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Development and Optimization of Fast Dissolving Tablets of Losartan Potassium Using Natural Gum Mucilage

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Abstract Current research work involves preparation of fast dissolving tablets of Losartan Potassium by direct compression method using different concentrations of *Plantago ovata* and *Lepidium sativum* mucilage as natural superdisintegrants. A two factor three level (3^2) factorial design is being used to optimize the formulation. Nine formulation batches (A1-A9) were prepared by taking two factors as independent variables (X_1- amount of *Plantago ovata* mucilage and X_2- amount of *Lepidium sativum* mucilage) were taken with three levels (+1, 0, -1). All the active blends were evaluated for precompression parameters (angle of repose, bulk density, carr's index, hausner's ratio) and formulated tablets were evaluated for post compression parameters (hardness, friability, weight variation, wetting time, disintegration time, water absorption ratio). *In vitro* drug release studies were carried out using USP II dissolution apparatus for 30 min. The software Design Expert (8.0.7.1) was used for generating experimental design, modeling the response surface and calculating the statistical evaluation. Tablet parametric tests of formulation batches (A1-A9) of FDT were found within prescribed limits. DT was observed in the range from 12±2 to 58.7±2.52 sec and WT from 10.3±1.52 to 49.7±5.13 sec for formulation batches (A1-A9). More than 87% drug release was observed in all formulation batches (A1-A9) within 15 minutes. Polynomial mathematical models, generated for various response variables using multiple linear regression analysis, were found to be statistically significant ($P < 0.05$). Formulation A7 was selected by the design expert software which exhibited DT (22.15sec), WT (17.31sec) and *in vitro* drug release (100%) within 15 minutes.

Keywords: Disintegration time, wetting time, factorial design, *plantago ovata*, *lepidium sativum*

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1. INTRODUCTION

Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical industries to survive, regardless of their size. Recent advances in novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance i.e., one, which will rapidly disintegrate in the mouth without need of water (fast dissolving tablet). Fast dissolving tablets has emerged as alternative oral dosage forms which is a major concern in the treatment of hypertension, diabetics and other diseases where they offer advantages over older formulation in terms of convenience, side-effect profiles, efficacy/ or a fast onset of action (Shirsand *et al*, 2006). The basic approach used in the development of FDT is the use of superdisintegrants (synthetic or natural) which lead to instantaneous disintegration of tablet after putting on tongue, thereby releasing the drug in saliva (Bhowmik *et al*, 2009). Mucilage and gums have been widely used in the pharmaceutical industries as thickeners, water retention agents, and emulsion stabilizers, suspending agents, binders and film formers. Mucilage of natural origin is preferred over synthetic compounds because they are cheaper, nontoxic and nonirritating in nature and easily available (Malik *et al*, 2012; Sharma *et al*, 2013). *Lepidium sativum* (Family: Cruciferae) is known as asaliyo and widely used as herbal medicine in India. It is widely available in market and has very low cost. The seeds contain higher amount of mucilage, dimeric imidazole alkaloids lepidine B, C, D, E and F and two new monomeric imidazole alkaloids semilepidinoside A and B. Mucilage of *Lepidium sativum* has various characteristic like binding, disintegrating, gelling etc (Patel *et al*, 2007). Ispaghula mucilage consists of epidermis of the dried seeds of *Plantago ovata* (Family: Plantaginaceae). It is mainly used as a dietary fibre. Psyllium mucilage absorbs excess water and is also reported as superdisintegrants (Shirsand *et al*, 2009). Losartan Potassium is an angiotensin II receptor antagonist used in the management of hypertension with half-life of approximately 1.5-2 h. The bioavailability of Losartan Potassium is poor (about 25-35%) which is due to extensive first pass metabolism (Avulapati *et al*, 2011). Present study involves the development of fast dissolving tablets of losartan potassium using 3^2 factorial design. The effect of amount of independent variables (*Plantago ovata* and *Lepidium sativum* mucilage) on dependent variables such as disintegration, wetting characteristics and time for 85% drug release ($T_{85\%}$) was evaluated.

2. MATERIALS AND METHODOLOGY

2.1 Materials

Losartan Potassium and Avicel PH-102 (Ontop Pharmaceutical Pvt. Ltd. Bangalore, India); Pearlitol 200 D (Signet chemical corporation Pvt. Ltd. Mumbai, India); Aspartame (IPZA Pharmaceutical Pvt. Ltd. Patiala, India) were obtained as gift samples. Seeds of *Plantago ovata* and *Lepidium sativum* were purchased from local market. All other chemical used were of analytical grade.

