https://doi.org/10.48047/AFJBS.6.6.2024.7807-7817

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

FORMULATION, EVALUATION OF MUCOADHESIVE BUCCAL FILM OF FELODIPINE USING FACTORIAL DESIGN

Siva Prasad Sunkara [1], Farhad F Mehta [2], Saman Aqeel [3], Attuluri Venkata Badari Nath [4], Susanta Kumar Behera [5], Manoj Kumar Katual [6], Ramandeep Kaur [7], Swalin Parija [8]*

1. Associate Professor, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Chowdawaram, Guntur, Andhra Pradesh, 522019
2. Assistant Professor, School of Pharmaceutical Sciences, UTD, RGPV University, Bhopal, Madhya Pradesh
3. Assistant professor, IIMT College Of Pharmacy, Plot No. 19 & 20, Knowledge Park III, Greater Noida, Uttar Pradesh 201310
4. Professor and HOD, Department of Pharmaceutics, Santhiram College of Pharmacy, Nerawada, PIN 518501, Nandyal District, AP
5. Assistant Professor, Institute of Pharmacy & Technology, Salipur, Cuttack, Odisha- 754202
6. Associate Professor & Head, Guru Kashi University Bhatinda Punjab 151302
7. Assistant professor, Guru Kashi Univeristy, Talwandi Sabo 151302
8. Assistant Professor, Institute of Pharmacy & Technology, Salipur, Cuttack, Odisha-754202

Corresponding Author: Dr. Swalin Parija
Designation and Affliction: Assistant Professor, Institute of Pharmacy & Technology, Salipur, Cuttack, Odisha-754202
Email id: swalinpharma@gmail.com

Article Info
Volume 6, Issue 6, May 2024
Received: 29 March 2024
Accepted: 30 April 2024
doi:
10.48047/AFJBS.6.6.2024.7807-7817

ABSTRACT:
The goal of the current study was to formulate and produce a felodipine buccal film that dissolves quickly utilising the solvent casting process. mucoadhesive polymers HPMC E15 and PVP were used to make mucoadhesive buccal films. Because HPMC E15 has a high mucoadhesive characteristic, it demonstrated an extended in-vitro residence period when compared to the other polymer. Weight variation, thickness, folding endurance, pH, in vitro disintegration, in vitro dissolution, tensile strength, and medication content were all used to evaluate mucoadhesive buccal films. A 40-minute investigation on in vitro drug release revealed that almost 99.12±0.05% of the medication was liberated. It was discovered that formulation LF9 had a tensile strength of 52.32 N/mm2. Formulation LF9's folding endurance was discovered to be 151. It was discovered that formulation LF9 has a disintegration time of 69.11 seconds. Consequently, it may be said the prepared formulation of buccal mucoadhesive film can be a novel treatment for hypertension.

KEYWORDS: Buccal film, Felodipine, Oral fast dissolving film, antihypertensive

INTRODUCTION:

One option for administering medications other than orally is through bioadhesive buccal delivery, especially for medications that require first pass metabolism. (1) By using the buccal route, issues related to oral medication administration, such as significant liver metabolism, drug degradation in the gastrointestinal tract from a harsh environment, and invasive parenteral injection, can be resolved. Because it has various advantages over oral delivery, the buccal route has drawn attention from drug delivery scientists during the past 20 years (3, 4, 5). This drug delivery method is thought to be the best since it can avoid hepatic metabolism's first-pass and avoid degradation in the gastrointestinal tract (6). Given its relative permeability, the buccal mucosa is a viable target for efficient, non-invasive active delivery. This alternate location can improve bioavailability while providing quick and direct distribution into the systemic circulation, ease of accessibility, and increased patient compliance (7, 8). Because buccal film adheres to the buccal mucosa easily, adapts better to the mucosal surface, and retains longer than other buccal dosage forms, it is the most advanced and popular drug delivery method (9, 10). Additionally, compared to conventional medication, it was revealed that felodipine delivered buccaly is likely to improve absorption and decrease metabolite production (11). Therefore, the buccal distribution of felodipine appears to be a beneficial and promising strategy that can overcome the obstacles preventing this medication from being delivered successfully. It is noteworthy that this medication administration method can lessen the development of felodipine metabolites, do away with the requirement for a diet low in tyramine, and be conveniently given to patients who have dysphagia (12).

One calcium channel blocker is Felodipine. It functions by interfering with calcium's entry into heart and blood vessel cells. (13, 14) Felodipine lowers the workload of the heart by relaxing blood vessels and supplying the heart with more blood and oxygen. is fully absorbed from the digestive system; however, only 15% of it is available systemically due to significant first-pass metabolism via the portal circulation. (15, 16) In the current study, mucoadhesive buccal films of felodipine utilising hydroxy propyl methyl cellulose and polyvinyl alcohol were made by solvent casting method in order to maximise its bioavailability, efficacy, and to minimise the negative effects associated with oral administration.

