EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 9
242-251
Year: 2016

MUCOADHESIVE TABLET OF LOSARTAN POTASSIUM FOR UNIDIRECTIONAL BUCCAL DRUG DELIVERY: DEVELOPMENT AND EVALUATION

Shinkar Dattatraya Manohar*[1], Gadakh Rohan Sunil[2] and Saudagar Ravindra Bhanudas[3]

[1]Department of Pharmaceutics, KCT's R.G.S. College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra.
[2]Department of Pharmaceutics, KCT's R.G.S. College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra.
[3]Department of Pharmaceutical Chemistry, KCT's R.G.S. College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra.

***Author for Correspondence: Shinkar Dattatraya Manohar**
Department of Pharmaceutics, KCT's R.G.S. College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra.

Article Received on 21/06/2016 **Article Revised on 11/07/2016** **Article Accepted on 03/08/2016**

ABSTRACT

Objectives: Losartan potassium having oral bioavailability is about 33% due to first pass metabolism. The formulation of Losartan potassium in to bioadhesive tablet will improve bioavailability, to reduce the dosing frequency and to improve the patient compliance. **Methods:** Tablets prepared by direct compression method. Nine formulations were developed with varying concentrations of polymers like Carbopol 934p, Casein. 32 optimization methods is applied. Tablets were tested for Hardness, Thickness, weight variation, surface pH, drug Content uniformity, swelling index, Mucoadhesive strength, in-vitro drug dissolution study, and Stability study. **Results:** FTIR and DSC studies show no drug polymers interaction. The most compatible in-vitro drug release profile was achieved with the formulation F9 is 95% after 12 hrs which contains the drug is 25 mg, Carbopol 934p is 60 mg, Casein is 40 mg. The surface pH, Mucoadhesive strength, and swelling index of formulation F9 was found to be 6.7±0.2, 0.1850±0.01N, and 162.83±0.32%, after 8 hrs respectively. The in-vitro release kinetics studies reveal that all formulations show anomalous or non-fickian diffusion. **Conclusion:** Hence, Carbopol 934p, Casein mucoadhesive polymer in various proportions can be used to prepare mucoadhesive tablet of Losartan potassium having prolong therapeutics effect with enhance patient compliance by avoiding first pass metabolism.

KEYWORDS: Mucoadhesive tablet, Losartan potassium, Carbopol 934p, Casein.

INTRODUCTION

Oral route is the most common route of drug administration among all other routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms[1]. Buccal drug delivery provides an attractive alternative to the oral route of administration[2], they are overcoming the problems such as first pass metabolism and drug degradation in the gastrointestinal tract environment. Moreover, the oral cavity is ease to administration and termination of therapy is easy. It is also possible to administer drugs to unconscious patient[3,4]. The mucoadhesive system which can be applied and remove directly by patient, represented a good recent alternative appropriate material for bioadhesion are mainly hydrogel–forming polymer which are called wet adhesive because they require moisture to exhibit adhesive property[5].

Losartan potassium is Angiotensin II Receptor Blockers used for treatment of hypertension. Losartan potassium having oral bioavailability is about 33% due to first pass metabolism. Plasma half life of Losartan potassium is 1-2.5 hours, molecular weight 461.01, and it does not have objectionable taste[6]. Casein, the major milk protein, comprises about 80% total protein content of milk casein forms an integral part of the daily diet in many part of the world. It is soluble in water, and organic solvent. Casein possesses a number of interesting properties that make it a good candidate as mucoadhesive polymer for conventional and novel drug delivery system. They also used as an adhesive, in preparation of casein paints and casein plastic as Industrially[7].

The aim of study was to prepare mucoadhesive buccal tablet of Losartan potassium to produced prolonged effect in buccal cavity.

MATERIALS AND METHODS

Materials

Losartan potassium was provided as gift sample from Abhinandan Rasayana, Mumbai, Carbopol 934p were obtained from Glenmark pharmaceuticals, (Nashik), Casein were obtained from S.D Fine Chemicals, Talc, Magnesium stearate, Mannitol were obtained from Research-Lab Fine Chem. Industry – Mumbai.

Formulation of mucoadhesive tablets

Direct compression method was employed to prepare buccal tablet of Losartan potassium using Carbopol 934p, Casein, and other excipient.

Factorial design

3^2 full factorial design was constructed, where the amounts of Carbopol 934p (X1) and Casein (X2) selected as independent factors and three dependent variables like In Vitro drug released (Y1), Mucoadhesive strength (Y2), Swelling strength (Y3) were selected. The levels of the two factors were selected on the basis of studies carried out before implementing the experimental design.

Table 1: Summarizes the experimental runs, their factor combinations and the translation of the coded levels to the experimental units used in the study.

factor	Name	units	Low	Medium	High
			(-)	(0)	(+)
X_1	Carbopol 934p	mg	20	40	60
X_2	Casein	mg	20	30	40

Preparation of Losartan potassium mucoadhesive tablets

Mucoadhesive tablets were prepared by direct compression method[8]. A drug with a various polymer mixtures were mixed thoroughly in polybags. The blend was lubricated with magnesium stearate and talc was added as glidant. this mixture triturated well in a glass mortar to produced homogeneous mixing. The mixture, blend was directly compressed on 10 station pilot press using 8 mm flat faced punches.

Table 2: Composition of Losartan potassium mucoadhesive buccal tablets

Formulation code	Drug (mg)	Carbopol 934p	Casein	Magnesium stearate	Talc	Manitol
F1	25	20	20	2	2	131
F2	25	40	20	2	2	111
F3	25	60	20	2	2	91
F4	25	20	30	2	2	121
F5	25	40	30	2	2	101
F6	25	60	30	2	2	81
F7	25	20	40	2	2	111
F8	25	40	40	2	2	91
F9	25	60	40	2	2	71

All the weights are taken in mg, total weight of tablet is 200 mg.