2.2 Methods

2.2.1 *Extraction of mucilage*

Isolation of Mucilage from Plantago ovata seeds: The seeds of *Plantago ovata* were soaked in distilled water for 48 h and then boiled for 1 h for complete release of mucilage into water and then filtered by squeezing in a muslin cloth to remove marc followed by addition of equal volume of acetone to precipitate the mucilage. The mucilage was separated and dried in oven at a temperature NMT 60 ± 2°C, powered and sieved (80 #), weighed and stored in desiccator until further use (Washi *et al*, 1985; Baveja *et al*, 1989; Chakraborthy *et al*, 2008).

Isolation of Mucilage from Lepidium sativum seeds : The seeds of *Lepidium sativum* contain the mucilage around the outer layer. The seeds were boiled with distilled water for 15 minute and the mass was filtered through buckner funnel without filter paper and the retained residues were boiled with distilled water for 15 minute and the combined liquid was passed through eight folds of muslin cloth. Then the mucilage was precipitated from the filtrate by adding ethanol (sufficient to cause precipitation). The precipitated mucilage was dried in oven at temperature NMT 45±2°C till it was completely dried. The powder was sieved through 80 #, weighed and stored in desiccator until further use (Hasegawa *et al*, 1992).

2.2.2 *Preparation of fast dissolving tablets (preliminary batches)*

Fast dissolving tablets (F1-F10) of Losartan potassium were prepared using direct compression method. All the ingredients were taken in sufficient quantity and passed through sieve no. 60. Then all the ingredients were co-grinded in a mortar and pestle and lubrication was done using talc and magnesium stearate. The two mucilages were used in 1%, 3%, 5%, 7% and 9% individually (i.e. F1-F5 using *Plantago ovata* mucilage and F6-F10 using *lepidium sativum*

mucilage). Single punch tablet compression machine was used to produce convex faced tablets weighing 140 mg each with a diameter of 8mm. The Composition of preliminary batches is given in Table 1.

Table 1. Composition of Preliminary batches (F1-F10)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Losartan potassium (LP)	25	25	25	25	25	25	25	25	25	25
Plantago ovata mucilage (PO)	1.4	4.2	7.0	9.8	12.6					
Lepidium Sativum mucilage (LS)						1.4	4.2	7.0	9.8	12.6
Avicel PH-102	75	75	75	75	75	75	75	75	75	75
Mannitol	33.6	30.8	28	25.2	22.4	33.6	30.8	28	25.2	22.4
Aspartame	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1	1	1

*All the ingredients are expressed in mg

2.2.3 *Evaluation of preliminary batches (F1-F10)*

The preliminary batches were evaluated for precompression parameters (Bulk density, Tapped density, Angle of repose, Carr's index, Hausner's ratio), post compression parameters (friability, hardness, weight variation, disintegration time, wetting time, water absorption ratio) and *in vitro* dissolution studies.

2.2.4 *Preparation of final batches using 3^2 factorial design*

A 3^2 factorial design was constructed using two independent variables X_1 (amount of *Plantago ovata* mucilage) and X_2 (amount of *Lepidium sativum* mucilage) and their effect on disintegration time, wetting time and percent cumulative release was determined. Each factor was tested at three levels (-1, 0, +1) indicating low, medium and high values. The levels were selected on the basis of preliminary studies. Design Expert (8.0.7.1) was used for generating experimental design, modeling the response surface and for statistical evaluation.

2.2.5 *Evaluation of Final Batches (A1-A9)*

2.2.5.1 Precompression Parameters

Angle of Repose: It is an indicative of the flow properties of the powder. Angle of repose is determined by the following formula

$$\text{Tan } \theta = h/r,$$

Where h is the height of the cone in cm and r is radius of the cone base in cm.

Bulk Density: Bulk density (D_b), is defined as the mass of the powder divided by the bulk volume. It is expressed in g/ml and is given by

$$D_b = M/V_b$$

Where M is weight of powder in g, V_b is bulk volume of powder in cm^3

Tapped Density: It is the ratio of total mass of the powder to the tapped volume of the powder. It is expressed in g/cm^3 and is given by

$$D_t = M/V_t$$

Where M is weight of powder in g and V_t is the tapped volume of powder in cm^3

Carr's Index: It indicates powder flow properties. It is expressed in percentage and is given by

$$I = D_t\text{-}D_b/D_t * 100$$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder

Hausner's Ratio: Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = D_t/D_b$$

Where, D_t is the tapped density; D_b is the bulk density

2.2.5.2 Post compression Parameters

Diameter and Thickness: A calibrated vernier caliper was used to evaluate diameter and thickness of the tablets. Tablet thickness should be controlled within a ±5% variation of a standard value.

