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FORMULATION AND EVALUTION ORAL BUCCAL PATCH

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ABSTRACT

Buccal route offer attractive route of administration for systemic drug delivery. Mucoadhesive Buccal Patch of Losartan potassium was prepared by using carbopol(grade 934,940), Sodium CMC. Losartan potassium (angiotensin II receptor blockers) which works by relaxing blood vessels. The polymeric film was composed of different proportions of sodium carboxymethylcellulose (Na CMC), Carbopol and prepared by solvent casting method. Glycerol was used as plasticizer. Carbopol 934 provide taste masking functionality in case of bitter taste. six formulation were prepared with varying concentration of carbopol and carboxymethylcellulose and evaluated for various parameter like weight variation, patch thickness, folding endurance, surface pH, drug content uniformity. The surface PH was found to be in range of saliva PH. Increase in concentration of Carbopol was found to be increase in the mucoadhesive strength. Based on the evaluation of these result it was concluded that the buccal patches of Na CMC and CP-934(800:400) showed moderate drug release for 6 hrs. Data of in vitro release from patches were fit to different equations and kinetic model to explain release mechanism.

KEYWORDS: Buccal patch, Mucoadhesiv, losartan potassium.

INTRODUCTION[1-8]

The various transmucosal routes, buccal route is an alternative oral route of administration owing buccal mucosa has excellent convenience and region of smooth muscles and relatively immobile mucosa, hence suitable for administration of mucoadhesive dosage form. The oral cavity has rich blood supply that drains directly into the systemic circulation and bypasses drugs from hepatic first pass metabolism by increasing the bioavailability.[1,2] These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery.[3] Mucoadhesion is the phenomenon between two materials which are held together for prolong period of time by interfacial force. It is generally referred as mucoadhesion when interaction occurs between.

polymer and epithelial surface.[4,5] 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 do. In addition, 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.[6] Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading high bioavailability.[7] Other advantages such as 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.[8] Therapeutically losartan potassium is advised in hypertension. It is slightly soluble in water. It is well absorbed from GIT but show only 33% bioavalibility due to extensive hepatic metabolism in liver by enzyme in liver via cytochrome p450 isoenzyme CYP2C9(plays major role) & CYP3A4. The drug has a short elimination half life of 1.5– 2 hours and is eliminated rapidly, repeated daily administration are required to maintain effective plasma concentration.

Hence In the present work, the main aim was to develop unidirectional buccal patches of Losartan potassium to improve the bioavailability by avoiding hepatic first-pass metabolism and there by improve the patient compliance and also to reduce the frequency of administration.

The present work deals with the formulation and characterization of buccal mucoadhesive patch of losartan potassium using mucoadhesive polymer like Carbopol-934 and sodium carboxymethyl cellulose.

ADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM[9,10]

Drug is easily administered and extinction of therapy in emergency can be facilitated.

- Drug release for prolonged period of time.
- Relatively large surface area
- Low metabolic activity
- Prolonged retention
- Intestinal alternative
- Zero-order controlled release
- Ease of use and Low variability
- In unconscious and trauma patient's drug can be administered.
- Drugs bypass first pass metabolism so increases bioavailability.
- Some drugs that are unstable in acidic environment of stomach can be administered by buccal delivery.
- Drug absorption by the passive diffusion.
- Flexibility in physical state, shape, size and surface.

LIMITATIONS OF BUCCAL DRUG DELIVERY SYSTEM[11]

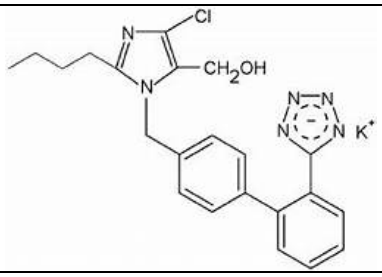
- Drugs which are unstable at buccal pH cannot be administered.
- Drugs which have a bitter taste or unpleasant taste or an obnoxious odor or irritate the mucosa cannot be administered by this route.
- Drug required with small dose can only be administered.
- Those drugs which are absorbed by passive diffusion can only be administered by this route.
- Eating and drinking may be restricted.
- Possibility of the patient to swallow the tablet.