MATERIALS AND METHODS:

Materials: Felodipine (98% purity), polyvinyl alcohol, methanol, dichloromethane, ethyl alcohol and triethanolamine were purchased from Sigma Aldrich (St. Louis, MO). HPMC E15 was obtained as a gift sample from Loba Chemie Pvt. Ltd. MumbaiCarbopol 971P, ethyl cellulose and hydroxypropyl methylcellulose (HPMC) K15 were received ex gratis sample from Ind-Swift Ltd., Parwanoo, Himachal Pradesh, India. Eudragit RS 100 (Evonik Röhm GmbH, Darmstadt, Germany), dibutyl phthalate (Loba Chemie Pvt Ltd, Mumbai, Maharashtra, India) and polyvinylpyrrolidone K30 (PVP K30) (Loba Chemie Pvt Ltd, Mumbai, Maharashtra, India) were purchased commercially.

Preparation of fast dissolving film by solvent casting method: Using the solvent casting method, hydroxyl propyl methyl cellulose (HPMC) and PVP were combined to create felodipine mucoadhesive buccal films. (17, 18) In order to create a uniform viscous mixture, water soluble polymers such as HPMC E15 and PVP were dissolved in hot water up to 40ºC while being stirred simultaneously at 1000 rpm. Bring this thick mixture to room temperature. Subsequently, the medicine was fully dissolved by sonicating the mixture including mannitol, citric acid, and peppermint oil, along with the addition of Felodipine

(API) and plasticizer (propylene glycol) for a duration of 15 minutes. Casting the final film solution on a regular petridish to defrost it. It is dried for three hours at 40 oC in a hot air oven. After the film was carefully taken out of the petridish, it was inspected for flaws and sliced to the proper size so that each strip would deliver the same dosage (2x2 cm2). (19, 20) Until further examination, the samples were kept in desiccators with a relative humidity of 30 to 35 percent. Mucoadhesive fast-dissolving buccal film formulation is displayed in Table 1.

Table 1: Formulation Of Mucoadhesive Fast Dissolving Buccal Film

Components	**FL1**	**FL2**	**FL3**	**FL4**	**FL5**	**FL6**	**FL7**	**FL8**	**FL9**
Felodipine (mg)	20	20	20	20	20	20	20	20	20
HPMC E15(mg)	500	500	500	550	550	550	600	600	600
PVP(mg)	300	350	400	300	350	400	300	350	400
Propylene Glycol(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Tween 80(ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Citric Acid (mg)	50.8	50.8	50.8	50.8	50.8	50.8	50.8	50.8	50.8
Mannitol(mg)	58.5	58.5	58.5	58.5	58.5	58.5	58.5	58.5	58.5
Peppermint oil	q.s.	q.s.	q.s	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water(ml)	10	10	10	10	10	10	10	10	10

Experimental Design:A 3^2 factorial design was used 2 factors were evaluated, each at 3 levels, experimental batches were performed at all 9 possible combinations. The amount of HPMC E15 (X1) and PVP (X2) were selected as independent variables, whereas tensile strength, cumulative % drug release were selected as dependent variables. (21, 22) The data were subjected to 3-D response surface methodology in PCP Disso 2.08 to determine the effect of types and amount of polymers on the various dependent variables. The values of variables in a 32 factorial design were indicated in table 2.Full factorial experimental design layout was shown in table 3.

Table 2: Amount Of Variables in a 3^2 Factorial Design

Variables	**Low**	**Medium**	**High**
HPMC E 15	500	550	600
PVP	300	350	400

Table 3: 3^2 Full Factorial Experimental Design

S. No.	**Batch Code**	**HPMC E-15**	**PVP**
		X1*	**X2***
1	FL1	-1 (500)	-1 (300)
2	FL2	-1 (500)	0 (350)
3	FL3	-1 (500)	+1 (400)
4	FL4	0 (550)	-1 (300)
5	FL5	0 (550)	0 (350)
6	FL6	0 (550)	+1 (400)
7	FL7	+1 (600)	-1 (300)
8	FL8	+1 (600)	0 (350)
9	FL9	+1 (600)	+1 (400)

*X1 - Amount of HPMC E-15, *X2 - Amount of PVP,

* -1, 0, +1 – Low, Medium and High amount of HPMC E-15 and PVP.

