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FORMULATION AND EVALUATION OF BUCCAL FILM OF AN ANTIHYPERTENSIVE DRUG

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Abstract

The aim of the study was to formulate and evaluate Losartan potassium buccal films, an angiotensin receptor blocker and is used to treat hypertension. Losartan potassium is having less bioavailability (33%), so the buccal films are expected to increase the bioavailability by avoiding hepatic metabolism. Ten formulations of buccal films were prepared by solvent casting method using HPMC K15 M as the main film-forming polymer in various proportions with various co-polymers such as Eudragit RL. 100, Carbopol 940, Ethyl cellulose. Physicochemical characteristics,*in vitro* buccal permeation, *in vitro* release study and residence time were evaluated. *In vitro* studies revealed that the release rate of Losartan potassium was higher for films containing HPMC K15 M and Eudragit RL100 in 3:1 ratio. The result of stability study indicated that no significant changes have occurredduring the period of study.

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Introduction

Buccal drug delivery is an important route of drug administration and it is one of the novel drug delivery systems. The buccal mucosa is relatively permeable and provides affluent blood supply and permits a prolonged retention of a dosage form, especially with the use of mucoadhesive polymers without much interference in processes such as mastication unlike the sublingual route.Administration of the drug via the mucosal layer is a novel technique that delivers treatment more effective and safe, for both typical and systemic diseases [1],

Buccal drug delivery is also a safer mode of drug delivery and can be able to remove in case of toxicity and adverse effect. Buccal mucosa has an excellent accessibility, which leads to direct access to systemic circulation through the internal jugular vein bypasses the drugs from hepatic first pass metabolism. The administration of drugs through buccal route provides a direct entry of drug molecule into the systemic circulation via avoiding the first pass metabolism. Buccal film is defined as the dosage form which dissolves into the buccal mucosa or mouth and releases the medicament to provide local or systemic drug delivery and employs a water dissolving polymer (hydrocolloid bio adhesive polymer). These polymers allow the dosage form to adhere, hydrate and dissolve into the mouth. Thin film strips are typically designedfor oral administration, with the user placing the strip on or under the tongue. As the strip dissolves, the drug can enter the blood stream enterically, or sublingually [2]

Material and Methods

Preformulation studies were conducted by evaluating physicochemical parameters. Tests for the identification of pure drugs and Compatibility studies of drug with excipients using FTIR spectroscopy were also carried out.

Development of Buccal Film of Losartanpotassium

Preparation of Buccal Films of Losartan Potassium

The buccal films of Losartan potassium were prepared by solvent casting method with HPMC alone and in combination with different copolymers namely Eudragit RL 100, Carbopol 940 and Ethyl cellulose with propylene glycol as plasticizer. Small films of 2cm diameter containing 25mg of drug were prepared. First the film forming polymer was dissolved in solvent ethanol. To this required quantity of drug was added. Finally, 1ml of propylene glycol was added as plasticizer and was mixed for about 30 min by using a magnetic stirrer. This solution was transferred into petridish slowly drop by drop in

order to get uniform spread of the solution and is kept for 24hrs at room temperature for drying. After drying these films were removed from the petridish and cut into definite shapes and are packed in butter paper and wrapped with aluminium foil and stored in desiccator until used for further study.

Table No.1: Formula Used For Development Of losartan Potassium Buccal Films

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Losartan potassium(mg)	50.5	50.5.5	50.5.5	50.5.5	50.5.5	50.5.5	50.5.5	50.5.5	50.5.5	50.5.5
HPMC K15(mg)	400	300	200	100	300	200	100	300	200	100
Eudragit RL100(mg)	-	100	100	100	-	-	-	-	-	-
Carbopol 940 (mg)	-	-	-	-	100	100	100	-	-	-
Ethyl cellulose (mg)	-	-	-	-	-	-	-	100	100	100
Propylene glycol (ml)	1	1	1	1	1	1	1	1	1	1
Ethanol (ml)	20	20	20	20	20	20	20	20	20	20
Citric acid (mg)	5	5	5	5	5	5	5	5	5	5
Peppermint oil(ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Characterization of the films

Formulated films were subjected to the preliminary evaluation tests.