LITERATURE REVIEW

1. **Vilasrao Kadam et.al (2008)[12]:** Developed and optimized mucoadhesive bilayered buccal patches of sumatriptan succinate using chitosan as the base. Gelatin and PVP K30 were added to enhance film properties. Using a 3^2 factorial design, effects of chitosan and PVP levels on swelling, mucoadhesive strength, and drug release were evaluated. Patches showed good physical and mechanical properties. A formulation with 3% dimethyl sulfoxide improved drug permeation without mucosal damage, suggesting buccal delivery as a viable alternative for sumatriptan succinate administration.
2. **Keshav. P. Giradkar et.al (2009)[13]:** Developed buccal patch of Tizanidine Hydrochloride was successfully developed using sodium carboxymethylcellulose and Carbopol 934. The formulation containing Na CMC and CP 934 in a 60:40 ratio demonstrated a moderate drug release profile over 8 hours, along with acceptable mucoadhesive strength and in vitro residence time. The surface pH of the patches was compatible with the buccal environment, and FTIR analysis confirmed the absence of drug-polymer interactions. These results indicate the potential of this buccal patch formulation as a viable alternative for sustained delivery of Tizanidine Hydrochloride, potentially improving patient compliance and therapeutic efficacy.
3. **Chandrakant. R. Kokare et.al (2013)[14]:** Reported the bilayered mucoadhesive buccal patch of zolmitriptan using xanthan gum (XG) as the mucoadhesive polymer and hydroxypropyl methylcellulose E-15 as the film-former. Polyvinyl alcohol (PVA) was added to enhance tensile strength. A 3^2 factorial design was used to analyze the effects of XG and PVA concentrations on drug release, mucoadhesive strength, and swelling. The optimized formulation showed rapid initial release (43.15% in 15 min) and sustained release over 5 hours. Additionally, 4% dimethyl sulfoxide improved drug permeability without causing mucosal damage. The findings suggest XG is effective as a mucoadhesive polymer for zolmitriptan patches.
4. **Krishnarajan D et.al(2016)[15]:** explored the development and evaluation of mucoadhesive buccal patches for the delivery of aceclofenac, a non-steroidal anti-inflammatory drug. A series of patches were fabricated using a solvent casting method, employing various proportions and combinations of hydrophilic polymers, including hydroxypropyl methylcellulose (HPMC), Carbopol 934-P, polyvinyl alcohol (PVA), polyvinyl pyrrolidone K-30 (PVP K-30), and Eudragit L-100.The resulting patches exhibited desirable physical attributes, appearing smooth and elegant with consistent thickness and uniform drug content. Notably, all formulations demonstrated a high folding endurance of 100 folds, indicating good mechanical strength and flexibility.
5. **Hossein Jafari et.al (2017)[16]:** Focused on developing Myrtus communis (L. Myrtle) oral patches for recurrent aphthous stomatitis (RAS) using hydrophilic polymers like PVP, gelatin, methylcellulose, and pectin via Box-Behnken design. Properties such as tensile strength, swelling, mucoadhesion, and drug release were analyzed. Results showed polyvinyl pyrrolidone enhanced drug release and reduced swelling, while pectin improved tensile strength. The optimal patch

formulation contained specific amounts of each polymer and 20 mg of myrtle extract, providing sustained release with suitable mechanical and mucoadhesive properties.

1. DRUG PROFILE: Losartan Potassium

Structural Formula	
Description	Losartan Potassium is the potassium salt of losartan, a non-peptide angiotensin II receptor antagonist with antihypertensive activity. Losartan selectively and competitively binds to the angiotensin II receptor (type AT1) and blocks the binding of angiotensin II to the receptor, thus promoting vasodilatation and counteracting the effects of aldosterone. Converted from angiotensin I by angiotensin-converting enzyme (ACE), angiotensin II stimulates the adrenal cortex to synthesize and secrete aldosterone, decreasing sodium excretion and increasing potassium excretion, and acts as a vasoconstrictor in vascular smooth muscle.
Molecular Formula	C22H22ClKN6O
Molecular weight	461.0 g/mol
IUPAC Name	2-butyl-5-chloro-3-[[4-[2-(1,2,3-triaza-4-azanidacyclopenta-2,5-dien-5-yl)phenyl]phenyl]methyl]imidazol-4-yl]methanol
Appearance	White to off white
Solubility	Slightly soluble in water and more soluble in organic solvent
Melting point	$263\text{-}265^0$
Indication	Treatment of hypertension, heart failure, and to protect kidneys from damage due to diabetes.
Dose	25 mg to 100 mg once daily (adjusted based on patient response)
BCS Classification	ClassII(low solubility and high permeability)