A statistical model incorporating interactive and polynomial terms was used to calculate the responses.

$$Y=b0+b1X1+b2X2+b12X1X2+b11X1X1+b22X2X2+\epsilon \quad 1$$

Where, in equation (1), Y is the dependent variable,b0 is the arithmetic mean response of the 9 trials, and bi (b_1,b_2,b_{12},b_{11}, and b_{22}) is the estimated coefficient for the corresponding factor Xi (X_1,X_2,X_1X_2, X_{12} and X_{22}, which represents the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1X_1 and X_2X_2) are included to investigate the nonlinearity and ϵ indicates random error.

Characterization of mucoadhesive fast dissolving buccal films: The prepared mucoadhesive buccal films were examined for weight fluctuation; the average weights of three films of each formulation were determined by weighing the films separately. Three films of each formulation were measured using a vernier calliper (Mitutoyo, Japan) at three distinct locations to determine the thickness of the film, and the mean value was computed. After determining the folding endurance, three films of each formulation were cut to the necessary size with a sharp blade. (23) The film (2 x 2 cm2) was to be folded repeatedly at the same location until it broke in order to assess folding endurance. The value of folding endurance is determined by the number of times the film could be folded in the same way without breaking. (24) One oral film was dissolved in 10 millilitres of distilled water, and the pH of the resulting solution was measured to ascertain the film's surface pH. (25) A tensile strength test was conducted on mucoadhesive films utilising a tensile strength device. After cutting the patch strip (2 x 2 cm2), it was clamped between these two clamps. The pulling force was raised by progressively adding weight to the pan until the patch broke. Tensile strength, or the amount of force needed to break the film, was computed as N/mm^2. The drug content uniformity of the film was assessed by cutting five film strips (2 x 2 cm2) from the centre and four corners of the moulded film. Every film strip was put into a different conical flask with 100 millilitres of purified water in it. For two hours, the flasks were shaken in a mechanical shaker. A UV-Visible spectrophotometer was used to filter and analyse each solution at a wavelength of 282 nm. The USP disintegration device (Veego Instrument Corporation, Mumbai) was used to conduct the in vitro disintegration test. A 2x2 cm2 film sample from each batch was submerged in 25 millilitres of artificial saliva. The moment a film begins to shatter or dissolve is known as the disintegration time. (26)

In-Vitro Dissolution Studies: Using 500 ml of simulated saliva (pH 6.8) maintained at 37 ± 0.5º C and agitated at 50 rpm, the USP Dissolution Test Apparatus II (Paddle Apparatus) was used to conduct the dissolution investigation. A 2 x 2 cm2 patch of film was cut, and it was submerged in a jar that contained a dissolving agent. At 5, 10, 15, 20, and 40 minute intervals, 5 millilitre samples were taken out, filtered, and subjected to UV-visible spectrophotometric analysis at 265 nm. (27)

Stability Studies: For the stability investigation, the optimised formulation was stored in a stability chamber for 30 to 45 days. Samples were taken at 30 and 45 days, and the formulation's tensile strength, drug content, and percentage drug release were examined over the course of 45 days at 40°C ± 5°C and 75% relative humidity. (28-32)

RESULT AND DISCUSSION:

Fourier Transform Infrared Spectroscopy study:FTIR analysis showed that the felodipine's basic peaks are still present in the physical combination. The formulation of a mucoadhesive, quickly dissolving felodipine film can be made using these polymers as the results indicated that there was no chemical interaction between felodipine and them. Figure 1 displays the FTIR spectra of the physical mixture of HPMC E 15 and PVP. Fast-dissolving mucoadhesive buccal film made using the solvent casting technique, with several characteristics.

