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DESIGN AND DEVELOPMENT OF MUCOADHESIVE BUCCAL TABLETS OF LISINOPRIL DIHYDRATE BY USING QUALITY BY DESIGN

VAMSIKA R*, PALLAVI V AND G.V. RAMIREDDY

Department of Pharmaceutics, Chalapathi Institute of Pharmaceutical Sciences, Chalapathi Nagar, LAM, Guntur-522034, Andhra Pradesh, India

***Corresponding Author: Dr. Ravipati Vamsika: E Mail: vamsikaravipati58@gmail.com**

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ABSTRACT

The current research was to develop mucoadhesive buccal tablets of Lisinopril dihydrate to treat high blood pressure. Lisinopril is an ACE inhibitor that has extensive first-pass metabolism and low oral bioavailability (25%). The objective of this study is to enhance the drug's bioavailability through the application of various polymers, such as Carbopol 934p, HPMC K100M, and Chitosan, using the direct compression technique following a Quality by Design (QbD) approach. The tablets were assessed for solubility characteristics, drug-carrier interaction through FTIR and DSC analysis, as well as *in vitro* and *in vivo* drug release profiles. The formulated tablets were optimized by Box-Behnken design. The optimization of these formulations was carried out to study the effect of independent variables like Carbopol(A), HPMC K100M(B), and Chitosan(C). In this design, three responses were evaluated Mucoadhesive strength(R1), Swelling index(R2), and Drug release(R3). Every formulation exhibited significant enhancements in mucoadhesive strength, swelling index, and *in vitro* drug release. However, formulation LD BT 18 was selected as the optimized formulation due to its *in vitro* drug release, which extended for 10 hours, surpassing that of the commercially available tablet. Pharmacokinetic parameters exhibited a threefold enhancement of bioavailability of lisinopril

buccal tablets than the pure drug and marketed formulation.

Keywords: Lisinopril dihydrate, Mucoadhesive buccal tablets, Box-Behnken design, Carbopol 934p, *invitro* drug release

1. INTRODUCTION:

Compared to conventional dosage forms, mucoadhesive administration systems offer a longer period of contact at the target site, which enhances patient compliance and lowers costs **[1]**. In the process of creating sustained, prolonged, and extended-release formulations, mucoadhesive polymers have drawn a lot of interest. Because this method of drug distribution through mucosal layers avoids first-pass hepatic metabolism and shields the medication from gastrointestinal enzymes and intestinal flora destruction **[2]**.

Lisinopril dihydrate is used to treat high blood pressure. It is an ACE inhibitor that has extensive first-pass metabolism and low oral bioavailability (25%). The extent of absorption is not influenced by food. Having a half-life of approximately 12 hours and no metabolism, the drug is excreted in its unchanged form through the urine **[3, 4]**.

2. MATERIALS AND METHODS:

2.1 Materials:

Lisinopril was a gift sample from Alkem Laboratories, Bangalore. Carbopol 934p, Chitosan, and ethyl cellulose were obtained from Loba chemicals. PVP K-30 and HPMC K100M were acquired from Merck Pvt ltd. Magnesium Stearate, Mannitol, and Talc were acquired from SD Fine Chem Ltd. Stevia Powder was obtained from Zero Enthalpy Labs Pvt. Ltd.

2.2 Development of buccal tablet by design approach using design expert tool:

2.2.1 Defining the Quality Target Product Profile (QTPP):

Step 1: To establish a Quality Target Product Profile (QTPP) for the core tablets.

Step 2: Determination of the Critical Quality Attributes (CQAs) of the core tablets.

Step 3: Incorporated a risk assessment exercise to identify the Critical Processing Parameters (CPPs).

Final step: Involved drafting an informal Design of Experiments (DoE) to determine optimal settings of the CPPs for the critical high-shear dry granulation process **[5]**.

2.2.2 Procedure for Identification of the Critical Quality Attributes (CQAs):

The CQAs are the critical attributes of the buccal tablet formulation which ensures consistency in the product performance. In the current study, the CQAs identified and optimized are mucoadhesive strength, swelling index, and drug release.

2.2.3 Procedure for Identification of the Critical Material Attributes (CMAs):

CMA parameters optimized were the ratio of HPMC K100M, Carbopol 934P and Chitosan used. The CPPs studied were blending time, lubrication time, and compression time. CPPs are selected based on the process parameters whose variations can affect Critical Quality Attributes (CQAs) and should be closely regulated to ensure the desired quality is achieved **[6]**.

2.2.4 Study of risk assessment matrix:

The risk assessment matrix was performed to identify potential risks associated with material attributes and process parameters that have a potential impact on CQAs. Risk assessment matrix the proportion of polymer, binding agent, lubricant, and backing membrane was determined to have a potential impact on drug product CQAs **[7]**.