Hardness: Hardness was measured using Monsanto tablet hardness tester. A tablet of hardness of about 3-5 kg/cm^2 is considered adequate for mechanical stability.

Weight variation test: The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch.

Friability test: Roche friabilator was employed to evaluate the friability of the tablets. Percent loss in weight was calculated by following formula:

$$\% \text{ Friability} = [(W_1 - W_2)100]/W_1$$

Where, W_1 and W_2 is the Weight of tablet before and after test

Disintegration Test: The disintegration time for all formulations was evaluated using USP tablet disintegration test apparatus as specified in USP.

Wetting Time: To determine the wetting time, five circular tissue papers of 10 cm diameter were placed in a petridish containing 0.2% w/v solution of eosin (3ml). A tablet was carefully placed on the surface of the tissue paper. The time required for developing reddish color on the upper surface of the tablets was noted as the wetting time or the time for complete wetting of the tablet was measured in seconds.

Water Absorption Ratio: A small piece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then reweighed. Water absorption ratio, R was determined by using following formula.

$$R = 100 \times (W_a - W_b / W_b)$$

W_b and W_a is the weight of tablet before and after water absorption respectively.

2.2.5.3 Fourier Transform Infrared Spectroscopy (FTIR)

IR spectra of pure drug, both mucilage powders and formulation batch were determined using FTIR spectrophotometer (Perkin Elmer Spectrum 400) by KBr pellet method. About 10 mg of sample was mixed with dried potassium bromide of equal weight. The mixture was properly grinded using pestle and mortar. Pellets were formed by compressing the mixture by using hydraulic press. Transparent pellets formed in this way are scanned. The spectra are scanned over a frequency range of 4000-400cm^{-1}.

2.2.5.4 In vitro Dissolution Test

All the formulations (A1-A9) were subjected to *in vitro* drug release studies using eight stage dissolution test apparatus (DISSO 2000, Lab India) using 900ml of dissolution medium (pH 6.8 phosphate buffer) maintained at 37±10°C for 60 minutes. The tablets were kept in the cylindrical basket and rotated at 50 rpm. Aliquots were withdrawn at specified time intervals (5, 10, 15, 30, 45 and 60 minutes) and absorbance of the samples was measured using UV spectrophotometer (Systronics, India) at 210 nm. Cumulative percent drug release was then calculated. The dissolution studies were performed in triplicate and expressed as mean± SD.

3. RESULTS AND DISCUSSION

3.1 Evaluation of Preliminary Batches (F1-F10)

3.1.1 *Precompression Parameters*

The results of bulk density and tapped density were ranged from (0.464 to 0.543 g/cc) and (0.522 to 0.627 g/cc) respectively. The results of angle of repose (11.3° to 29.7°) indicate good flow properties which were further supported by Carr's index values (11.14% to 13.33%) and Hausner's ratio data (1.12 to 1.19). The results of precompression parameters are given in Table 2.

Table 2. Results of Pre-compression parameters of preliminary batches (F1-F10)

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Bulk density (g/cc)	0.499	0.464	0.521	0.492	0.468	0.501	0.528	0.512	0.543	0.521
Tapped density (g/cc)	0.573	0.522	0.595	0.557	0.531	0.599	0.609	0.585	0.627	0.599
Angle of repose (°)	27.14	28.88	29.7	25.9	27.66	13.99	11.30	12.49	13.33	11.87
Carr's index (%)	12.9	11.14	12.43	11.75	11.86	11.9	13.32	12.49	13.33	13.02
Hausner's ratio	1.14	1.12	1.14	1.13	1.13	1.19	1.15	1.13	1.15	1.14

3.1.2 *Fourier Transform Infrared Spectroscopy (FTIR)*

FTIR of pure drug, *Plantago ovata* and *Lepidium sativum* mucilage and formulation batch (F1) are shown in Figures 1, 2,3 and 4 respectively. The presence of characteristics peaks of drug OH (3198 cm^{-1}), CH Stretching Aromatic (3034 cm^{-1}), CH Stretching Aliphatic (2956 cm^{-1}) C=0 (1642 cm^{-1}), C=C (1578 cm^{-1}), C-O-C Ether Linkage (1189 cm^{-1}) in IR spectrum of formulation (Figure 4), indicated no interaction of drug with the polymer and other excipients.