POLYMER PROFILE

Carbopol[17]: It is a high molecular weight cross linked polymer of acrylic acid, while sodium CMC(carboxymethyl cellulose in a water soluble cellulose derivative.

Carbopol is often used in formulations for thickening and gelation while sodium CMC acts as a thickener, binder and stabilizer.

Application: Carbopol is used in various industries, including pharmaceutical, personal care and food for its ability to form gels and thicken liquids.

Sodium CMC[18]: (carboxymethyl cellulose): sodium CMC is a water cellulose derivative with carboxymethyl group attached to the cellulose backbone.

It has god suspension and thixotropic properties, making it useful as a thickener, binder, and stabilizer in various formulations.

Application: Sodium CMC is widely used in food, pharmaceutical, and personal care products.

PROCEDURE

Weight amount of Carbopol 934,940 was added to 1\3 portion of the required double distilled water.

↓

Kept undisturbed until a clear solution was formed.

↓

Stirred for 1 hour

↓

Drug was dissolved in a minimum volume of DDW and added to NaCMC contained in a dry beaker

↓

The remaining 2\3 portion of DDW was added to the above mixture with stirring to form homogenous dispersion

↓

The carbopol 934,940 solution and required volume of glycerol were added to the dispersion of NaCMC and stirred for 3 hrs

The gel then obtained was kept overnight undisturbed under refrigerator

↓

To ensure bubble free gel which was finally poured in borosillication glass \ petridish

↓

Allowed to settle and dried under convective flow of hot air at temperature 40-45c^0 for 48-72hrs till flexible film was formed

↓

After drying the films were cut into smaller piece of 1.1*1.1 sizes wrapped in aluminium foil and stored in a glass container

↓

Preconditioned at room temperature and relative humidity 60%

EVALUATION

1. **Surface pH[19]:** 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 6.5 ± 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.

Fig: 1. Electronic pH meter.

2. **Content Uniformity[19]**

Drug content uniformity was determined by dissolving the patch by homogenization in 100 ml of an isotonic phosphate buffer (pH 6.6) for 8 h under occasional shaking. The 5 ml solution was taken and diluted with isotonic phosphate buffer pH 6.6 up to 10ml, and the resulting solution was filtered through a 0.45 µm Whatman filter paper. The drug content was then determined after proper dilution at 207nm using a UV-spectrophotometer.

3. **Swelling Study[20]**

Weight in increase due to the swelling was measured. Patch of 92.4mg was weighed on a preweighed cover slip and patch initial weight was recorded (W0). It was kept in a petridish of diameter 4cm and 5ml of phosphate buffer, pH 6.6 was added. At time interval of 0.5, 1, 1.5,2,3,4,5,6,7,8 hr the cover slip was removed and excess of water was carefully removed and swollen patch were weighed (Wt). The difference in the weights gives the weight increase due to absorption of water and swelling of patch. The experiment was repeated three times. The swelling state of the polymer was reported to be crucial for its bioadhesive behavior. Adhesion occurs shortly after the beginning of swelling but the bond formed between mucosal layer and polymer is not very strong. The adhesion will increase with the degree of hydration until a point where over hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer/tissue interface.

4. **Folding Endurance[21]**

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. This test was done on three patches.

5. **In vitro diffusion study**

In vitro diffusion study of buccal patch were carried out in modified diffusion cell using Dialysis membrane (dry, unwashed, flat width:28.46mm, inflated diameter:17.5mm, length:1mm).