Evaluation of mucoadhesive buccal tablets

Compatibility Studies

Infra red spectrum

The infra red spectrum of losartan potassium was recorded with Bruker Opus 7.5 the wave number of 4000 to400 cm-1 by using Fourier Transform Infra red spectrophotometer[9,10].

Differential scanning Calorimetry

The formation of inclusion complex was conformed using a Mettler Toledo differential scanning calorimeter equipped to a computerized data station. The sample of pure drug, physical mixture of complex, and complex prepared by kneading and co-precipitation method was weighed and heated at a scanning rate of 10 °C/min between 40 and 200 °C and 40 ml/min of nitrogen flow[11].

Thickness test

The tablets were evaluated for their thickness using a micrometer. Average of three readings were taken and the results were tabulated (n = 3).

Hardness test

The tablets were evaluated for their hardness using Pfizer hardness tester. Average of three reading were taken and tabulated (n = 3).

Weight uniformity

Twenty tablets were taken and weighed individually. Average weight was calculated standard deviation was computed.

Surface pH

Three tablets were allowed to swell for four hour in simulated saliva fluid .pH was found out by placing the electrode of pH meter just in contact with the surface of the tablets. Average of three readings was computed[12].

Drug content uniformity

From each batch three randomly selected tablets were weighed accurately and powdered in a glass mortar with pestle. Powder equivalent to 10 mg of drug was transferred into 10 ml volumetric flask containing 10 ml of pH 6.8 phosphate buffer and kept aside with constant

shaking for 24 hrs to extract the total drug present in the tablet. Then the solution was filtered and the volume was made with phosphate buffer and analyzed for drug content at λmax of 224 nm against drug devoid phosphate buffer as blank. Averages of triplicate readings were taken. The content of drug was calculated using standard graph[13].

Swelling studies

Preparation of simulated saliva solution

Weigh accurately 2.38g of Na2HPO4, 0.19 g KH2PO4, 8.00g NaCl and dissolve in 1000 ml of distilled water to produce simulated saliva solution; finally adjusted the pH with phosphoric acid to 6.75.

Three tablets were weighed individually (W1) and immersed in a petridishes containing simulated saliva fluid (pH 6.75) for predetermined times (15min, 30 min,1, 2, 3, 4, 5, 6, 7, 8 hrs). After immersion tablets were wiped off by the excess surface water by the use of filter paper and weighed (W2). The % swelling index was calculated by:

% Swelling Index = [W2- W1] / W2 x 100

Where W1 is the initial weight of the tablet and W2 is the weight of the tablet after the particular swelling time interval[14].

Mucoadhesive strength

Mucoadhesive strength was conducted on modified physical balance. The equipment was fabricated by us in the laboratory as polypropylene disc (A), also locally fabricated. The apparatus consist of a modified double-beam physical balance in which the right pan has been replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A teflon block of 3.8 cm diameter and 2 cm height was fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This was kept in beaker filled with buffer media pH 6.75, which was then placed below right side of the balance. The right pan (D) was replaced with a lighter pan so that, the left pan weighs more than the right pan. The lower polypropylene block was intended to hold the mucosal tissue (B) of goat cheek pouch and to be placed in a beaker containing simulated saliva solution pH 6.75 (C). Goat cheek pouch was obtained commercially; the cheek pouch was collected into a sterile container containing sterile buffer solution of pH 6.75. The cheek pouch brought was stored in a refrigerator until use. The following procedure was used for all the test formulations using the above equipment. The cheek pouch was removed from refrigerator and allowed to attain equilibrium with ambient conditions in the laboratory. The goat cheek pouch was carefully excised, without removing connective and adipose tissue and washed with simulated saliva solution. The tissue was stored in fresh simulated saliva solution. Immediately afterwards the membrane was placed over the surface of lower polypropylene cylinder (B) and secured. This assembly was placed into beaker containing simulated saliva solution pH 6.75 at 37 ± 2°C. From each batch, one tablet at a time was taken and stuck to the lower surface of polypropylene cylinder with a standard cynoacrylate adhesive. The beaker containing mucosal tissue secured upon lower cylinder (B), was manipulated over the base of the balance so that, the mucosal tissue is exactly below the upper cylinder (A). The exposed part of the tablet was wetted with a drop of simulated saliva solution, and then a weight of 20 gms was placed above the expanded cap, left for 10 minutes. After which the tablet binds with mucin. The weight was removed. Then slowly and gradually weights were added on the right side pan till the tablet separates from the mucosal surface/ membrane. The weight required for complete detachment is noted (W1) (W1-5.25gm) gives force required for detachment expressed in weight in grams. Procedure was repeated for two more tablets. Average was computed and recorded[14].

***In vitro* release method for Losartan Potassium tablets**

The drug release from buccal tablets was studied by using USP type II (paddle type) dissolution test apparatus. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed one side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus containing 900 ml of pH 6,8 phosphate buffer and paddle was rotated at 50 rpm at a temperature of 37 ± 0.5°C. Samples of 5 ml were collected at different time intervals up to 12 hrs and analyzed spectrophotometrically at λmax 224nm from which percentage of losartan potassium was calculated using calibration curve. The procedure was repeated for three more tablets similarly and average was computed[15].

Drug release kinetics

In the present work the data obtained from drug release was fitted to various kinetic equations to find the mechanism of drug release from Sustain release mucoadhesive tablets[16,17].

Stability studies

The mucoadhesive tablets were subjected for a period of three months as per ICH guideline at the 40 ^{0}C temperature and relative humidity 75% RH. The samples were withdrawn at 7 days, 15 days, 1, 2, 3 months for given temperature condition. The formulations were evaluated mainly for drug content at the predetermined intervals[18].