3.1.3 *Postcompression Parameters*

The prepared tablets from all formulations possessed good mechanical strength with sufficient hardness in the range of (2.6 ±0.2 kg/cm^2 to 3.07 ±0.06 kg/cm^2). Friability values below 1% indicated good mechanical resistance of tablets. All

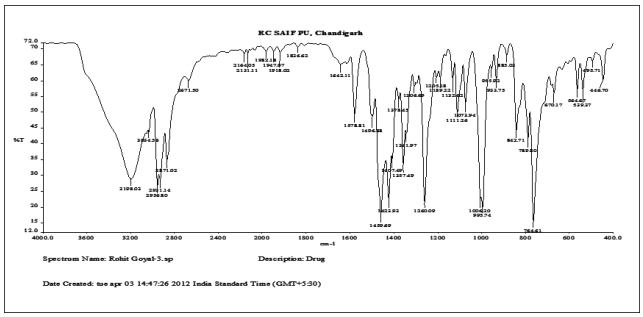

Figure 1. FTIR spectra of pure drug (Losartan Potassium)

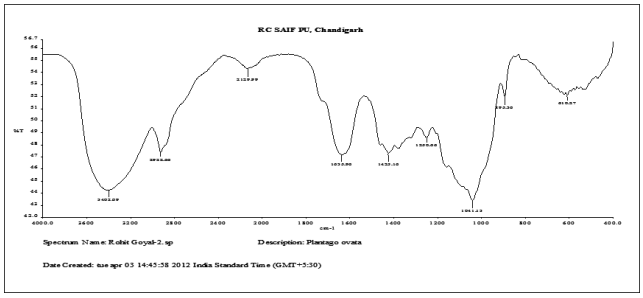

Figure 2. FTIR spectra of Plantago ovata mucilage powder

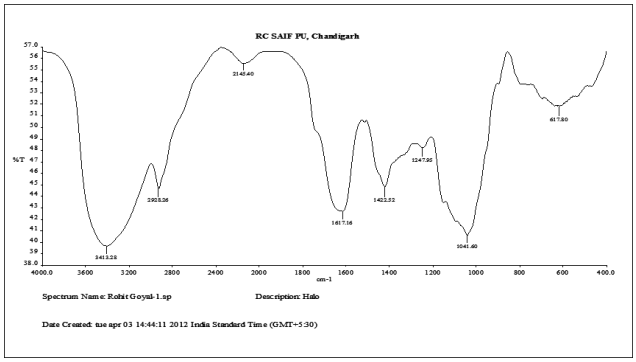

Figure 3. FTIR spectra of Lepidium Sativum mucilage powder

tablet batches passed weight variation test as % weight variation was within pharmacopoeial limits. All the batches showed wetting time in the range of (10.33±1.52 sec to 23±1.73 sec). Disintegration time (DT) value of less than 1 min was observed in all formulations and it varied between (14.7±2.51 sec to

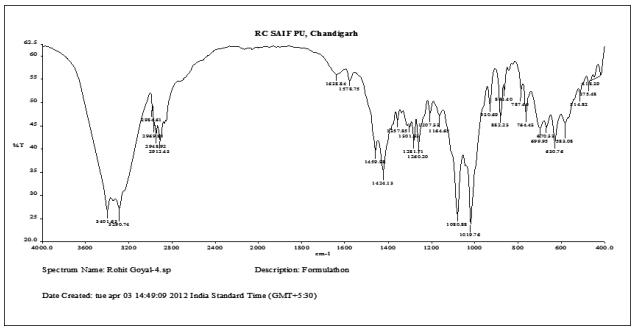

Figure 4. FTIR spectra of formulation batch

53.7±2.89 sec). All the formulation batches showed water absorption ratio in the range of (110.3±1.52 % to131.7±2.08%). Disintegration time was decreased with increasing amount of superdisintegrant *Plantago ovata mucilage* (batch F1 to F4) and (batch F6 to F9). Further increase in concentration of mucilage (9% *Plantago ovata* in batch F5 and 9% *Lepidium sativum* in batch F10) leads to increase in DT. This may be due to formation of viscous plugs at higher concentration of the mucilage. The same was observed in batches containing *Lepidium Sativum* mucilage (batch F6- F10). The results of post compression parameters are given in Table 3.