The membrane was soaked in phosphate buffer of pH 6.8 for 8 hrs. The patch was spread evenly on the membrane and clamped at end of hollow dialysis cell. 20ml of phosphate buffer was placed in receptor compartment. The donor compartment was kept in contact with receptor compartment. The assembly was placed on magnetic stirrer and stirred continuously using magnetic bead and temperature 37^0 C.1ml sample was withdrawn at suitable time intervals (1hr) and replacing with equal amount of fresh dissolution media. The sample were analysed by UV spectroscopy at 207nm and percentage drug release was calculated.

Fig. 2: Franz Diffusion Assembly.

6. Drug Release Study

To characterize the release mechanism of Losartan Potassium from mucoadhesive buccal patch (optimized batch F2), was subjected to various kinetic model fitting. The results indicate that release mechanism for batch F2.

Table 1: Composition of mucoadhesive buccal patch of Losartan Potassium.

Batch	Amount of losartan potassium (mg)	NaCMC(mg)	Carbopol (934/940)	Glycerol (% v/v of gel)	Water(ml)
F1	92.4	960	240	1.2	45
F2	92.4	800	400	1.2	45
F3	92.4	600	600	1.2	45
F4	92.4	600	600	1.2	45
F5	92.4	960	240	1.2	45
F6	92.4	800	400	1.2	45

RESULT AND DISSCUSION

1. Identification of drug

Determination of max by UV Visible Spectrophotometer

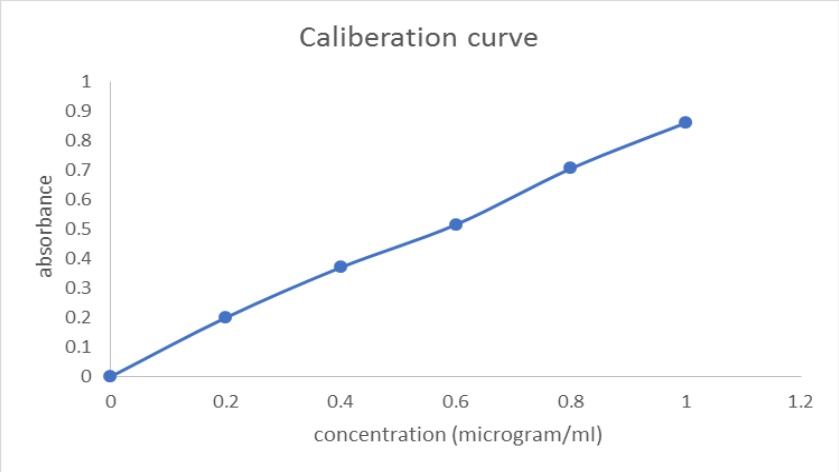
The absorption maxima of Losartan Potassium were determined by scanning the sample drug solution concentration in double beam UV spectrophotometer for range of 207nm and standard specification gives in Indian Pharmacopoeia or literature.

Calibration curve of Losartan Potassium buffer pH 6.8

The calibration curve for Losartan Potassium in pH 6.8 in concentration range of 0.2 to 1.0 ug/ml was found to pass through the origin and was a straight line. The results are shown in below table.

Volume (ml)	Readings
0.2	0.200
0.4	0.370
0.6	0.515
0.8	0.705
1.0	0.860

This table no 2 shows the standard calibration readings for Losartan Potassium.



Graph for Caliberation of Losartan Potassium.

2. CHARACTERIZATION OF BUCCAL PATCHES

a. Ph of the Formulation

It is known that normal physiological PH of oral mucosa is 6.8 – 7.4

Table no 3.

Batches	pH
F1	7.01
F2	6.8
F3	6.9
F4	7.02
F5	7.01
F6	6.9

b. Drug Content Determination

The drug content of buccal patches was determined by UV Spectrophotometer 207 nm. The drug concentration range from 75-100%.

Formulation batch of F2 shows highest drug content.

Drug Content Uniformity
Table no 4.