Physicochemical characteristics

Physical appearance:

All the films were visually inspected for color, clarity, flexibility, and smoothness.

Film thickness

The thickness of film is measured by micrometer screw gauge. The thickness was evaluated at five different locations (four corners and one at center) and it essential to ascertain uniformity in the thickness of film since it is directly related to accuracy of dose distribution in the film.

Weight uniformity

For the mass uniformity, six films from each formulation were taken and weighed individually on electronic balance. The average weight was calculated.

Folding endurance

Folding endurance gives the brittleness of a film. It is measured by manually repeated folding of film at some place till it breaks. The number of times the film is folded without breaking is the folding endurance value.

Surface pH

Surface pH of the film can be determined by allowing three films of each formulation to swell for two hours on an agar plate surface. A pH paper was placed on the surface of the swollen film and a mean was calculated.

Drug content uniformity

Three films of each formulation were taken in separate 100ml volumetric flask; 100ml of pH 6.8 phosphate buffer was added and stirred continuously for 24 h. The solutions were filtered, diluted suitably and analyzed using UV spectrophotometer.

Swelling index

Three films of each formulation were weighed individually and allowed the sample to swell by placing it on the surface of an agar plate kept in an incubator at 37^{0}C .An increase in the weight of the film was noted at 1h intervals up to 5h .The percentage swelling, %S was calculated using the following equation

Percentage swelling (%S) = $[(X_t-X_0)/X_0] \times 100$

Xt=the weight of the swollen film after time t,

Xo =the initial film weight at zero time.

In-vitro release study

Dissolution studies were carried out in a USP dissolution apparatus using 900ml of dissolution medium at 37± 0.5°C, and a rotation speed of 50 rpm was used. An aliquot of sample was periodically withdrawn and replaced with fresh medium. The samples were filtered through whatman filter paper and analyzed spectrophotometrically.

Drug release kinetic studies

The drug release kinetic studies were done by various mathematical models. The model that gives high 'r' value is considered as the best fit of the release data. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r2) was determined.

Kinetic Data Analysis: Drug release models

Mathematical models:

Zero order release kinetics

Zero order release kinetics refers to the process of constant drug release from a delivery device. In its simplest form, zero order release can be represented as

$Q = Qo+Kot$

Where Q is the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves), Qo is the initial amount of drug in solution (it is usually zero), and Ko is the zero order release constant.

The plot made: cumulative% drug release vs. time (zero order kinetic model).

First order release kinetics

The release the drug is proportional to the amount of drug remaining in its interior, in such a way that the amounts of drug released by unit time diminish.

$\text{Log } C = \text{Log } C_o - k/2.303$

Where, CO is the initial concentration of drug and K is first order constant.

The plot made: log cumulative of % drug remaining vs. time (first order model).

Higuchi Model

Higuchi was the first to describe the release of a drug from an insoluble matrix as the square root of a time-dependent process based on Fickian diffusion.

Qt-kH(t) 0.5

Where, Qt is the amount of drug released in time t, and kH is the release rate constant for the Higuchi model. The linearity of the plots can be checked by carrying out linear regression analysis and determination of regression coefficient of the plot.

The plot made: cumulative % drug release vs. square root of time (Higuchi model).

Determination of Diffusion exponent

Korsmeyer et al (1983) derived a simple relationship which described drug release from a polymeric system, to find out the mechanism of drug release.

Mt/M∞= Ktn

Where Mt/M∞, is fraction of drug released at time t, k is the rate constant and n is the release exponent.