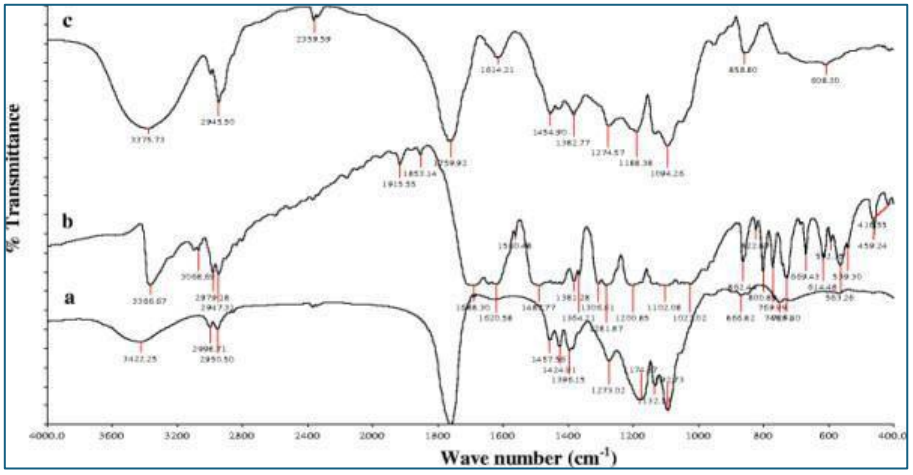

Fig. 1: FTIR.a) Felodipine; b) HPMC formulation; c) PVP formulation

Physical evaluation of film: The weight of the polymer causes the film's weight to grow as well. The films from batches LF1–LF9 were found to weigh between 94.11 and 115.45 mg. Film thickness: The thickness of the film grows along with the polymer content. For formulations LF1–LF9, the range of film thickness was 0.17–0.27 mm. It was discovered that formulation LF9 had a thickness of 0.27 mm. The film's physical consistency is indicated by the low standard deviation numbers. The folding endurance gauges a film's resistance to rupture. The manual folding endurance measurement revealed that the folding endurance of the film rises with an increase in polymer concentration. Table 4 displays the results of the folding endurance test, which put the film's value between 137 and 151. Formulation LF9's folding endurance was discovered to be 149. The films were found to have optimal folding endurance values, which translated into good mechanical and physical properties. For every formulation, the surface pH of the film was determined to be between 6.7 and 7.2; table 4 displays the results. It was discovered that formulation LF9's surface pH was 7.2. Every film had a surface pH that fell between salivary pH ranges. There was no discernible variation in the surface pH of any formulation. All of the formulations had surface pH measurements that were almost neutral, which indicates that there is less chance of irritation to the buccal mucosa and, as a result, the formulations should be rather comfortable.

Table 4: Evaluation Of Fast Dissolving Mucoadhesive Buccal Film

Formulation	Weight Variation (mg)*	Thickness (mm)*	Surface pH*	Folding Endurance*
LF1	94.11±0.08	0.17± 0.03	7.0±0.05	137±0.5
LF2	93.11±0.02	0.19± 0.01	6.7±0.02	139±0.5
LF3	97.25±0.03	0.20±0.01	7.1±0.01	141±1.7
LF4	93.28±0.03	0.22±0.05	7.0±0.05	143±0.5
LF5	95.20±0.02	0.23±0.02	7.0±0.02	146±0.5
LF6	96.56±0.02	0.24±0.05	7.2±0.01	147±0.6
LF7	97.76±0.01	0.25±0.05	7.0±0.05	147±0.5
LF8	104.01±0.01	0.24±0.04	6.9±0.01	149±1.1
LF9	115.45±0.03	0.27±0.03	7.2±0.05	151±0.5

*mean ± S.D. n = 3

Table 5: Evaluation Of Fast Dissolving Mucoadhesive Buccal Film

Formulation	Disintegration Time(sec)*	Drug Content*	Tensile Strength (N/mm^2)*
LF1	79.36±0.01	96.32 ± 1.42	11.90±0.21
LF2	78.03±0.04	97.45 ± 0.4r	16.06±0.31
LF3	77.02±0.03	99.11 ± 4.32	17.50±0.22
LF4	76.59±0.04	98.27 ± 1.43	22.91±0.15
LF5	74.04±0.04	97.59 ± 0.53	26.31±0.05
LF6	77.04±0.53	98.33 ± 5.64	34.32±0.12
LF7	72.50±0.01	97.54 ± 3.51	35.65±0.16
LF8	75.02±0.73	98.28 ± 4.75	38.87±0.24
LF9	69.11±0.32	99.86 ± 5.64	49.00±0.13

*mean ± S.D. n = 3

All batches' drug contents fell between the range of 96.32 to 99.86%, as indicated in Table 5. It was discovered that formulation LF9 had a 99.86% drug content. The fact that it was significantly closer to 100% indicates that no substance was lost throughout the film's production. The disintegration time was determined to be between 69.11 and 79.36 seconds, as indicated in Table 5.

Tensile strength study: The film's tensile strength was determined to be between 11.90 and 50.00 N/mm2. It was discovered that formulation LF9 had a tensile strength of 49.00 N/mm2. Table 5 displays the results of the tensile strength test, and Figure 2 displays the response surface plot. The surface response plot makes it evident that there was an increase in tensile strength as the amount of HPMC E15 increased. This could be because of hydrogen bonds between the drug and the polymer, as well as an increase in tensile strength when the polymer blend's PVP content increased. Two independent variables are shown in opposition to one another. The HPMC E 15 and PVP contour plot demonstrates that the tensile strength improves with the highest concentration of both substances. Figure 3 displays an interaction plot of the tensile strength, where dependent variables are shown against independent variables. Three lines are displayed; these lines indicate that HPMC E15 and PVP do not significantly interact. It suggests that the tensile strength is affected independently by two separate variables.