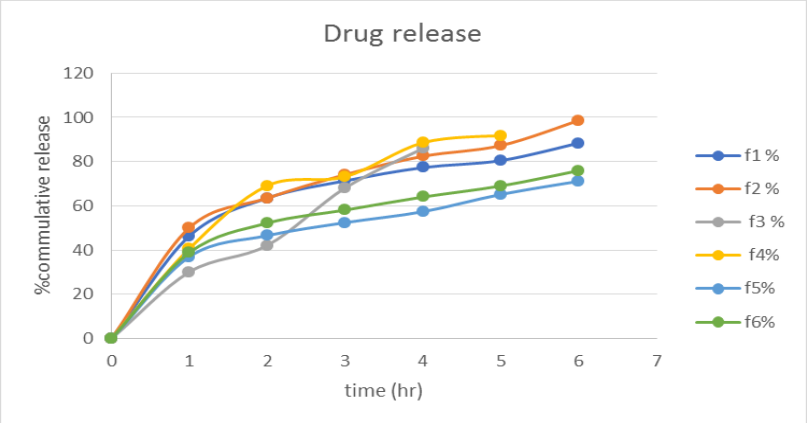
Batch	Absorbance	Percentage
F1	0.133	80%
F2	0.254	99%
F3	0.135	82%
F4	0.115	75%
F5	0.147	85%
F6	0.180	90%

c. Drug Release Kinetics

The buccal patch was evaluated to explain the release the kinetic. Calculated release drug release were in the following table no 5. The optimized batch from the Content Uniformity was F2.

Table no. 5.

Time	F1	F2	F3	F4	F5	F6
1hour	46.41	50.16	30.14	40.78	37.03	38.91
2hour	63.52	63.54	42.16	69.12	46.59	52.23
3hour	71.35	74.18	68.15	73.22	52.45	58.12
4hour	77.33	82.44	86	88.59	57.40	64.04
5hour	80.52	87.30		91.84	65.19	69.04
6hour	88.42	98.66			71.14	75.95



Graph for % Drug Release.

3. Physicochemical Parameter

a. Apperance

The patches from all the batches were translucent and flexible without any sign of crack.

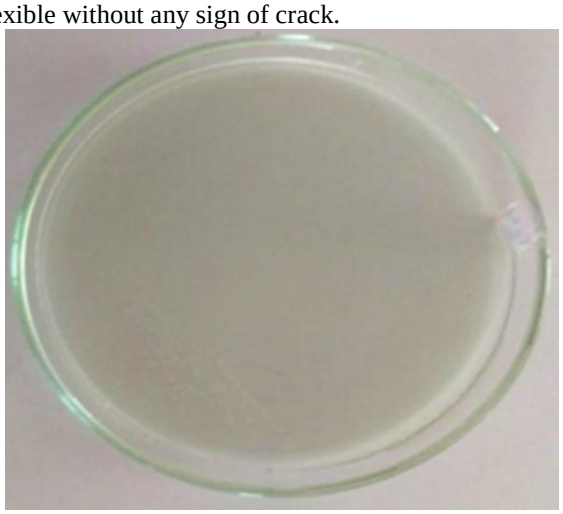


Fig: 3. Apperance.

b. Swlleing index(Optimized batch)

Table no. 6.

Time	Weight after time interval(g)
30min	0.05
30min	0.15
1hour	0.17
1hour	017
1hour	0.18
1hour	0.18
1hour	0.19
1hour	0.19
1hour	0.22

Fig. 4: Performed swelling index.

c. Thickness and Folding Endurance

Table no 7.

Batch	Thickness(mm)	Folding Endurance
F1	0.62	>300
F2	0.72	>300
F3	0.68	>300
F4	0.69	>300
F5	0.66	>300
F6	0.64	>300

SUMMARY AND CONCLUSION

The optimized batch CN-2, Losartan Potassium buccal mucoadhesive patch gave a reasonable in vitro residence time (245±12min), which is important for prolonging the adhesion of the patch with the buccal mucosa, thus improving the overall therapy of muscle spasticity. Increase in CP 934concentration resulted in decreasing the swelling index and surface pH. The mucoadhesive strength and in vitro residence time is slightly increased beyond 30% concentration of Carbopol 934.The prepared buccal mucoadhesive patch, batch CN-2 provided a controlled and prolonged invitro release of losartan(for6hr). This would be important for better patient compliance because of the decrease in the frequency of administration. Additionally, it may avoid the tolerance formation of losartan.

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