Table 3. Results of post compression parameters of preliminary batches (F1-F10)

Code	Weight variation	Hardness (Kg/cm^2)	Wetting time (WT) (Sec)	Water absorption ratio (%)	Friability (%)	Disintegration time (DT) (Sec)
F1	Pass	2.6±0.2	22±6	112.3±4.93	0.68±0.02	53.7 ±2.89
F2	Pass	3.07±0.06	18±2	120.3±3.51	0.77±0.02	40±4
F3	Pass	2.8±0.1	14.33 ±2.08	128±2	0.71±0.01	19.7 ±3.78
F4	Pass	3.03 ±0.15	12.67 ±1.15	130±3.5	0.73±0.03	15.7±2.1
F5	Pass	2.73±0.06	15.67±2.08	131.7±2.08	0.80±0.03	18.7±2.52
F6	Pass	2.93 ±0.06	23 ±1.73	110.3±1.52	0.66 ±0.04	53±2.64
F7	Pass	2.98 ±0.006	16 ±2.64	119.3±2.52	0.79±0.02	38 ±5.29
F8	Pass	2.93±0.06	11.7±0.577	126.3±1.52	0.74±0.06	18.7±3.05
F9	Pass	2.76 ±0.06	10.33 ±1.52	127.3±2.89	0.71±0.01	14.7 ±2.51
F10	Pass	3.07±0.06	14.67±4.04	128.7±3.51	0.83±0.03	17±2.64

3.1.4 *In vitro dissolution studies*

More than 83% drug release was observed in all formulation batches (F1-F10) with maximum (100%) in batch F3 within 15 min. *In vitro* dissolution of all formulation batches (F1-F10) is given in Figure 5.

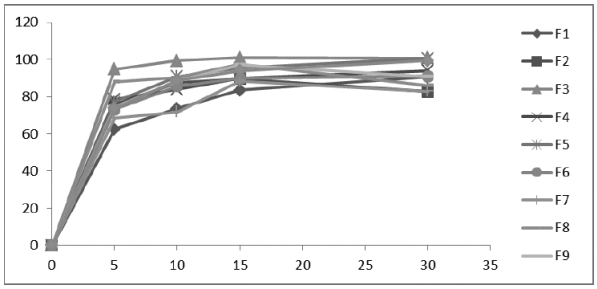

Figure 5. *In vitro* drug release of Preliminary batches (F1-F10)

3.2 Evaluation of Final Batches (A1-A9)

3.2.1 *Precompression Parameters*

The results of bulk density and tapped density were ranged from (0.458 g/ml to 0.515 g/ml) and (0.548 g/ml to 0.605 g/ml) respectively. The results of angle of repose (20.30° to 25.64°) indicate good flow properties which were further supported by Carr's index values (11.7 % to 17.6 %) and Hausner's ratio data (1.13 to 1.21). The results of pre compression parameters are given in Table 4.

Table 4. Results of pre compression parameters of final batches (A1-A9)

Batch code → Parameter↓	**A1**	**A2**	**A3**	**A4**	**A5**	**A6**	**A7**	**A8**	**A9**
Bulk density (g/ml)	0.481	0.484	0.458	0.514	0.515	0.504	0.482	0.484	0.514
Tapped density (g/ml)	0.584	0.548	0.550	0.587	0.589	0.590	0.570	0.556	0.605
Angle of repose (°)	20.30	24.70	21.30	22.78	22.78	21.30	22.29	23.74	25.64
Carr' s index (%)	17.6	11.7	16.6	12.5	12.5	14.6	15.2	12.9	15
Hausner's ratio	1.21	1.13	1.20	1.14	1.14	1.17	1.18	1.14	1.17

3.2.2 *Postcompression Parameters*

The prepared tablets from all formulations possessed good mechanical strength with sufficient hardness in the range of (2.67±0.21 kg/cm^2 to 3.23±0.252 kg/cm^2). Friability values below 1% are good indication of good mechanical resistance of tablets. All tablet batches passed weight variation test as % weight variation was within pharmacopoeia limits of (±7.5%) of weight. All the batches showed wetting time in the range of (10.3±1.52 sec to 49.7±5.13 sec). All the formulation batches showed disintegration time (DT) value of less than 1 minute varied between (12±2 sec to 58.7 ±2.52 sec). All the formulation batches Water absorption ratio of more than 100% indicated enhanced swelling characteristics due to presence of mucilage (Table 5).