The plot made: log cumulative % drug release vs. log time

Values of the exponent n are found that would indicate a diffusion controlled drug release mechanism

Table No.2: Interpretation of Diffusional Release Mechanisms from Formulations

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.5<n<0.89	Non – fickian transport
0.89	Case II transport
Higher than 0.89	Super case II transport

Table No.3: Mathematical Models Used To Describe Drug Release Kinetics from Various Matrices

Kinetic model	Mathematical relation	Systems that follow the model
Zero order	Release independent of drug concentration	Osmoticsystems,transdermal systems
First order	Release proportional to the amount of drug remaining	Water soluble drugs in porous matrix
Higuchi	Release proportional to square root of time	Diffusion matrix formulations

In-vitro residence time

The *in vitro* residence time was determined using IP disintegration apparatus maintained at a temperature of 37±2° C using 900ml of the disintegration medium. The portion of porcine mucosa, each of 2cm length, were glued to the surface of a glass slab, which is then vertically attached to the apparatus and allowed to move up and down. The films of each formulation were hydrated on one surface and upon contact with the mucosal membrane, the film was entirely dipped in the buffer solution. The time required for complete detachment of the film from the mucosal surface was recorded.

In-vitro buccal permeation study

Porcine buccal mucosa obtained from a local slaughter house has been used within 2h of slaughter. The film was attached with the mucosa and the compartments were clamped together. The donor compartment was filled with 1 ml of phosphate buffer (pH 6.8) and the receptor compartment of 20 ml capacity was filled with phosphate buffer (pH 7.4). One ml of the sample was withdrawn at 1-hour interval for a period of 6 hours and analyzed. The experiments were performed in triplicate.

Stability studies

Films were stored at different temperatures like 27±2° C, 5-8± 2°C, 40±2°C for a period of30 days, and the drug content was estimated at anintervals of 10 days. [30]

Results and Discussion

Preformulation Studies

Table no.4 organoleptic properties

Character	Property of the drug
Color	White to off-white
Odor	Odorless
Taste	Tasteless
Texture	Crystalline powder

Solubility study

Solubility studies shown that Losartan potassium was freely soluble in water and methanol, soluble in isopropyl alcohol , slightly soluble in acetonitrile and methyl ethyl ketone ,insoluble in chloroform .

Identification of pure drug

Melting point determination

It was found to be 183-185^{0}C in accordance with the reference standard of 184^{o}C

FTIR spectra of the drug

The Fourier transform infrared spectroscopy studies were carried out for pure drug (Losartan potassium). Drug exhibited characteristic peaks at 1259, 1460, 2669, 2856, and 2925 cm-1. It was found in accordance with the reference standard (IP 2007).

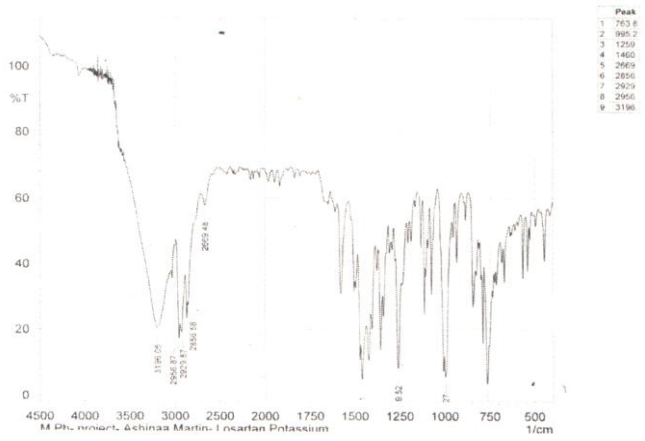

Fig.no.1: FTIR Spectrum of Losartan Potassium

Determination of λmax

The λmax of the drug was found to be 218 nm .The wavelength of the maximum absorption was noted and UV spectrum was recorded.

Compatibility studies of drug with excipients using FTIR spectroscopy.

The Fourier transform infrared spectroscopy studies were carried out for Losartan potassium- polymer physical mixtures. There were no changes in themajor peaks of Losartan potassium in the presence of various polymers .This revealed thatthe drug and the polymers are compatible with each other.