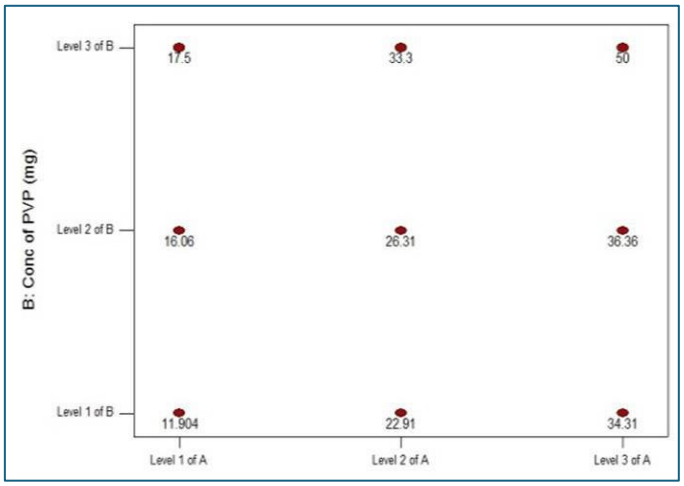

Fig. 2: Contour Plot Of Tensile Strength

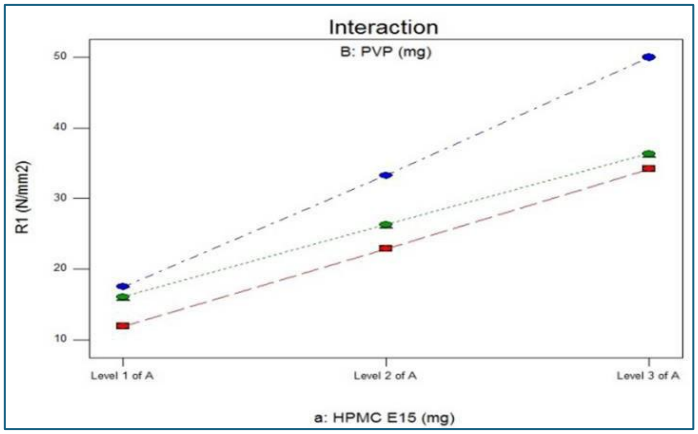

Fig. 3: Interaction Plot Of Tensile Strength

In vitro drug release studies: Table 5 and Figure 4 illustrate the drug's percentage cumulative release. At first, HPMC E15 absorbs water and gels. Based on the average of LF1-LF9, the results showed that the medication release percentage during the first five minutes was almost 50%. The drug release in the first five minutes of formulation LF1-LF3, which contains 500 mg of HPMC E15, was shown to increase from 47.06% to 49.56%. The similar outcomes with drug release of 49.98% to 50.87% and 50.98% to 52.98% were found for the LF4-LF6 (containing 550 mg HPMC E 15) and LF7-LF9 (containing 600 mg HPMC E 15). for the drug's full release, which was discovered in 40 minutes. Drug release was enhanced by these formulations because they contained higher concentrations of HPMC E15—500 mg, 550 mg, and 600 mg for LF1, LF4, and LF7, respectively. According to the comparative data, the percentage of medication release increases as HPMC E15 concentration rises. Figure 4 illustrates the initial, fast drug release from the film. The burst effect, or quick release of medication from the mucoadhesive film, may be caused by the drug's surface dissolving quickly.

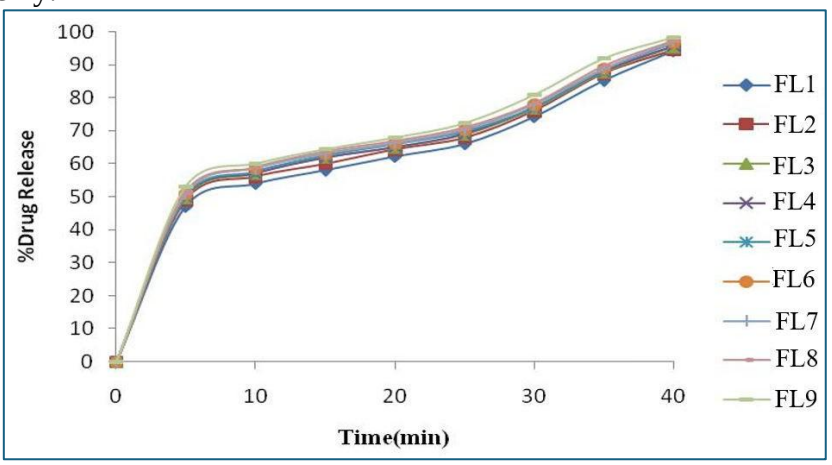

Fig. 4: % Cumulative Drug Release of all Batches

Two independent variables were displayed against one another in Figure 5 of the contour plot. The HPMC E 15 and PVP contour plot indicates that the percent drug release increases with the maximum concentration of both substances. Figure 6 displays an interaction plot showing the percentage of medication release. Three lines are displayed; these lines indicate that HPMC E 15 and PVP do not significantly interact. It suggests that two independent factors with separate effects on the percentage of drug release.