RESULT AND DISCUSSION

Compatibility studies

Infra red spectrum

IR studies were carried out for the pure drug Losartan Potassium and physical mixture (formulation F9) and their spectra shown in **fig. 1** and **fig. 2** respectively. The result is clearly showed that there was no interaction

between the drug and the excipient in the prepared formulation F9.

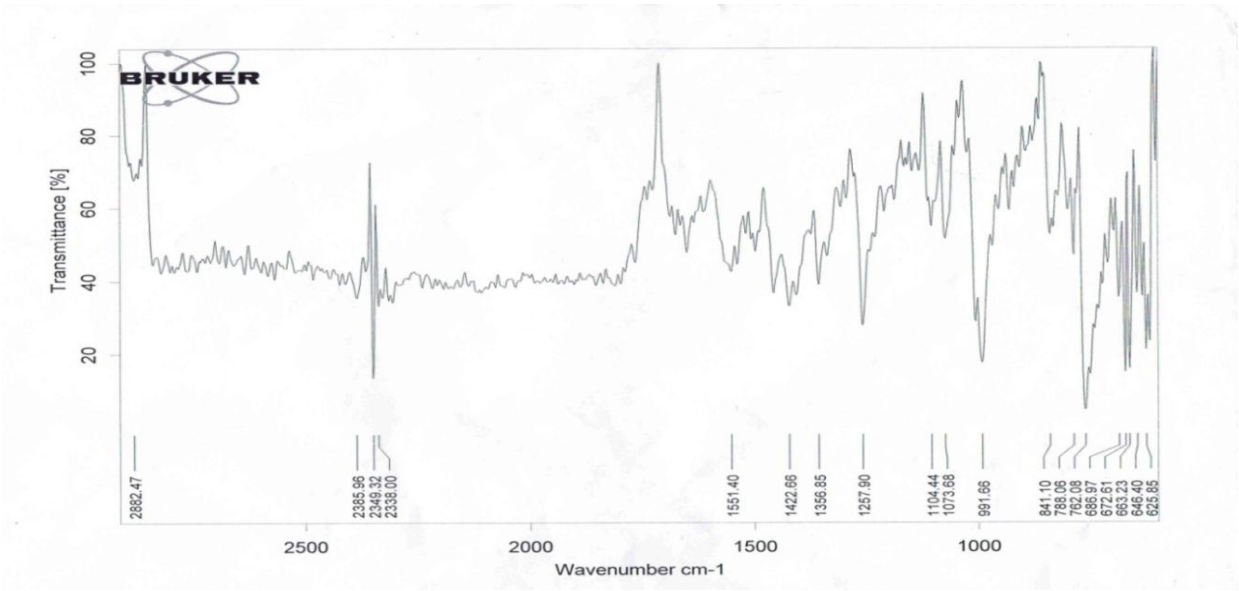

Fig. 1: IR spectra data for pure drug Losartan potassium

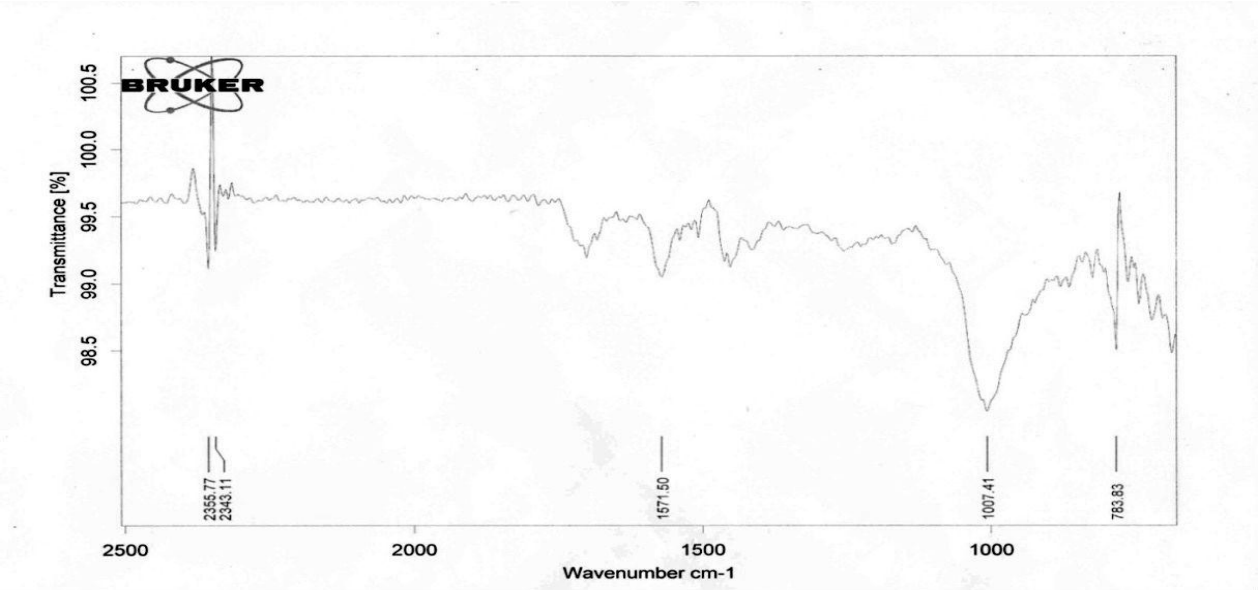

Fig. 2: IR spectra of optimized physical mixture (formulation F9)

Differential scanning Calorimetry

Thermal characterization and analysis of DSC curves of the pure drug, physical mixture of formulation F9 was carried out. The studies provided thermal behavior of the pure drug, its physical mixture with Carbopol, Casein. Losartan Potassium showed an endothermic peak at at 255.46 ^{0}C **(fig.3)**. Physical mixture of Formulation F9 showed an endothermic peak at 251.25 ^{0}C **(fig.4)** they are almost similar to pure drug peak. The above results indicated that there was no possible interaction between the drug and the excipients in the mucoadhesive buccal formulation.