Table 5. Response of post compression parameters of final batches (A1-A9)

Code	Weight variation	Hardness (Kg/cm^2)	Wetting time (Sec)	Water absorption ratio (%)	Friability (%)	DT (Sec)
A1	Pass	2.73±0.05	49.7±5.13	127.3±2.08	0.53±0.15	58.7±2.52
A2	Pass	2.97±0.153	39±1	131.7±3.05	0.78±0.06	50±2
A3	Pass	2.67±0.21	35.7±3.51	133.3±2.08	0.8±0.05	46.7±3.21
A4	Pass	3.23±0.252	33±4.36	136±2.64	0.85±0.05	40±2
A5	Pass	2.73±0.208	30.3±3.21	137.7±1.53	0.91±0.01	33.7±4.04
A6	Pass	2.93±0.06	23.7±1.52	138±3.60	0.50±0.09	26±3.46
A7	Pass	3.07±0.006	17±2.64	140±3.45	0.44±0.04	21.3±1.15
A8	Pass	2.8±0.264	15±1.73	141±2.64	0.65±0.05	17±1
A9	Pass	3±0.1	10.3±1.52	145.7±2.08	0.86±0.05	12±2

3.2.3 *In vitro dissolution studies*

More than 87% drug release was observed in all formulation batches (A1-A9) with maximum release (100%) in batches A4 and A7 within 15 min. *In vitro* dissolution of all formulation batches (A1-A9) is shown in Figure 6.

3.3 Experimental Design

To optimize the ratio of mucilage in FDT that can lead to rapid disintegration and enhanced dissolution of drug, 9 formulations were prepared according to 3^2 factorial design (Table 6). The design provided an empirical second order polynomial model. Regression polynomials for the individual dependent

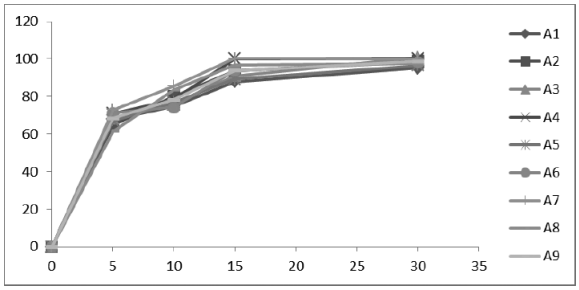

Figure 6. *In vitro* drug release profile of Final batches (A1-A9)

Table 6. Composition and responses for 3^2 factorial design

Batch Codes	Variable levels*		Response		
	X_1	X_2	Disintegration time (DT)	Wetting time (WT)	$T_{85\%}$
A1	-1	-1	58.7±2.52	49.7±5.13	32.2± 2.85
A2	-1	0	50±2	39±1	26.3± 1.13
A3	-1	1	46.7±33.21	35.7±3.51	25.3± 1.09
A4	0	-1	40±2	33±4.36	20.1± 3.1
A5	0	0	33.7±4.04	30.3±3.21	19± 0.45
A6	0	1	26±3.46	23.7±1.52	14.4± 0.67
A7	1	-1	21.3±1.15	17±2.64	12± 1.85
A8	1	0	17±1	15±1.73	10.4± 2.01
A9	1	1	12±2	10.3±1.52	9.4± 0.78

*Translation of coded levels in actual units

Coded level	-1	0	+1
X_1 : Plantago Ovata (mg)	1.4(1%)	7(5%)	11.2(8%)
X_2: Lepidium Sativum (mg)	1.4(1%)	7(5%)	11.2(8%)

variables (DT, WT and $T_{85\%}$) were calculated and applied to approximate the surface responses and contour plots. The general model equation was generated to fit the data.

$$Y= b_0+b_1X_1+b_2X_2+b_{12}X_1X_2+b_{11}X_1^2+b_{22}X_2^2$$

$b_0, b_1, b_2, b_{12}, b_{11}, b_{22}$ represents the regression coefficients of independent variable (X_1 and X_2). The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction term

(X_1 X_2) shows changes in the response when two factors are simultaneously changed. The polynomial terms X_1^2 and X_2^2 are included to investigate non linearity.