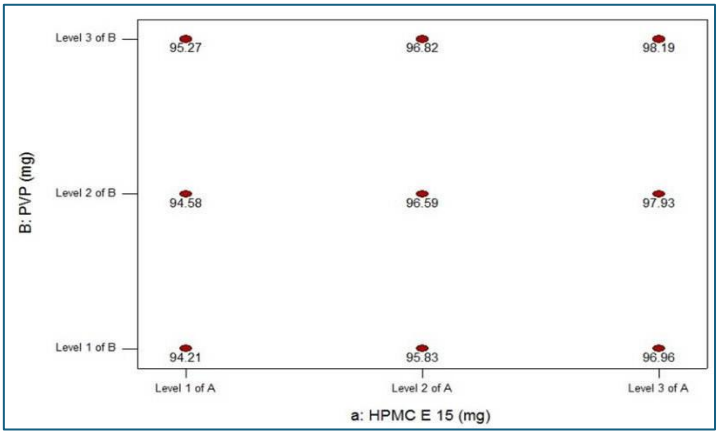

Fig. 5: Contour Plot Of % Drug Release

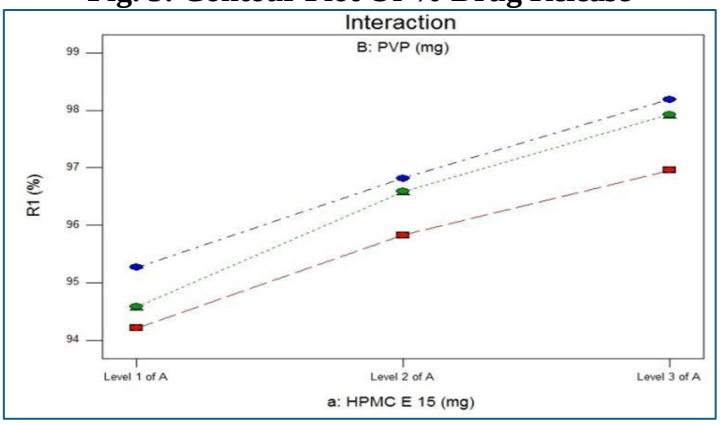

Fig. 6: Interaction Plot Of % Drug Release

Surface response plot of Tensile strength: The arithmetic mean of the nine experimental batches is b0 = 27.11. The positive X1 coefficient shows that the tensile strength increases with the concentration of X1. The positive X2 coefficient shows that the tensile strength increases with increasing X2 concentration. The fact that the X1X1 coefficient is negative means that the tensile strength is negatively impacted by the multiplicity of X1. The response surface plot shows that the positive term X2X2 implies that there is a positive effect on tensile strength when the quantity of X2 is increased. The response surface plot figure 7 shows that the positive X1X2 coefficient suggests a favourable effect on tensile strength.

$$Y1 = 27.11+12.22X1+5.29X2 - 0.124X1X1+2.64X2X2+1.74X1X2 \quad ...1$$

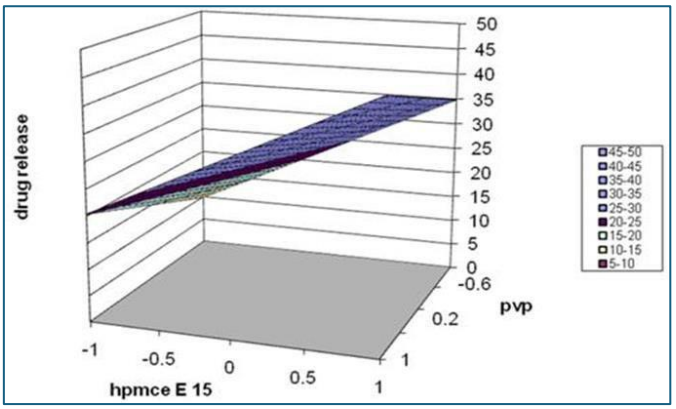

Fig. 7: Response Surface Plot For Tensile Strength

Surface response plot of % drug release: The arithmetic mean of the nine testing batches is b0 = 99.65. The positive X1 coefficient suggests that the percentage of medication release increases as X1 concentration rises. The positive X2 coefficient suggests that the percentage of medication release increases along with the X2 concentration. The fact that the X1X1

coefficient is negative means that the % drug release is negatively impacted by the multiplicity of X1 concentration. As can be observed in the response surface figure, the positive word X2X2 denotes the moment when X2 multiplied positive effect on % drug release. Figure 8 of the response surface plot shows that the positive X1X2 coefficient implies a favourable effect on the % drug release.

