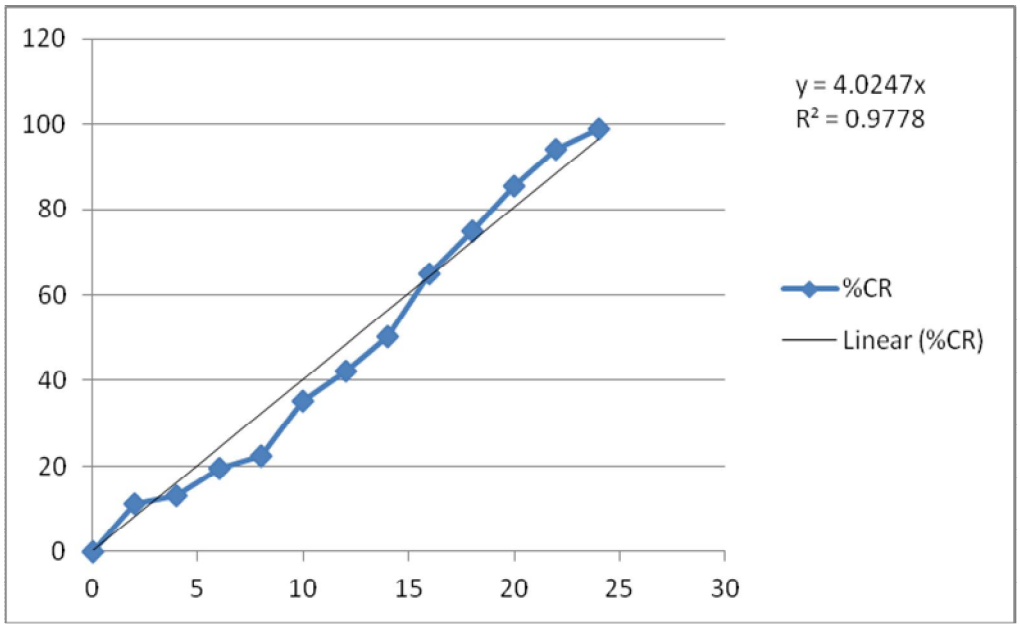


**Figure 6: Zero order: Time in hrs vs. %diffusion. $R^2$ = 0.9778**

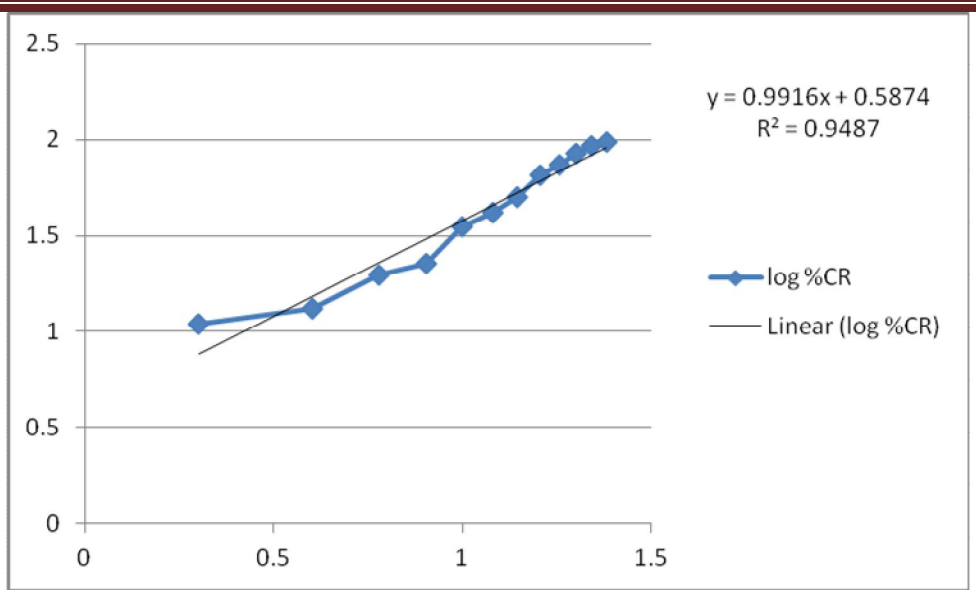


**Figure 7: Kores-meyer pepaas: Log time(hrs) vs. Log% diffused. $R^2$= 0.9487**

**CONCLUSION:**

Buccal patches of Glimepride using polymers like EC, HPMC, and CP 934 P in various proportions showed satisfactory physicomechanical characteristics. The proportional amounts of various polymers in various formulations have influence on drug release from these formulated buccal patches. Patches containing more amount of CP 934 P and HPMC showed better mucoadhesive strength and sustained the release of the drug for 24 hours. Patches containing more amount of EC in comparison to HPMC and CP 934 P showed lesser swelling index and could retard the release of the drug upto 18 and 20 hours only. They also showed lesser residence time as EC has lesser mucoadhesive strength.

Mucoadhesive strength: CP 934 P > HPMC > EC

Sustaining the release: CP 934 P> HPMC >EC

Swelling index: CP 934 P> HPMC> EC

The optimized batch F5 of Glimepride buccal mucoadhesive patch gave a reasonable in vitro residence time(500 mins), which is important for prolonging the adhesion of the patch with the buccal mucosa, thus improving the overall therapy of diabetes.From the present investigation, it can be concluded that such buccal patches of Glimepride may provide sustained buccal delivery for prolonged periods in the management of diabetes, which can be a good way to bypass extensive hepatic first-pass metabolism.

**REFERENCES**


1. Hoogstrate AJ, Verhoef JC, Tuk B et al. In vitro buccal delivery of fluorescein isothiocyanate-dextran 4400 with glycodeoxycholate as an absorption enhancer in pigs. J Pharm Sci. 1996; 85:457–60.
2. Patel VM, Prajapati BG, Patel MM. Design and characterization of chitosan-containing mucoadhesive buccal patches of propranolol hydrochloride. Acta Pharm. 2007; 57:61–72.