2.2.5 Development of LD by QbD approach using Box-Behnken design:

The optimization studies were conducted using the Box-Behnken statistical tool, with the assistance of Design Expert software (version). The primary factors influencing mucoadhesive strength, swelling index, and drug release in buccal tablets were identified as Carbopol 934p (A), HPMC K100M (B), and Chitosan (C). Following the Design of Experiments (DoE) methodology, a total of 17 runs were recommended. Buccal tablet formulations were then prepared and subjected to characterization, focusing on the dependent variables, namely mucoadhesive strength (R1), swelling index (R2), and drug release (R3).

The ANOVA studies were generated from the software to assess the p-values, F-ratio, and lack of fit. 3D plot predictions were done to estimate the model's accuracy. The following regression equation was used for the prediction of the responses, where R is the response A, B, and C are the response factors, and β_0, β_1, β_2, and β_3 are the coefficients of the factors.

$$R = \beta_0 + \beta_1 A + \beta_2 B + \beta_3 C + \beta_{12} AB + \beta_{23} BC + \beta_{13} AC + \beta_{11} A + \beta_{22} B + \beta_{33} C$$

Where, R= the response, A, B, and C are the independent factor, and β_0, β_1, β_2, β_3.

2.2.6 Formulation Development of LD BT:

The composition of the LD BT is shown in **Table 1**, each tablet contains 20 mg of Lisinopril Dihydrate. All the ingredients were screened through sieve no 60. The backing layer (EC) was compressed using an 8.0 mm flat-faced punch a on tablet compression machine. LD was mixed manually with different ratios of polymers such as Carbopol 934p, HPMC K-100M, and Chitosan. To this, PVP K-30(binder), Mannitol (diluent), and Stevia powder (sweetening agent) were added

and mixed for 10 min. The mixture described above was blended with Talc which is a glidant, magnesium stearate, a lubricant, for 2 minutes. Subsequently, tablets were directly compressed using an eight-station CADMACH rotary tablet-punching machine, employing the direct compression technique with 8.0 mm flat-faced punches.

Table 1: Composition of the LD BT by trial-and-error method

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17
Lisinopril Dihydrate	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Carbopol 934p	7.5	7.5	10	5	7.5	5	7.5	7.5	5	10	10	5	5	10	7.5	7.5	7.5
HPMC K100M	20	15	17.5	17.5	15	20	20	17.5	17.5	17.5	20	17.5	15	15	17.5	17.5	17.5
Chitosan	0	15	0	0	10	7.5	15	7.5	7.5	15	7.5	15	7.5	7.5	7.5	7.5	7.5
PVP K-30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Mannitol	30.5	20.5	30.5	35.5	25.5	25.5	15.5	25.2	28	15.5	20.5	20.5	30.5	25.5	25.5	25.5	25.5
Stevia Powder	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Ethyl cellulose	47	47	47	47	47	47	47	47	47	47	47	47	47	47	47	47	47
Total weight	160	160	160	160	160	160	160	160	160	160	160	160	160	160	160	160	160

3. EVALUATION TESTS:

3.1 Measurement of mucoadhesive Strength:

The *ex vivo* mucoadhesive strength of LD BT was assessed using a modified physical balance, with porcine buccal mucosa serving as the model substrate and PB (phosphate buffer) with a pH of 6.8 used as the moistening fluid. LD BT was in contact with the mucosal membrane for 5 minutes. After this duration, weights were applied to the right side of the pan to detach the tablet from the membrane, maintaining a constant weight of 100 mg for a total period of 5 minutes **[8]**. The force required to separate the tablet from the porcine buccal mucosa was recorded in grams. The temperature was maintained at 37±0.2°C throughout the study. The mucoadhesive force was calculated using the following formula:

$$N = W*g/1000$$

Where, N= is mucoadhesive force,

W=is the weight required for detachment of the tablet from the porcine buccal mucosa in grams, g = is the acceleration due to gravity at 9.81 m/sec^2

3.2 Swelling Index Study:

LD BT with a backing membrane was used for the test. Weighing each buccal tablet

separately resulted in the initial weight being recorded as W_1. Then, to guarantee total submersion in the buffer solution, the tablets were put in a petri dish filled with 5 mL of PB (phosphate buffer), which has a pH of 6.8. The buccal tablets were gently removed from the petri dish using forceps at predetermined intervals of one, two, three, four, five, six, seven, and eight hours. Any extra PB (pH 6.8) surrounding the tablet was wiped away with Whatman's filter paper. Next, the swelled tablet was weighed again (W_2), and the following formula was used to determine the degree of swelling **[9]**:

Degree of Swelling = W1*W2/W1 *100

W_1 = initial weight of tablet (gm)

W_2 = final weight of tablet (gm)

3.3 *In vitro* drug release studies:

The release of LD from buccal tablets was investigated using the USP Type-II dissolution apparatus, specifically the rotating paddle method. The dissolution medium consisted of 900 mL of PB with a pH of 6.8, and it was maintained at a constant temperature of 37±0.2°C while the paddle rotated at 25 rpm. To facilitate unidirectional drug release from the buccal tablet, the tablet's backing layer was affixed to a glass slide using adhesive, and the glass slide was positioned at the bottom of the dissolution vessel.