$$Y2=98.65+1.49X1+0.54X2 - 0.23X1X1+0.13X2X2+0.068X1X2 \quad 2$$

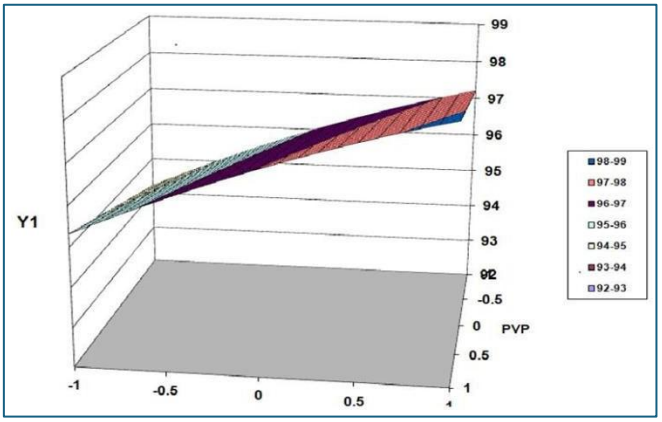

Fig. 8: Surface Response Plot Of Cumulative Drug Release

Stability Studies: In order to conduct a stability analysis, formulation batch LF9 was maintained in a stability chamber for 30 to 45 days. Samples were taken at 30 and 45 days, and the results of analyses for tensile strength, drug content, and percent drug release after 40 minutes reveal modest variations, as indicated in table 5. According to the stability investigations, formulation batch LF9 remained stable at 40°C ± 5°C and 75% relative humidity for 45 days.

Table 5: Evaluation Of Optimized Formulation LF9 For Stability

Parameters	**Time period ***		
	Before	**After 30 days**	**After 45 Days**
Disintegration time	69.11±0.32	70.17±0.23	71.32±0.05
Drug content (%)	99.86 ± 5.64	98.23±3.52	98.23±4.43

*mean ± S.D. n = 3

CONCLUSION:

Using the solvent casting approach, a fast dissolving mucoadhesive felodipine buccal film was effectively created for this study. These felodipine fast-dissolving mucoadhesive buccal films are developed to avoid side effects and first pass effects associated with high doses of the drug, while also improving the drug's bioavailability and therapeutic efficacy. Each formulation had good mucoadhesion, was free of irritation, and delivered the medication entirely by a mechanism of diffusion. Thus, it may be said that a new treatment for hypertension may be possible using the produced formulation of buccal mucoadhesive film.

REFERENCES:

1. Castán H, Ruiz MA, Clares B, Morales ME. (2014). Design, development and characterization of buccal bioadhesive films of Doxepin for treatment of odontalgia. Drug Deliv [Epub ahead of print 27 March 2014]
2. Chen JJ. (2010). Parkinson's disease: health-related quality of life, economic cost, and implications of early treatment. Am J Manag Care 16(Suppl. Implications):S87–93
3. Clarke A, Brewer F, Johnson ES, et al. (2003). A new formulation of selegiline: improved bioavailability and selectivity for MAO-B inhibition. J Neural Transm 110:1241–55
4. Connolly BS, Lang AE. (2014). Pharmacological treatment of Parkinson disease: a review. JAMA 311:1670–83