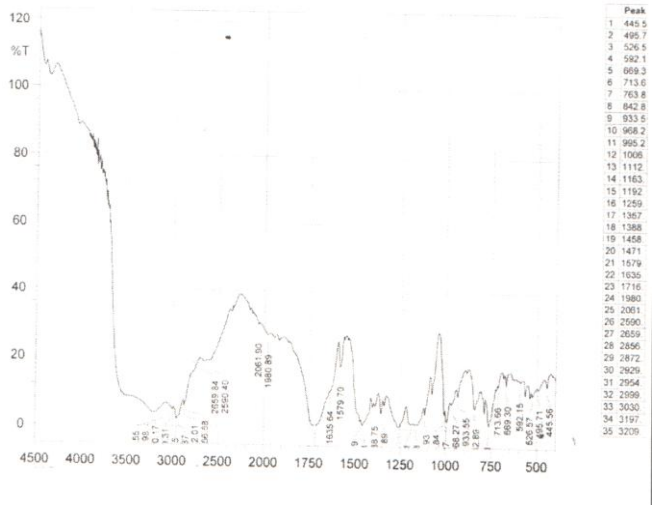

Fig.no.2: FTIR Spectrum of losartan potassium +HPMC K15 M

Development of Buccal films of Losartan Potassium

Preparation of buccal films of Losartan Potassium

Ten formulations of buccal films were prepared using different polymers in different proportions as per table no.1.Formulation F4 showed extensive tackiness and hence was excluded from further studies. This may be possibly due to the low concentration of HPMC K 15M-Eudragit RL 100 polymer mixture. All other films obtained were of good quality.

Evaluation

Physicochemical characteristics

Physical Appearance

All polymer combinations used for fabrication of buccal films showed good film forming properties and reproducibility. The fabricated films were thin, flexible, elastic and smooth.

Film thickness

The thickness of each film was determined; it was an average of 0.20±0.26 mm and indicated that there was no much difference in thickness within the formulations.

Weight uniformity

The weight of films ranges from 0.15 mg to0.19 mg.

Folding endurance

The films has values >200 and indicated that all formulations have ideal film characteristics.

Surface pH

All the formulation were found to have pH between 6 to 7 and reveals that it may not cause any irritation to buccal mucosa since value is almost equal to the buccal pH.

Drug content uniformity

The average percentage drug content in various films ranged from 81.2% to 90.8%and observed that there was no significant difference in the drug content between the samples taken from the same formulation.

Swelling index

The average swelling index was found to be 92%. Results showed that all formulations showed good swelling properties, and found that when the concentration of polymer increases, the swelling of films also increases

***In vitro* drug release**

The release of Losartan Potassium from the buccal films varied according to the type and concentration of polymer.

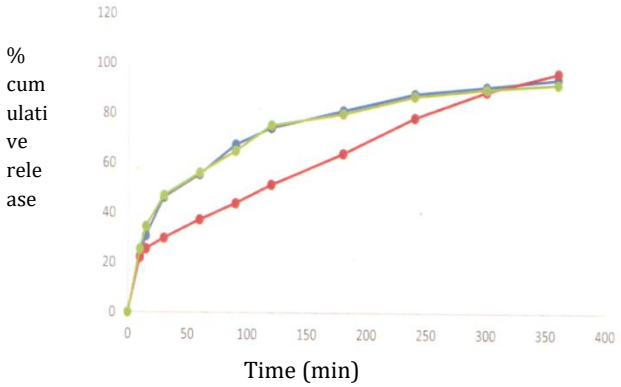

Fig.no.3:%Cumulative drug release of F2 formulation

Drug release kinetic studies

The results obtained from in vitro release studies were plotted in different kinetic models. Regression coefficient (R^2) values of different kinetic models are shown in figure 6, 7 and 8. The criteria for selecting the most appropriate model was on the basis of goodness of best fit.