At pre-determined intervals, 2 mL samples were withdrawn from the dissolution medium, and an equivalent volume of buffer solution was added to maintain the volume **[10]**. Each sample was filtered through a 2µm Whatman filter paper and subsequently analyzed after appropriate dilution using a UV spectrophotometer at 210 nm.

3.4 Evaluation of *in vivo* drug release in rabbits and pharmacokinetics study:

In the *in vivo* studies, White New Zealand rabbits weighing 1.98±0.14 kg each were utilized. The rabbits were divided into two groups: Group A (LD BT18) and Group B (LD-API), each consisting of three rabbits. Before the study, the animals were subjected to an overnight fast and placed in individual cages. Anesthesia was administered to the rabbits by intradermal injection, which included 1.9 mg/kg of xylazine and 9.3 mg/kg of ketamine. Blood samples of 0.5 mL were drawn from the rabbit's ear vein at specified time intervals: 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, and 24 hours after dosing. These blood samples were collected in heparinized tubes, mixed, and then centrifuged at 4500 rpm for 5 minutes to separate the plasma. The clear supernatant plasma layer was carefully collected into Eppendorf tubes and promptly stored at -20°C until further analysis. In Group B (LD-API), a dose of 20 mg was

administered through a gastric tube using an oral gavage needle, mixed with water. Subsequently, blood samples were periodically collected, and the plasma was separated similarly.

The factors like t_{max}, C_{max}. AUC, F bioavailability, F adjusted, AUMC,and mean residence time were calculated from the obtained data from *in vivo* studies using the software **[11, 12]**.

4. RESULTS AND DISCUSSION:

4.1 Preformulation studies:

4.1.1 Fourier Transform Infra-Red (FT-IR) spectroscopy:

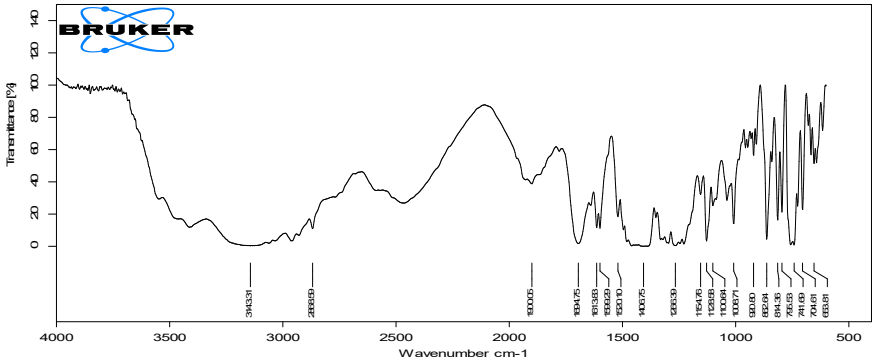


Figure 1: FTIR spectra of pure drug LD

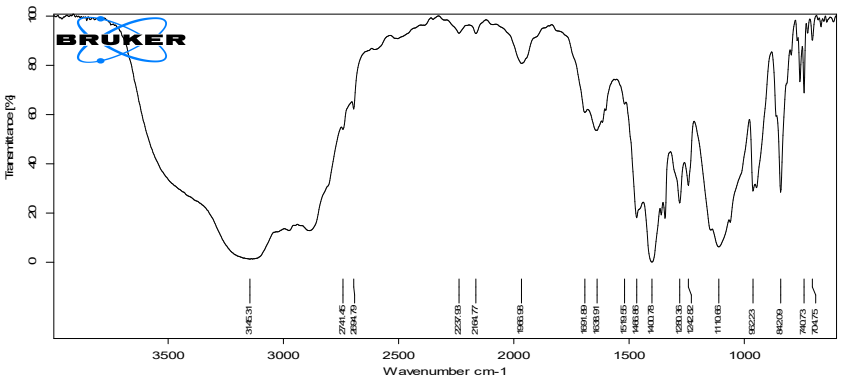
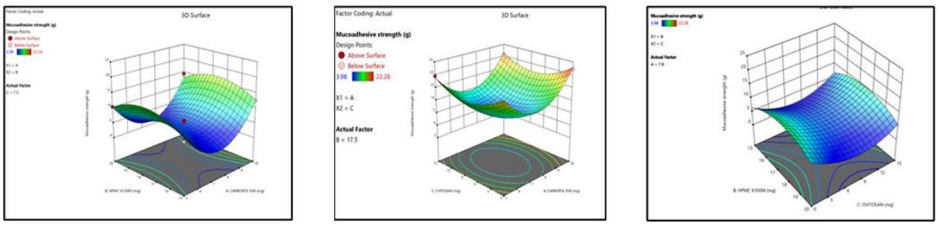