3. Vashmi Vishnu Y, Chandrasekhar K, Ramesh G, Madhusudan Rao Y. Development of mucoadhesive patches for buccal administration of carvedilol. Curr Drug Deliv. 2007; 4:2739.
4. Khairnar A, Jain P, Baviskar D, Jain D. Development of mucoadhesive buccal patch containing aceclofenac: in-vitro evaluation. Int J Pharm Sci. 2009; 1(1):91–5.
5. Hao J, Heng PWS. Buccal delivery systems. Drug Dev Ind Pharm. 2003;29 (8):821–32.
6. Smart J.D, The basics and underlying mechanisms of mucoadhesion, Adv. Drug
7. Deliv. Rev. 2005; 57:1556-1568.
8. Ahuja A et al. Mucoadhesive drug delivery systems, Drug Dev. Ind. Pharm., 199723;(5) : 489-515.
9. Jasti B, Li X, Cleary G, Recent advances in mucoadhesive drug delivery system, Drug
10. Deliv. Polymers, Business Briefing: Pharmatech, 2003, 194-196.
11. Johnston T, Miller S, Chittchang M, The use of mucoadhesive polymers in buccal drug delivery, Adv. Drug Deliv. Rev., 2005;57:1666-1691.
12. Semalty A, Mucoadhesive polymers: a review, Available at: http://www.pharmainfo.net/reviews/mucoadh esive-polymers-review [updated on 2006 Dec].
13. Patel V et al. Effect of hydrophilic polymers on buccoadhesive eudragit patches of propranolol hydrochloride using factorial design, AAPS PharmSciTech. 20078; (2): E1-E8.
14. Shojaei A. Buccal mucosa as a route for systemic drug delivery: a review. J. Pharm. Pharmaceut. Sci. 1998;1 (1):15-30.
15. Shidhaye S.S et al. Mucoadhesive bilayered patches for administration of sumatriptan, AAPS PharmSciTech. 2009; 9(3):909-916.
16. Nakamura F, Ohta R, Machida Y, Nagai T. In-vitro and in-vivo nasal mucoadhesion of some water-soluble polymers. Int J Pharm 1996;134:173-81
17. Sultana Y, Aqil M and Ali A. Ocular inserts for controlled delivery of pefloxacin mesylate: Preparation and evaluation. Acta Pharm. 2005;55:305-314