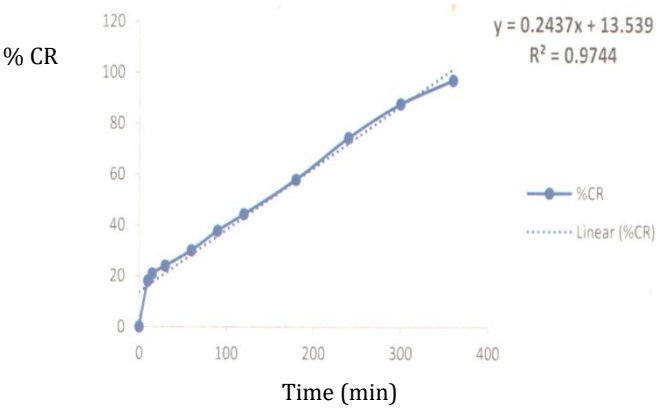

Fig.no.4: Zero order plot for F2

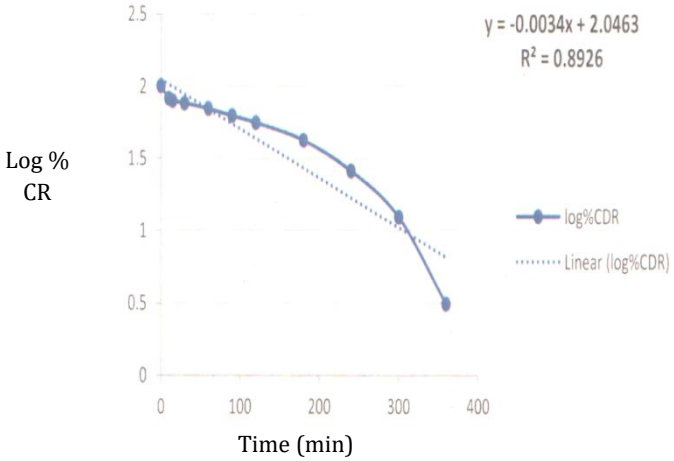

Fig.no.5: First order plot for F2

The release kinetics data indicates that F2 follows zero order kinetics as the correlation value is higher in case of zero order equation.

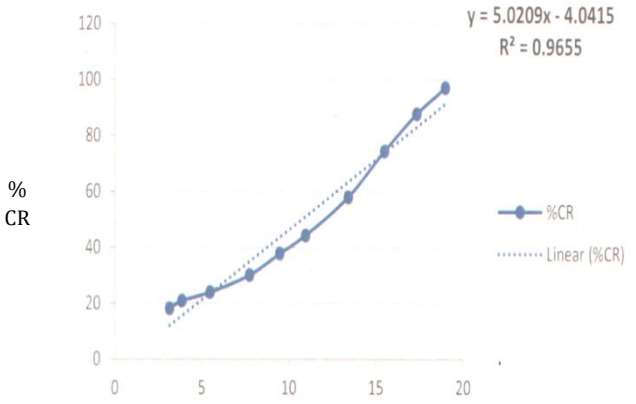

Fig.no.6: Higuchi plot for F2

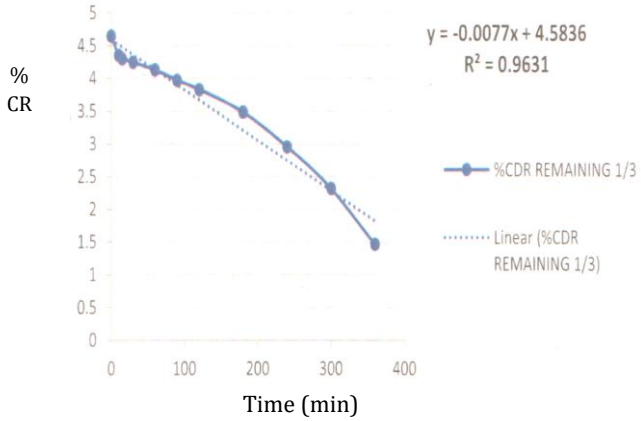

Fig.no.7: Hixson Crowell model for F2

The R^2 value of Higuchi model is found to be higher than Hixson Crowell model, shows that the mechanism of drug release was diffusion controlled