Figure 2: FTIR spectra of pure drug LD + physical mixture

4.2 Development of LD BT by QbD approach by using DoE tool:

4.2.1 Result of mucoadhesive strength for LD BT 1-17 through 3D contour plot:

The prepared LD BT from the DoE trials showed the mucoadhesive strength between 3.98 to 22.28g from the batch numbers LD BT 1 to LD BT 17.



(A) 3D plots of mucoadhesive strength with respect to HPMC K100M and Carbopol 934p

(B) 3D plots of mucoadhesive strength with respect to Chitosan and Carbopol 934p

(C) 3D plots of mucoadhesive strength with respect to HPMC K100M and Chitosan

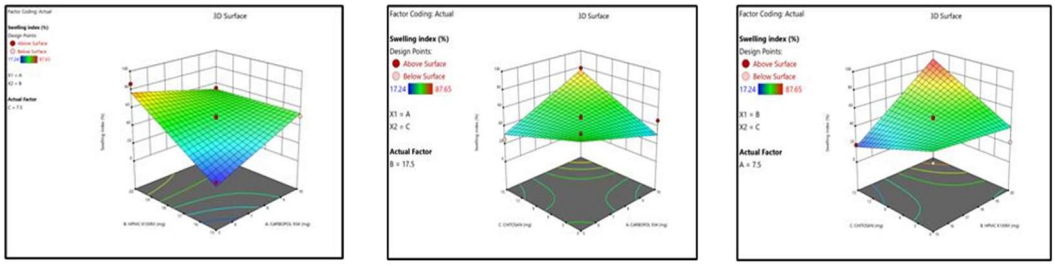
Figure 3: Results of the experimental DOE study for mucoadhesive strength LD-BT

From the above 3D images of contour plots of **Figure 3 (A),** it was observed that with an increase in polymer ratio of HPMC K100M and Carbopol 934p from 5 to 10 mg the mucoadhesive strength was also increased from 3.98 to 22.28 g as shown in **Table 2**. Similarly, **Figure 3 (B)** demonstrates that with the increased ratio of Chitosan and Carbopol 934p, the mucoadhesive strength was also increased but there is not much significant impact. **Figure 3 (C)**, shows there was no significant impact on the polymer ratio between HPMC K100M and Chitosan. The final equation was generated in the coded form by the software given below.

$$R_1=5.13+1.37A+0.21B-0.54C-0.01AB-0.17AC-0.57BC+10.40A^2-4.06B^2+5.20C^2$$

4.2.2 Result of a swelling index for LD BT 1-17:

The prepared LD BT from DoE trials showed a swelling index between 17.24 to 87.65%.



(A) 3D plots of swelling index with respect to HPMC K100M and Carbopol 934p

(B) 3D plots of swelling index with respect to Chitosan and Carbopol 934p

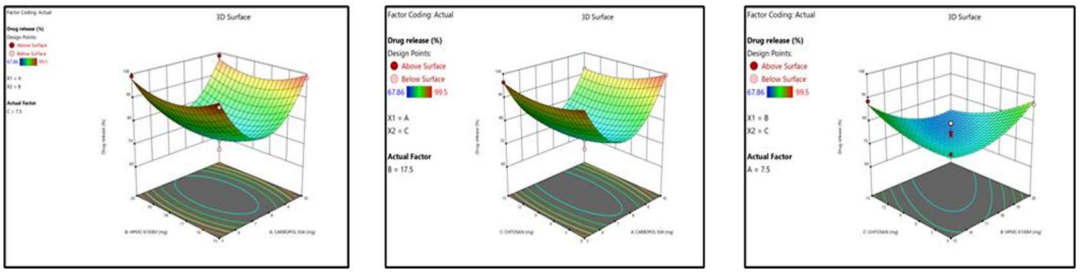
(C) 3D plots of swelling index with respect to HPMC K100M and Chitosan

Figure 4: Results of the experimental DOE study for swelling index LD-BT

Analysis of the 3D contour plots in **Figure 4 (A)** reveals that as the polymer ratio of HPMC K100M and Carbopol 934p increases, the swelling index also increases, ranging from 17.24% to 87.65%. However, this increase does not have a significant impact, as indicated in **Table 2**. Likewise, **Figure 4 (B)** illustrates that an increase in the ratio of Chitosan and Carbopol 934p leads to an increase in mucoadhesive strength. In **Figure 4 (C),** it is observed that as the polymer ratio between HPMC K100M and Chitosan increases, there is a corresponding increase in swelling properties. The final equation, generated by the software, is presented in coded form below:

$$R_2=49.26+4.51A+15.77B-4.77C-16.32AB+18.48AC+20.76BC$$

4.2.3 Result of drug release for LD BT 1-17: The prepared LD BT from DoE trials showed the drug release between 67.86 to 99.5%.