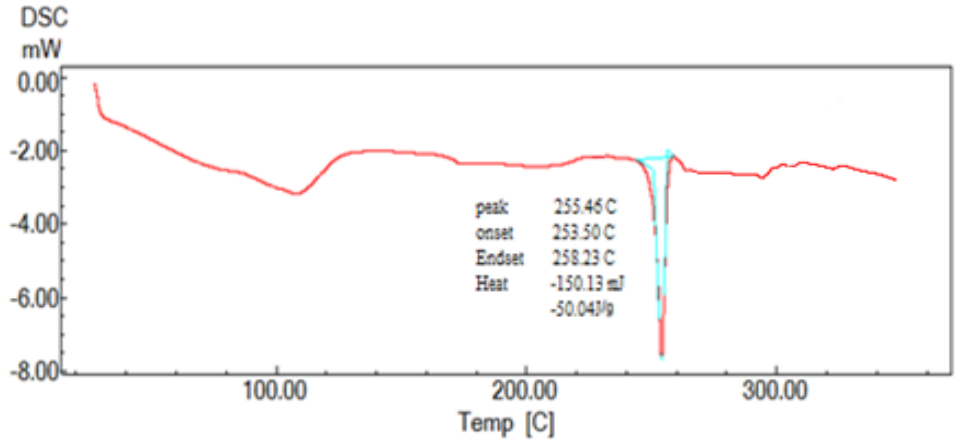

Fig. 3: DSC thermogram of pure drug losartan potassium

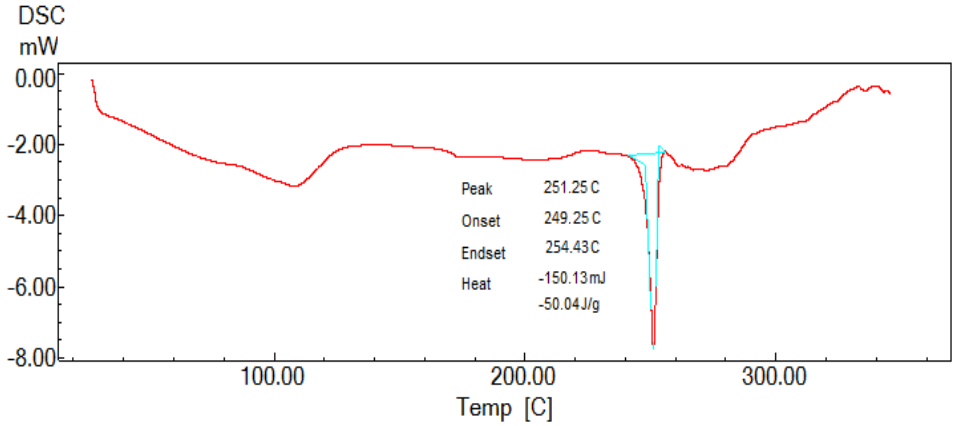

Fig. 4: DSC thermogram of physical mixture of formulation F9

Table 3: Evaluation of Physical Characteristics of mucoadhesive tablets containing Losartan potassium

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Weight variation (mg)	%Drug content	Surface pH
F1	4.44±0.051	2.90±0.03	196±1.5	90.88±0.5	6.4±0.25
F2	4.28±0.036	2.89±0.06	195±1.2	93.14±0.84	6.8±0.3
F3	4.03±0.02	2.86±0.06	198±1.0	91.29±0.56	6.5±0.3
F4	5.15±0.04	2.92±0.03	198±1.5	95.04±0.63	6.9±0.3
F5	4.46±0.04	2.95±0.04	196±1.6	92.18±0.64	6.7±0.37
F6	4.13±0.06	2.91±0.06	198±1.0	94.77±0.47	6.8±0.05
F7	5.09±0.05	2.96±0.04	198±1.5	91.18±0.67	6.9±0.30
F8	4.24±0.07	2.93±0.04	196±1.0	93.18±0.14	6.6±0.15
F9	4.95±0.05	2.88±0.008	195±1.7	95.60±0.61	6.7±0.2

The adequate tablet hardness is necessary requisite for consumer handling and acceptance. Hardness of tablet from F1 to F9 were found to be in between 4.13±0.06 to 5.15 ±0.04 kg/cm^2 indicating good binding and satisfactory strength of tablet.

Thickness of tablet was found to be almost uniform in all formulation F1 to F9, The thickness was found in range between 2.88±0.008 to 2.95±0.04 mm.

Weight variation was found to be uniform with low standard deviation values from 195±1.2 mg to 198±1.5mg which comply with the weight variation test as per IP.

The Drug content of each batch of all the formulation was evaluated and result are shown in the Table 3. Drug content was found in the range of 90.88±0.5to 95.60±0.61 this result was found within the Pharmacopoeial limit.

Surface pH for all formulation was found in between 6.4±0.25 to 6.9±0.30 which are within the limit. The acceptable pH of saliva in range 5-7. Hence it was concluded that all formulation could not produced any local irritation in buccal mucosa.

Swelling study

Swelling index is of great significance, as variation in water content causes significant variation in the mechanical properties of formulation. The swelling study was conducted for all formulation. i.e. F1 to F9 and result ware found in the range of 80.61±0.51 to 162.83±0.32 at 8 hrs. Swelling studies was found to be the order F9 >F6 >F3 >F8 >F5 >F2 >F4 >F7 >F1 respectively. Formulation F9 showed higher swelling index which containing carbopol 934p 60 mg and casein 40 mg. The swelling of tablet increases with increase in polymer concentration.