The polynomial equation for DT, WT and $T_{85\%}$ was generated by multiple linear regression to quantitatively explain the effect of both the mucilage on these responses. Various equations are as follows:

$$DT = +32.87- 17.52X_1-5.88X_2+0.68X_1X_2+1.05X_1^2+0.55X_2^2$$

$$WT=+28.91111-13.683X_1-5.00X_2+1.82500X_1X_2-1.21667X_1+0.13333X_2^2$$

$$T_{85\%} = +17.61-8.66X_1-2.53X_2+1.075X_1X_2+1.433X_1^2+0.333\ X_2^2$$

The results of multiple linear regression analysis and ANOVA are represented in Table 7.

Table 7. Summary of results of Regression Analysis and ANOVA for measured response

RESPONSE	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}
DT						
Full Model	32.87	-17.52	-5.88	0.68	1.05	0.55
P value	0.0009	0.0001	0.0033	0.4789	0.4403	0.6738
Regression	DF	SS	MS	F	R^2	
Full Model	5	2053.32	410.86	146.59	0.9891	
WT						
Full Model	28.91	-13.68	-5.00	1.83	-1.22	0.13
P value	0.0034	0.0005	0.0100	0.1803	0.4723	0.9341
Regression	DF	SS	MS	F	R^2	
Full Model	5	1289.72	257.94	58.59	0.973	
T-85%						
Full Model	17.61	-8.67	-2.53	1.08	1.43	0.33
P value	0.0046	0.0007	0.0228	0.2311	0.2528	0.7642
Regression	DF	SS	MS	F	R^2	
Full Model	5	498.13	99.63	48.35	0.9673	

3.3.1 *Disintegration time (DT)*

The response surface plot demonstrated the effect of amount of *Plantago ovata* mucilage and *Lepidium sativum* mucilage on disintegration time (DT). The polynomial equation indicated that disintegration time was decreased

from 58.7±2.52 sec to 46.7±33.21 sec and from 21.3±1.15 sec to 12±2 sec at low and high level of *plantago ovata* respectively, as the concentration of the *lepidium sativum* was increased. And the DT value decreased from 58.7±2.52 sec to21.3±1.15 sec and from 46.7±33.21 sec to12±2 sec at low and high levels of *Lepidium sativum* respectively, as the concentration of *Plantago ovata* was increased. Though both the natural polymers resulted in decreasing the disintegration time of the tablets with their increased amount but increased concentration of *Plantago ovata* mucilage has more significant effect on DT as compared to that observed with increased amount of *Lepidium sativum* mucilage. Figure 7a showed the response surface plot for the effect of concentration of *Plantago ovata* and *Lepidium sativum* mucilage on DT.

3.3.2 *Wetting time (WT)*

The response surface plot demonstrated the effect of amount of *Plantago ovata* mucilage and *Lepidium sativum* mucilage on wetting time (WT). The polynomial equation indicated that wetting time was decreased from 49.7±5.13 sec to 35.7±3.51 sec and from 17±2.64 sec to 10.3±1.52 sec at low and high level of *plantago ovata* respectively, as the concentration of the *lepidium sativum* was increased. And the WT value decreased from 49.7±5.13 sec to 17±2.64 sec and from 35.7±3.51 sec to 10.3±1.52 sec at low and high levels of *Lepidium sativum* respectively, as the concentration of *Plantago ovata* was increased. Though both the natural polymers resulted in decreasing the wetting time of the tablets with their increased amount but increased concentration of *Plantago ovata* mucilage has more significant effect on WT as compared to that observed with increased amount of *Lepidium sativum* mucilage. Figure 7b showed the response surface plot for the effect of concentration of mucilage of *Plantago ovata* and *Lepidium sativum* on wetting time.

3.3.3 $T_{85\%}$

The response surface plot demonstrated the effect of amount of *Plantago ovata* mucilage and *Lepidium sativum* mucilage on $T_{85\%}$. The polynomial equation indicated that $T_{85\%}$ value was decreased at both low and high levels of *Plantago ovata* (32.2 ± 2.85 min to 25.3± 1.09 min) and (12 ± 1.85 min to 9.4 ± 0.78 min) respectively with increasing concentration of *Lepidium sativum*. The decrease was more significant at low and high levels of *Lepidium sativum* (32.2± 2.85 min to 12 ±1.85 min) and (25.3 ± 1.09 min to 9.4 ± 0.78 min) respectively with increasing concentration of *Plantago ovata*. Figure 7c showed the response surface plot for the effect of concentration of *Plantago ovata* and *Lepidium sativum* on $T_{85\%}$.