(A) 3D plots of drug release with respect to HPMC K100M and Carbopol 934p

(B) 3D plots of drug release with respect to Chitosan and Carbopol 934p

(C) 3D plots of drug release with respect to HPMC K100M and Chitosan

Figure 5: Results of the experimental DOE study for drug release LD-BT

From the above 3D images of contour plots **Figure 5(A)** it was observed that with an increase in polymer ratio of HPMC K100M and Carbopol 934p, the release of the drug increased from 67.86 to 99.5 % as shown in **Table 2**. Similarly, **Figure 5 (B)** demonstrates that with an increase in the ratio of Chitosan and Carbopol 934p the drug release increased.

Figure 5 (C), shows that there is a change in polymer ratio between HPMC K100M and Chitosan, but there was no change in drug release. The final equation was generated in the coded form by the software given below.

$$R_3=73.58-0.22A-1.10B-1.88C-0.22AB-1.56AC-5.99BC+19.73A^2+5.20B^2+3.14C^2$$

Table 2: Results of data obtained from experimental DoE Study of LD BT 1-17

	Factor 1	Factor 2	Factor 3	Response1	Response 2	Response 3
	Independent variable			Dependent variable		
Run	CARBOPOL 934 p (mg) (A)	HPMC K100M (mg) (B)	CHITOSAN (mg) (C)	Mucoadhesive strength (gm)	Swelling index (%)	Drug release(%)
1	7.5	20	0	6.74	22.86	87.24
2	7.5	15	15	6.94	19.56	88.59
3	10	17.5	0	22.28	46.57	99.5
4	5	17.5	0	20.48	66.36	97.25
5	7.5	15	0	6.66	37.82	80.29
6	5	20	7.5	10.43	86.4	99.05
7	7.5	20	15	4.73	87.65	71.58
8	7.5	17.5	7.5	5.84	50.77	75.26
9	7.5	17.5	7.5	5.28	47.01	79.25
10	10	17.5	15	20.64	79.35	92.54
11	10	20	7.5	14.44	54.65	98.59
12	5	17.5	15	19.53	25.24	96.54
13	5	15	7.5	8.47	17.24	98
14	10	15	7.5	12.53	50.78	98.42
15	7.5	17.5	7.5	5.96	48.58	73.58
16	7.5	17.5	7.5	3.98	49.35	67.86
17	7.5	17.5	7.5	4.57	47.23	71.95

4.3 Optimized formula by QbD for the preparation of the LD BT:

Table 3: Results of predicted formulation by QbD

RBOPOL934P (gm)	HPMCK100M (gm)	CHITOSAN (gm)	Mucoadhesivestrength (gm)	Swellingindex (%)	Drug release (%)	Desirability
10.000	17.753	15.000	21.314	79.066	92.106	0.861

4.4 Results of characterization of optimized LD BT 18:

4.4.1 Results of mucoadhesive strength of optimized LD BT 18:

Mucoadhesive strength is considered a Critical Quality Attribute (CQA), and any alterations in concentration can potentially affect mucoadhesive strength. In terms of Mucoadhesion order, the polymers rank as follows: **HPMC K100M < Chitosan < Carbopol 934p (Table 4, Figure 6)**.

4.4.2 Results of the swelling index of optimized LD BT 18:

Typically, when tablets swell, the process begins with the outermost hydrophilic polymer layer, which hydrates and swells initially. This hydrated layer then gradually dissolves or disperses. The study provides clear evidence that the choice of polymer ratios established through the Quality by Design (QbD) approach can indeed influence the swelling index and the rate at which the tablet disperses in water **(Table 5, Figure 7)**.

Table 4: Mucoadhesive strength of optimized formulation of LD BT 18.