Mucoadhesive strength

Mucoadhesive strength was determined by measuring the force required to detach the formulation from mucosal surface that is detachment stress. The mucoadhesive characteristics were affected by the concentration of mucoadhesive polymer. Increase in concentration of polymer increased mucoadhesive strength of formulation hence results reveal that increase in carbopol 934p and casein concentration increases the mucoadhesive strength. This was due to interaction of polymeric chains with the mucin strands to form weak chemical bonds due to stronger mucoadhesive force. The mucoadhesive strength was conducted for all formulation. i.e F1 to F9 and result ware found in the range of 0.0722±0.02 to 0.1850±0.01 N at 8 hrs. Mucoadhesive strength was found to be the order F9 >F6 >F3 >F8 >F5 >F2 >F4 >F7 >F1.

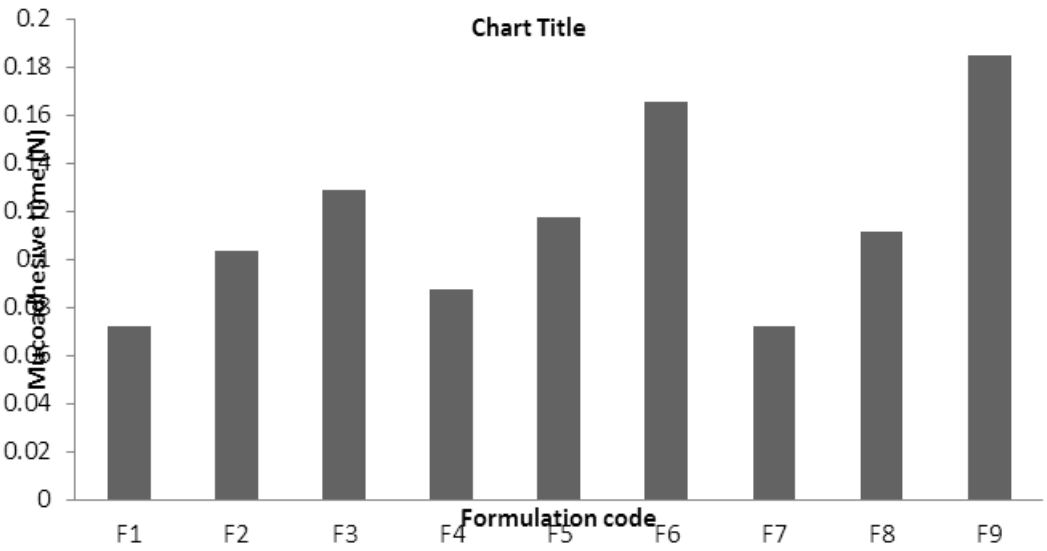

Fig. 5: Mucoadhesive Strength of F1 to F9 formulation

***In vitro* drug release study**

In vitro dissolution studies of all the formulation of mucoadhesive were carried out in 6,8 phosphate buffer. The study was performing for 12 hrs. The variation in drug release was due to different concentration of polymer in all the 9 formulation. When % CDR was plotted Vs Time it was observed that for increased in polymer concentration increase in drug released rate. Increasing the concentration of carbopol 934p and casein in the formulation, the drug release rate form the tablet was found to be increased this is may be due to increased hydration or Swelling characteristics of polymer with increasing concentration.

Among all formulation, F9 batch showing higher drug release i.e. 95.59 % at the end of 12 hrs also it show better mucoadhesive and swelling property thus it was considered as an optimized formulation.

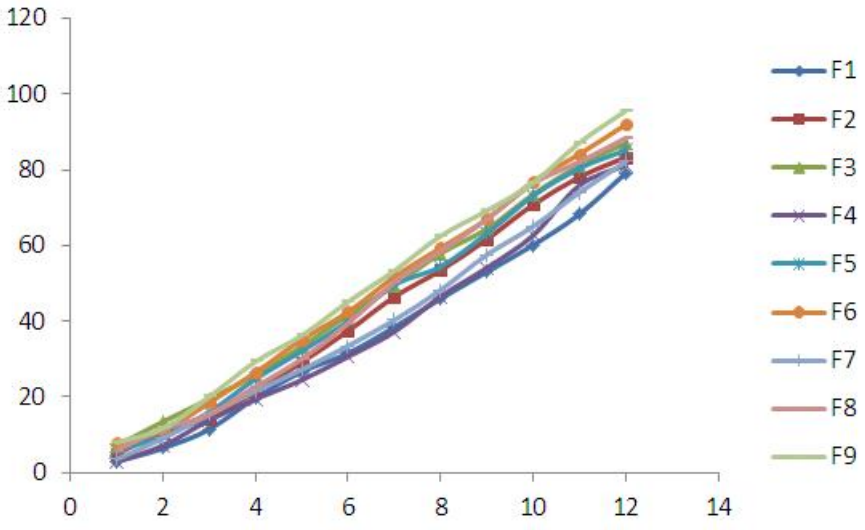

Fig 6: In-vitro drug release of formulations F1 to F9

Drug release kinetics

Table 4: Released kinetics of different formulation F1-F9

Formulation	Zero order	First Order	Hihuchi	Korsemeyer-Peppas	
	R^2	R^2	R^2	R^2	n
F1	0.993	0.887	0.949	0.994	0.553
F2	0.995	0.917	0.995	0.996	0.662
F3	0.998	0.920	0.998	0.997	0.818
F4	0.994	0.898	0.965	0.998	0.567
F5	0.996	0.910	0.996	0.991	0.704
F6	0.997	0.925	0.997	0.987	0.807
F7	0.993	0.890	0.951	0.999	0.570
F8	0.993	0.925	0.954	0.991	0.709
F9	0.998	0.922	0.969	0.989	0.828

In vitro drug release kinetics was studied for all the formulations using different kinetic models. From the regression value it can be predicted that formulation follows first order because regression value was greater than 0.9 (concentration dependent mechanism) Higuchi and Connor's and Korsemeyer's Peppas release kinetics (r2 value greater than 0.9), the n value of Korsemeyer's Peppas release kinetics was greater than 0.5 from which we can conclude that mechanism of drug released for all formulation is non- Fickian diffusion type.