5. Ammar H.O. and Ghorab M., Polymeric matrix system for prolonged delivery of tramadol hydrochloride, part 2nd: biological evaluation, AAPS Pharmaceutical Science Technology, 2009;10(3);1065-1070.
6. Paschal M., Patel H., Bagada A.,Vadalla K., Formulation and evaluation of mouth dissolving film of ropinirole hydrochloride by using pullulan polymer, International Journal of Pharmaceutical Research and Sciences, 2012;1; 60-72.
7. K. Vijaya Sri et. al., Montelukast sodium oral thin films: formulation and In-vitro evaluation, Asian Journal of Pharmaceutical and Clinical Research, 2012; 5;266-270.
8. Shinkar D. M. et.al, UV Spectrophotometric method for the estimation of nebivolol HCL in bulk and pharmaceutical formulations, Journal of Advanced Pharmacy Education & Research, 2013;3(3);244-247.
9. Sonawane S.H. et.al, Formulation and evaluation of famotidine fast dissolving oral film, World Journal of Pharmaceutical Research, 2012;1;1095-1084.
10. Parejiya P.B. et.al, Quick dissolving films of nebivolol hydrochloride: formulation and optimization by a simplex lattice design, Journal of Pharmaceutical Investigation, 2013;43; 343-351.
11. Dalpiaz A, Contado C, Mari L, et al. (2014). Development and characterization of PLGA nanoparticles as delivery systems of a prodrug of zidovudine obtained by its conjugation with ursodeoxycholic acid. Drug Deliv 21:221–32
12. Dorsey ER, Constantinescu R, Thompson JP, et al. (2007). Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 68:384–6
13. El-Mahrouk GM, El-Gazayerly ON, Aboelwafa AA, Taha MS. (2014). Chitosan lactate wafer as a platform for the buccal delivery of tizanidine HCl: in vitro and in vivo performance. Int J Pharm 467:100–12
14. Fang JY, Hung CF, Chi CH, Chen CC. (2009). Transdermal permeation of selegiline from hydrogel-membrane drug delivery systems. Int J Pharm 380:33–9
15. Feiger AD, Rickels K, Rynn MA, et al. (2006). Selegiline transdermal system for the treatment of major depressive disorder: an 8-week, double-blind, placebo-controlled, flexible-dose titration trial. J Clin Psychiatry 67:1354–61
16. Frampton JE, Plosker GL. (2007). Selegiline transdermal system in the treatment of major depressive disorder. Drugs 67:257–65
17. Giovino C, Ayensu I, Tetteh J, Boateng JS. (2012). Development and characterisation of chitosan films impregnated with insulin loaded PEG-b-PLA nanoparticles (NPs): a potential approach for buccal delivery of macromolecules. Int J Pharm 428:143–51
18. Jaipal A, Pandey MM, Charde SY, et al. (2014). Controlled release effervescent buccal discs of buspirone hydrochloride: in vitro and in vivo evaluation studies. Drug Deliv 1–7 [Epub ahead of print 3 June 2014]
19. Jay S, Fountain W, Cui Z, Mumper RJ. (2002). Transmucosal delivery of testosterone in rabbits using novel bi-layer mucoadhesive wax-film composite disks. J Pharm Sci 91:2016–25
20. Jenner P, McCreary AC, Scheller DK. (2011). Continuous drug delivery in early- and late-stage Parkinson's disease as a strategy for avoiding dyskinesia induction and expression. J Neural Transm 118:1691–702
21. Kocbek P Obermajer N, Cegnar M, et al. (2007). Targeting cancer cells using PLGA nanoparticles surface modified with monoclonal antibody. J Control Release 120:18–26
22. Kalyan S., Bansal M., Recent trends in the development of oral dissolving film, International Journal of Pharmaceutical Technology, 2012;4;725-733.

23. Siddiqui M., Garg G., Sharma P., A novel approach in oral fast dissolving drug delivery system and their patents., Advances in Biological Research, 2011;5(6); 291-303.
24. Satishbabu B.K., et.al, Preparation and evaluation of buccoadhesive film of atenolol. Indian Journal of Pharmaceutical Sciences, 2008; 209(2);175-179.
25. Doijad R., Manvi F., Malleswara, V., Patel, P, Buccoadhesive drug delivery system of Isosorbide dinitrate: formulation and evaluation, Indian Journal of Pharmaceutical Sciences, 2006;68(6);744-748.
26. Hao J. et. al., Buccal drug delivery system, Drug Development Industrial Pharmacy, 2003;19(8);821-32.
27. Pavankumar G., Ramakrishna V., William G, Formulation and evaluation of buccal films of salbutamol sulphate, Indian Journal of Pharmaceutical Sciences,2005; 6(2);160-164.
28. Panigrahi L., Pattnaik S., Ghosal S., Design and characterization of mucoadhesive buccal patches of diclofenac sodium, Indian Journal of Pharmaceutical Sciences, 2005; 67(3); 319-335.
29. Ramana N., Nagda C., Himaja M, Design and evaluation of mucoadhesive buccal drug delivery system containing metoprolol tartrate, Indian Journal of Pharmaceutical Sciences, 2007;69(4);515-518.
30. Bharath Kumar.V.et.al, Formulation design, in vitro evaluation and stability studies on mucoadhesive buccal films of anti-anginal calcium channel blocker, Journal of Applied Pharmaceutical Science, 2011;1(6);136-142.
31. N. G. Raghavendra Rao et.al, Formulation and in-vitro evaluation of mucoadhesive buccal patches containing zolmitriptan using gel forming polymers, Der Pharmacia Sinica, 2012; 3(1); 47-57.
32. Heer D. et.al, Development of fast dissolving oral films and tablets of cinnarizine: effect of superdisintegrants, International Journal Pharmacy and Pharmaceutical Sciences, 2014; 6; 186-191.