Variables	Predictedresponse	Observedresponse	% Predictederror (% PE)	Acceptance criteria for % PE
lucoadhesivestrength (gm)	21.31	22.28	±0.35	Less than 5.0 %

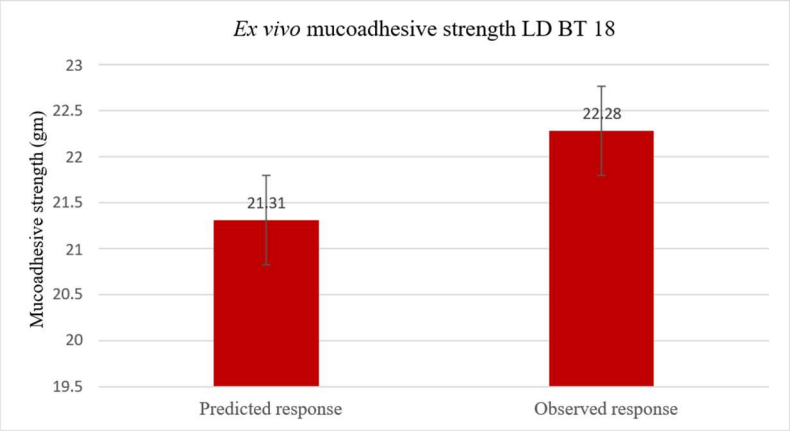


Figure 6: Graphical representation of mucoadhesive strength for optimized LD BT 18

Table 5: Swelling index of optimized formulation of LD BT 18

Variables	Predictedresponse	Observed response	% Predictederror (% PE)	Acceptance criteria for % PE
Swellingindex (%)	79.06	79.35	±0.35	Less than 5.0 %

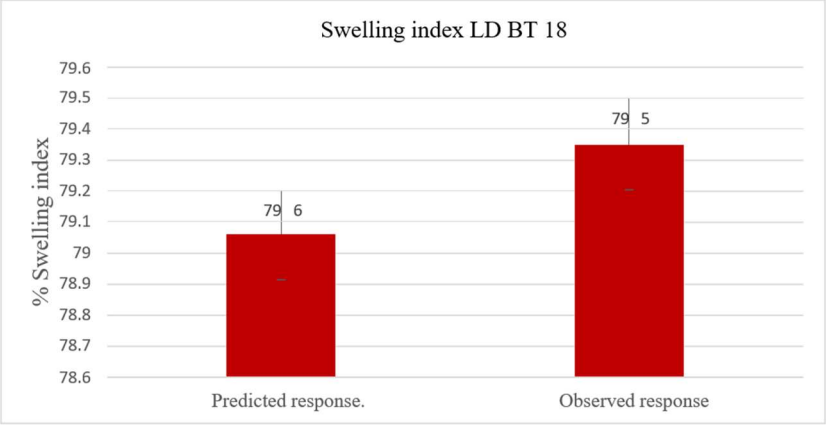


Figure 7: Graphical representation of swelling index for optimized LD BT 18

4.4.3 Results of *in vitro* drug release of optimized LD BT 18:

The drug release was determined to be 98.4%, which closely aligned with the anticipated response of 92.10% as projected by the Quality by Design (QbD) approach. The percentage error was calculated to be ±4.12%, which is below the 5% threshold and therefore within the acceptable range.

Table 6: Evaluation of *In vitro* drug release of optimized formulation of LD BT 18

Time (hrs)	1	2	3	4	5	6	8	10
Drug release -LD BT 18(%)	14.4 ± 2.22	22.2 ± 1.89	37.3 ± 2.19	48 ± 3.48	60.2 ± 4.17	78.4 ± 2.44	89.7 ± 3.64	98.4 ± 4.12

Table 7: *In vitro* drug release of optimized formulation of LD BT 18

Variables	Predictedresponse	Observed response	% Predictederror (% PE)	Acceptance criteria for %PE
Drug release (%)	92.10	98.4	±4.12	Less than 5.0 %

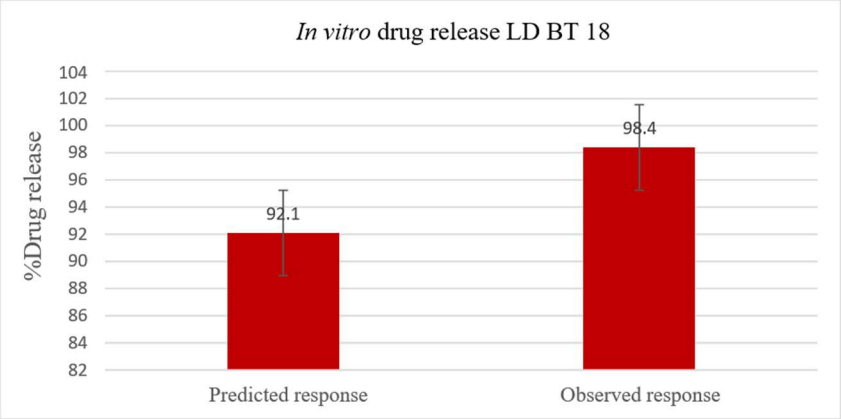


Figure 8: Graphical representation of *in vitro* drug release for optimizedLD BT 18

The *in vitro* dissolution of the marketed product was performed and was compared with the optimized LD BT 18. The marketed tablet released the drug completely at 8thhr, but the LD BT 18 sustained the drug release up to 10thhr. The polymers such as HPMC K100M have slow erosion of drug release; Carbopol 934p sustains the drug release behavior and Chitosan influences the retention time of the formulated buccal tablet**.** This could be a possible approach to avoid the first-pass metabolism upon buccal administration. Swelling of the mucoadhesive tablet to the optimum extent is crucial to ensure the prolonged and steady release of the drug with successful Mucoadhesion.