Statistical analysis

The purpose of using 3^2full factorial design was to conduct comprehensive study of effect of process parameters like carbopol 934p (X1) and Casein (X2) and their interactions using a suitable statistical tool (Design expert software version 7.0.0) by applying one way ANNOVA at 0.05 levels. A mathematical modelling was carried out. Polynomial equation was obtained depending on significant influences among 2 factors on their experimental design.

Response surface methodology

The influence of main effects on responses was further elucidated by response surface methodology. It is widely used tool in the development and design of dosage form. The three dimensional response surface plot and corresponding two dimensional contour plots were generated by the software. The response surface plot is very useful for determination of main and interaction effects of the independent variables whereas two dimensional plots gives visual representation of values of responses.

In case of swelling index the three dimensional response surface plot depicted the increase in swelling index as polymer concentration increases. The two dimensional contour plot relating X_1 X_2(interaction between carbopol 934p and casein was nonlinear indicating interaction between two variables.

In case of mucoadhesive strength the three dimensional response surface plot depicted the increase in mucoadhesive strength as polymer concentration increases. The two dimensional contour plot relating X_1 X_2(interaction between carbopol 934p and casein was nonlinear indicating interaction between two variables.

In case of *in vitro* drug release the three dimensional response surface plot depicted the Increase in drug release as polymer concentration increases. The two dimensional contour plot relating X_1 X_2 (interaction

between carbopol934p and casein was nonlinear indicating interaction between two variables.

Response surface plots are shown in figures 7, 8 and 9 and contour plots are shown in figures 10, 11 and 12 for in Swelling Index, mucoadhesive strength, in-vitro drug released respectively.

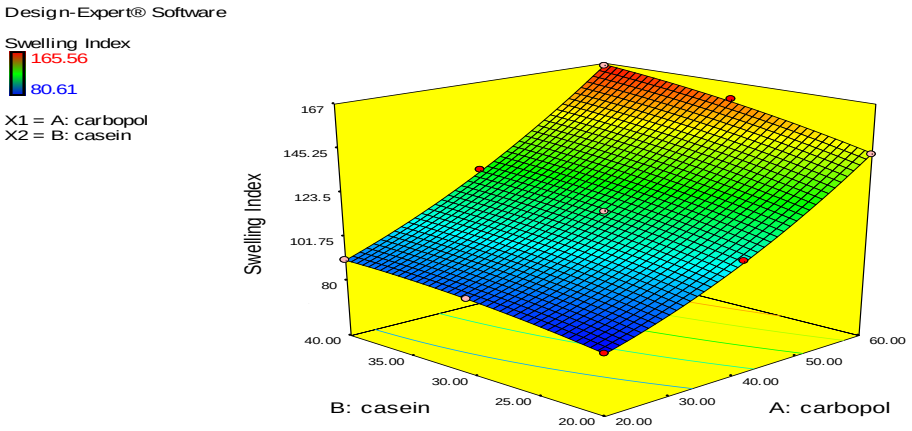

Fig. 7: Surface response plot showing Effect of Carbopol 934P and Casein on Swelling Index

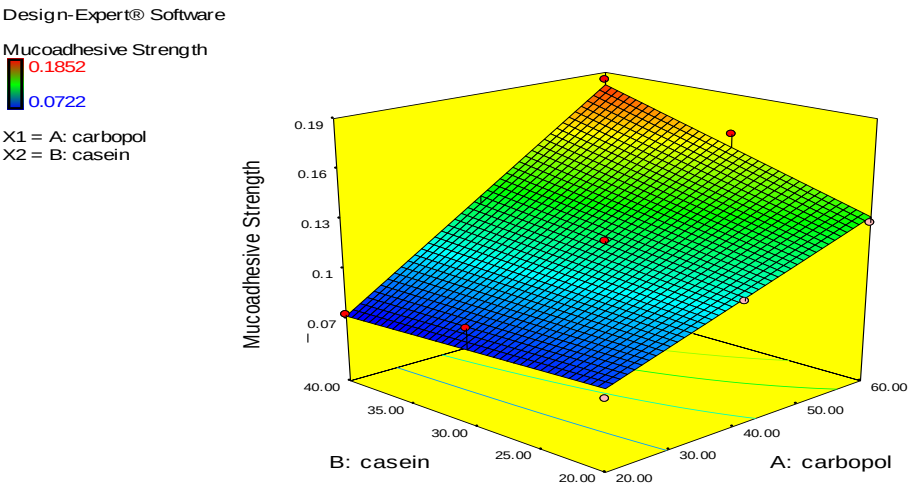

Fig. 8: Surface response plot showing Effect of Carbopol 934P and Casein on Mucoadhesive Strength

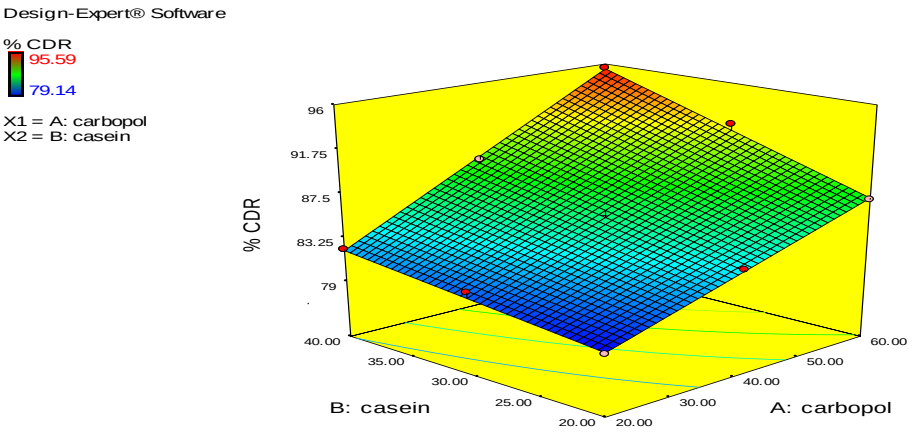

Fig. 9: Surface response plot showing effect of Carbopol 934p and Casein on drug release.