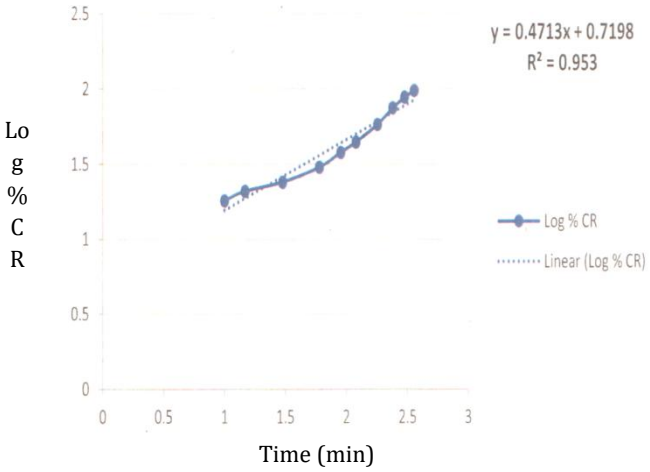

Fig.no.8: Korsmeyer-Peppas model for F2

The value of diffusion exponent (n) for F2 was found to be 0.4713 which is greater than 0.45 indicating that the drug release was non-fickian mediated.

***In vitro* residence time**

In vitro residence time was determined. Time required for the complete erosion or detachment of buccal films from the mucosa was found satisfactory. The *in vitro* residence time was found to be in the range of 3.20 to 4.10 h.

***In vitro* buccal permeation study**

Formulation F2 has showed maximum release (93%) compared to all other formulations.

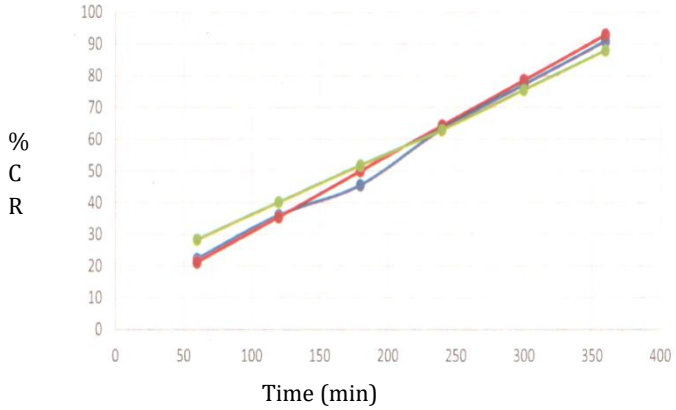

Fig.no.8 cumulative release of formulation F2

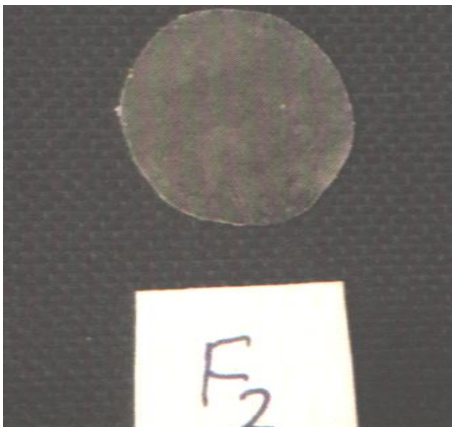

Fig.no.9 Best formulation F2 selected

Stability studies

The selected formulations were subjected to stability testing. Changes in the appearance, surface pH, folding endurance, and drug content of the stored films were investigated for a period of 1 month and there was no deviation from the original value.

Conclusion

The results of the study confirm the benefits of using Losartan potassium in the form of buccal films prepared by using HPMC K15 M as the main film-forming polymer and Carbopol 940, Eudragit RL 100, Ethyl cellulose as the copolymers in optimized concentration for giving immediate relief for hypertensive patients.

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Conflict of interest

No Conflict of interest

Ethical approval and Inform Consent

Not Required

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