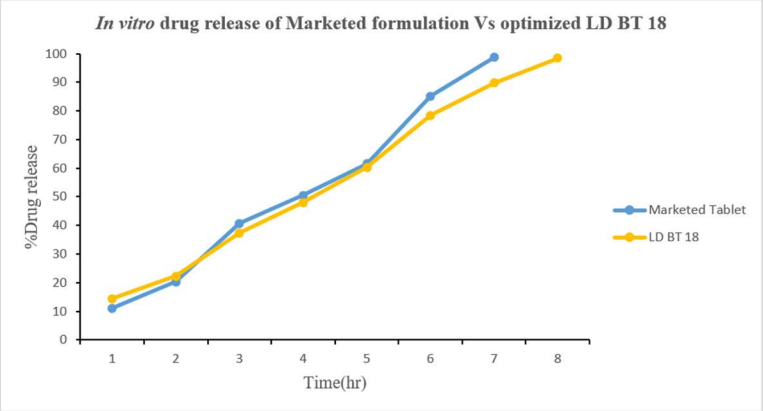


Figure 9: Comparative *in vitro* release of optimized LD BT 18 with the marketed product

4.4.4 Results of evaluation of LD blend for the buccal tablet (LD BT 18):

Table 8: Evaluation of flow properties of LD BT 18 blend

Formulation Code	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Carr's compressibility index
LD BT 18	36.5 ± 0.2	0.46± 0.08	0.60± 0.08	1.30	23.33

4.4.5 Results of quality control tests for LD BT 18:

Table 9: Quality control tests for LD BT 18

F Code	Uniformityof weight (mg) mean ±SD(n= 20)	Thickness (mm) mean ±SD (n= 5)	Hardness ($Kg/cm^{2)}$ mean ±SD (n= 5)	Friability (%) mean ±SD (n=10)	Disintegration time (min)	Drug content (mg)
F18	163.42 ±7.5	2.24± 0.02	4.65±0.68	0.54±0.01	226.67 ± 1.21	18.6±0.64

4.4.6 Results of Stability Studies for LD BT 18:

LD BT 18 underwent a stability study in which the sample was stored in a humidity chamber at 25°C ± 2°C and 60% RH ± 5% for six months. The sample was evaluated at 0, 1, 2, 3, and 6 months to assess any alterations in various parameters, including physical appearance, weight variation (mg), thickness (mm), hardness (Kg/cm^2), friability (%), and drug content (mg), following the ICH guidelines for the stability testing of new drug substances and products **(Q1A) (R2) (ICH 2003)**. The results indicated that there were no significant changes during the storage period.

Table 10: Results of the stability studies for LDBT 18

Description	Storage conditions (25°C ± 2°C/60% ± 5% RH)				
	Initial	After 1 month	After 2 months	After 3 months	After 6 months
Physical appearance	Off-white color tablet	Off-white color tablet	Off-white color tablet	Off-white color tablet	Off-white color tablet
Hardness (Kg/cm^2)	4.65±0.68	4.64±0.61	4.54±0.68	4.57±0.61	4.54±0.62
Friability (%)	0.54±0.12	0.51±0.12	0.52±0.12	0.54±0.12	0.54±0.12
Thickness (mm)	2.24±0.02	2.24±0.02	2.24±0.02	2.23±0.02	2.24±0.02
Weight variation(mg)	159.42±7.5	159.22±7.5	159.24±7.5	159.51±7.5	159.39±7.5
Drug content (mg) labeled claim	18.6±0.52	18.1±0.02	18.4±0.11	18.2±0.46	18.1±0.02

4.4.7 *In vivo* Studies for Drug Release Study for LD BT 18:

The % drug absorption in rabbits, it was found that the API of the drug was absorbed till 12 hrs whereas the formulated drug was absorbed till 20 hrs.