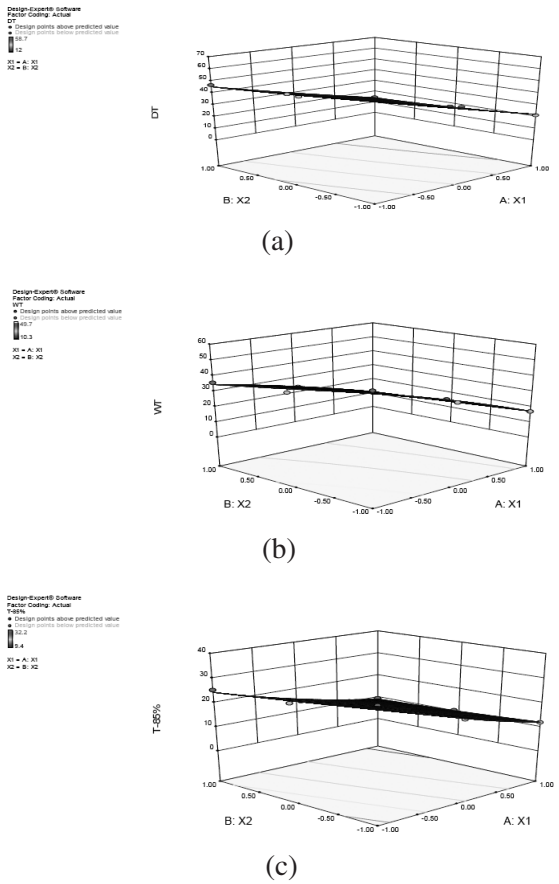

Figure 7. Response surface plots for (a) DT; (b) WT and (C) $T_{85\%}$

3.3.4 *Numerical Optimization*

A numerical optimization technique using the desirability approach was employed to develop a new formulation with the desired responses. Figure 8 shows the overlay plot indicating the optimum composition and predicted responses. Upon the evaluation of the research, the formulation composition with *plantago ovata* concentration and the amount of *lepidium sativum* was fulfilled maximum requirements of an optimum formulation, desirability 0.983 because of least disintegration time, wetting time and better regulation of release rate. The optimized formulation was formulated and evaluated for various dependent variables. The response variables were calculated and compared to the corresponding predicted values. The prediction error for the response parameters ranged from 0.035 to 6.38% (Table 8).

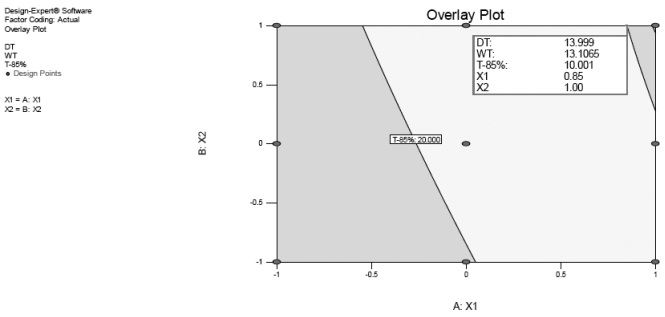

Figure 8. Overlay plot indicating optimized composition

Table 8. Predicted and experimental observed responses of the optimized formulation with % prediction error

Response parameters	Constraints set	Predicted value	Observed value	% Prediction error
Disintegration time	Minimize	22.15	23.66	6.38
Wetting time	Minimize	17.31	17.66	1.98
In vitro drug release	Maximize	100.017	100.0527	0.035

4. CONCLUSION

Natural polymers also exhibited great potential in formulation of modified drug delivery systems. Fast disintegrating tablets of losartan potassium can be prepared using natural mucilage as superdisintegrant. Natural mucilage may act by enhanced wetting and swelling of tablets which further leads to better disintegration and dissolution characteristics of tablet. A statistical approach can reduce the number of experimental runs and provide several formulation options with desired disintegration characteristics. It was revealed that several combinations of *Plantago ovata* mucilage and *Lepidium sativum* mucilage can produce tablets of DT less than 1 min and less than 30 min $T_{85\%.}$ *Plantago ovata* mucilage has a more significant effect on disintegration and wetting characteristics than *Lepidium sativum* mucilage.

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