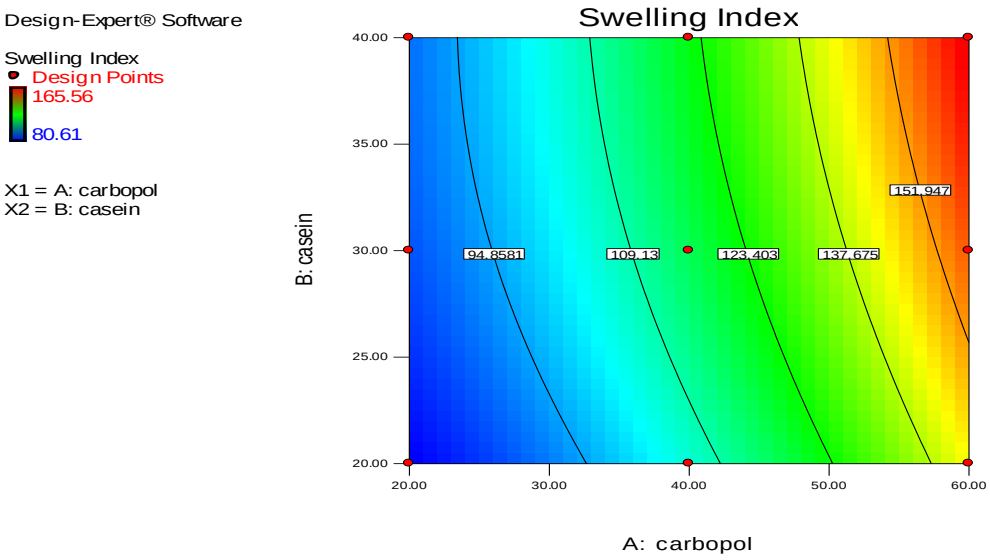

Fig. 10: Contour plot showing Effect of Carbopol 934p and Casein on Swelling Index

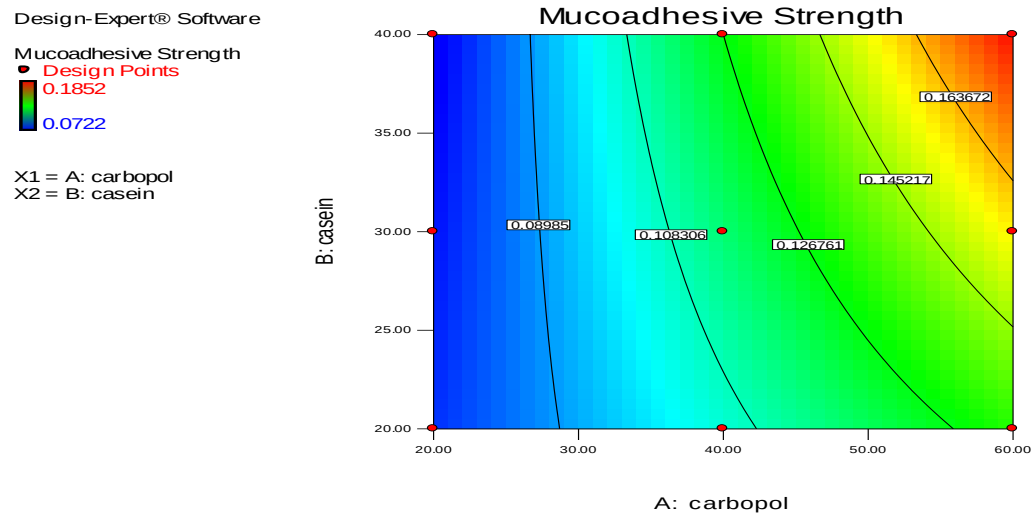

Fig. 11: Contour plot showing Effect of Carbopol 934p and Casein on Mucoadhesive Strength

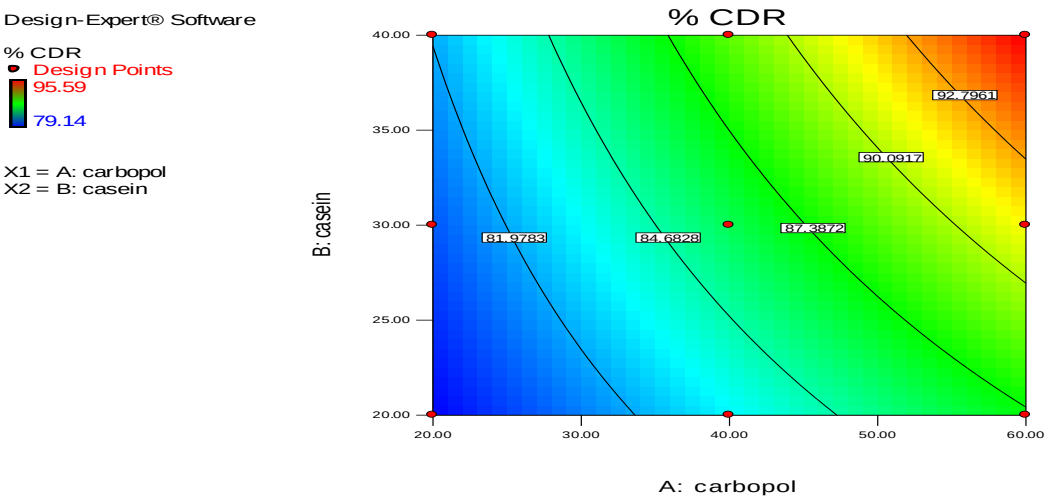

Fig. 12: Contour plot showing Effect of Carbopol 934p and Casein on drug release.