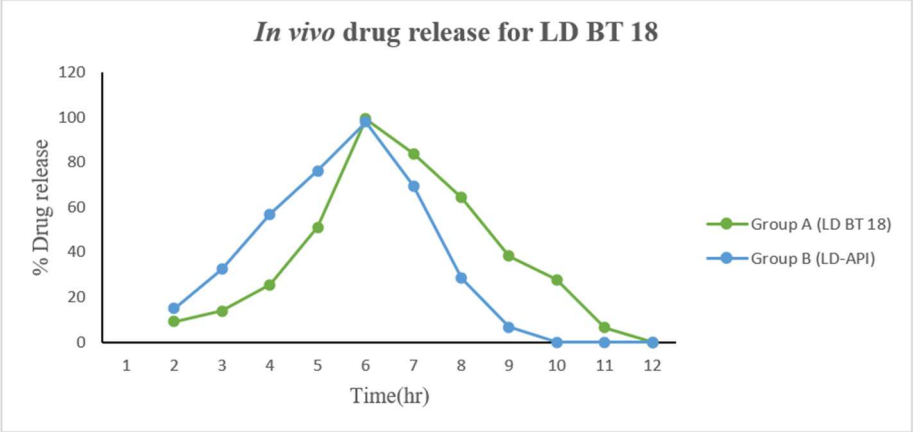


Figure 10: *In vivo* drug release study LD BT 18

5. CONCLUSION:

The current study focuses on developing a buccal tablet for Lisinopril dihydrate, tailored to provide sustained drug release for the treatment of hypertension. The optimized LD BT 18 blend displayed a bulk density of 0.46 ± 0.08 gm/cm^3 and a tapped density of 0.60 ± 0.08 gm/cm^3. The Hausner's ratio for the blend was 1.30, and the Carr's compressibility index was 23.33%. The drug release data for LD BT 18 was analyzed using various kinetic models, and the highest linearity was achieved with an R^2 value of 0.9903. The release component 'n' was determined to be 1.0200, indicating a non-Fickian super case II diffusion mechanism. This suggests that drug release from the prepared tablets occurs through a combination of stress-induced effects, swelling, and slow erosion of the polymer.

In the stability study, the optimized formulation of Lisinopril dihydrate was found to be stable, with no significant changes observed. *In vivo,* studies conducted on rabbits demonstrated that the pharmacokinetic parameters exhibited a threefold enhancement in the bioavailability of Lisinopril buccal tablets compared to the pure drug and the marketed formulation.

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7. REFERENCES:

[1] Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P, Bannerjee SK. Drug delivery systems: An updated review. International journal of pharmaceutical investigation.2012 Jan; 2(1):2-11.

[2] Madhav NS, Shakya AK, Shakya P, Singh K. Oro transmucosal drug delivery systems:a review. Journal of controlled release. 2009 Nov 16;140(1):2-11.

[3] Viswanadhan PV, Padole A, Abraham A, Mathew ST, Buccal tablets of Lisinopril by direct compression method for buccal drug delivery, Intl. R. J. of Pharmaceuticals, 2(2), 2012, 30-38.

[4] Prasanth VV, Mudiyala S, Mathew ST, Kamalakkannan V, Mathappan R, Mucoadhesive tablets of lisinopril for buccal drug delivery: Development and characterization, Drug Invention Today, 3(5), 2011, 49-51.

[5] Aksu B, Mesut B. Quality by design (QbD) for pharmaceutical area. Journal of Faculty of Pharmacy of Istanbul University. 2015 Jan 1;45(2):233-251.

[6] Borde SD, Shahi SR, Kale KV, Jadhav AC, Parakh DR. Formulation and evaluation ofPaliperidone HCl mouth dissolving tablet by QbD approach. Pharmaceutical and Biological Evaluations. 2016;3(6):528-540.

[7] Vora R, Shah Y. Investigation of Quality Target Process Parameters (QTPP) And Critical Material Attributes (CMA) of Nanocellulose as A Potential Excipient. International Journal of Applied Pharmaceutics. 2019 Jul 7:386-395.

[8] Lodhi M, Dubey A, Narayan R, Prabhu P, Priya S. Formulation and evaluation of buccal film of Ivabradine hydrochloride for the treatment of stable angina pectoris. International journal of pharmaceutical investigation. 2013 Jan;3(1):47-53.

[9] Sunitha M, Padma A, Balaji B, Krishna VR. Formulation and *in vitro* evaluation of buccal mucoadhesive tablets of Chlorpheniramine Maleate. International Journal of Pharmaceutical, Chemical & Biological Sciences. 2014 Jul 1;4(3):457-462.

[10] Patil BS, Motagi AM, Kulkarni U, Hariprasanna RC, Patil SA.

Development and evaluation of time-controlled pulsatile release Lisinopril tablets. Journal of Pharmaceutical Science and Bioscientific Research. 2012 Feb; 2:30-5.

[11] Patel H, Panchal DR, Patel U, Brahmbhatt T, Suthar M. Matrix type drug delivery system: A review. J Pharm Sci Biosci Res. 2011 Nov;1(3):143-151.

[12] Shivanand K, Raju SA, Nizamuddin S, Jayakar B. *In vivo* bioavailability studies of sumatriptan succinate buccal tablets. DARU: Journal of Faculty of Pharmacy, Tehran University of Medical Sciences. 2011;19(3):224.