After generating model equations relating main effects and responses, various Mucoadhesive tablet formulations containing Losartan Potassium were optimized based on in vitro drug release (Y1), Swelling index (Y2), mucoadhesive strength. The optimal values for responses were obtained by numerical analysis based on the criteria of desirability, and optimal batch was selected. Optimized batch was having highest drug release, optimal swelling and mucoadhesive strength. This reveals that mathematical model obtained by factorial design to produce optimized responses was well fitted.

Stability study

After 3 month, storage of F9 formulation at 40 ^{0}C temperature and relative humidity 75% RH, physical parameters and drug content were checked and found to be almost similar to the initial value. So it can be said that Losartan potassium mucoadhesive tablet prepared with Carbopol 934p and casein is stable.

CONCLUSION

Losartan potassium mucoadhesive buccal tablets could be formulated using the drug, Carbopol 934p and Casein by 3^2 factorial designs. It can be seen that by increasing concentration of Carbopol 934p and Casein, the drug release rate found to be increased. The formulated system provides sustained in vitro release of drug for 12 hrs. The release kinetics studies reveal that all formulation fits well with zero order kinetics followed by korsmeyer-peppas, Higuchi and first order kinetics model and mechanism of drug release is non-fickian diffusion. The Buccal adhesion time could be significantly improved owing to higher Swelling Index and mucoadhesive strength. Buccal administration will give increased bioavailability due to absence of hepatic first pass metabolism, thus enhancing better patient compliance.

ABBREVIATIONS

GIT-Gastrointestinal tract, S.D-Standard Deviation, R.H-Relative Humidity , ANOVA- Analysis of Variance, Fig-Figure, hrs-Hours, ^{0}C-Degree Celsius, cm-Centimetre, cm^2- Centimetre Square, mm- Milimeter, mg-Miligram, DSC- Differential Scanning Calorimetry, IR- Infra Red Spectrum, ICH- International Conference on Harmonisation.

ACKNOWLEDGEMENTS

Authors wish to thank Ravindra Gambhirro Sapkal College of Pharmacy, Anjaneri, Nashik, for providing research laboratory to carry out this project work.The authors also wish to show their deep gratitude to Abhinandan Rasayana, Mumbai for providing the gift sample of Losartan potassium.

REFERENCES

1. Lim ST, Martin GP, Berry DJ, Brown MB. Preparation and evaluation of the in vitro drug release properties and mucoadhesion of novel microspheres of hyaluronic acid and chitosan. Journal of Controlled Release 2000; 66: 2-3, 15: 281-292.
2. Mohire NC, Yadav AV. J Pharm Res 2010; 3: 650-657.
3. Wong CF, Yuen KH, Peh KK, International Journal of Pharma 1999; 178: 11-22.
4. Remunna LC, Porter A, VilaJato JL, Alonso MJ. Journal of Control Release 1998; 55: 143-52.
5. Gupta A, Garg S, Khar RK. Interpolymer complexation and its effect on bioadhesive strength and dissolution characteristics of buccal delivery system, drug development and industrial pharmacy 1994; 20: 315-325.
6. Velmurugan S. Formulation and *in -vitro* evaluation of Losartan potassium mucoadhesive buccal tablets. Asian Journal of Pharmaceutical and Clinical Research 2013; 6(3): 125-130.
7. Balaji A. Formulation and evaluation of mucoadhesive buccal tablets by using natural polymer. International journal of pharmaceutical science and research 2014; 5(11): 4699-4708.
8. Debjit M, Chandira M, Chiranji B. Formulation, design and development of buccoadheshive tablets of verapamil hydrochloride. International Journal of Pharm Tech Research 2009; 1(4): 1663-1677.
9. Optizen 2120 UV Instruction Manual.
10. Pavia DL, Lampman GM, Kriz GS, Vyvyan JR. "Spectroscopy", Infra red spectroscopy, cengage learning 2007; 26-107.
11. Ahemad MO, Gibly EL, Ahemad SM. Effect of cyclodextrins on physicochemical properties and antimycotic activity of clotrimazole. International Journal of Pharmaceutics 1998; 121: 111-121.
12. Lachman L, Liberman HA. Compression and consolidation of powdered solids. Chapter 4, 3rd ed. Varghese Publishing House (Bombay) p:67.
13. Dhake AS, Shinkar DM, Shayle S, Patil SB, Setty CM. Development and evaluation of mucoadhesive tablets of clotrimazole and its β-cyclodextrin complex for the treatment of candidiasis. International Journal of Pharmacy and Pharmaceutical Sciences 2011; 3(3): 159-64.
14. Luana P, Ambrogi V, Daniela R, Stefano G, Maurizio R. Novel mucoadhesive buccal formulation containing metronidazole for the treatment of periodontal disease. Journal of Control Release 2004; 95: 521-533.
15. Soliman MS, Rahim BN, Golamhosein Y. Formulation and *in-vitro* evaluation of prednisolone buccoadhesive tablets. Il Farmaco 2005; 60: 339-344.
16. Bramhankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics A treatise. Vallabh prakashan 2008; 212-229.
17. Costa L, Lobo JS. Modeling and comparison of dissolution profiles. European Journal of Pharmaceutical Sciences 2001; 13: 123-133.
18. Korsemeyer RW, Gurny R, Doclker E, Buri P, Nikolas AP. Mechanism of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics 1983; 15: 25-35.