WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Formulation and Evaluation of Fast-Dissolving Tablets of Losartan Potassium Using Co-Processed Excipients and Statistical Optimisation Using Central Composite Design

Paka Bhavana [a], Dr. M. Sunitha Reddy [b]

[a] Centre for Pharmaceutical sciences, UCEST, JNTUH, Kukatpally, Hyderabad,500085, India
[b] Centre for Pharmaceutical sciences, UCEST, JNTUH, Kukatpally, Hyderabad,500085, India
DOI: https://doi.org/10.55248/gengpi.4.1223.123526

A B S T R A C T

Losartan potassium is a medication that is commonly used to treat high blood pressure. It is an effective medication that can help to lower blood pressure and reduce the risk of cardiovascular disease. It is an orally active, nonpeptide angiotensin II receptor antagonist. Losartan potassium has low bioavailability and the risk of first-pass metabolism. To overcome these limitations, the formulation of Losartan Potassium as a fast-dissolving tablet using co-processed excipients and super disintegrants is explored. The goal was to promote faster disintegration and better hardness. Four different co-processed excipients were tested for flow properties, and tablets were prepared using the direct compression method. The tablets prepared with Disintequik ODT showed the best flow properties and fastest disintegration time compared to other co-processed excipients. Central Composite Design response surface methodology was used to optimize the formulation of the tablets. The study focused on two independent variables: X1 (amount of co-processed excipient) and X2 (amount of super disintegrant). Two responses were measured: Y1 (Hardness) and Y2 (Disintegration time). All formulations showed notably faster disintegration and better hardness. The co-processed excipient Disintequik ODT and super disintegrant Sodium starch glycolate were used. A response surface plot was created to graphically represent the effect of independent variables on disintegration time and hardness. The concentration of co-processed excipients and super disintegrant was optimized for a disintegration time of 25 seconds. In-vitro drug release for optimised formulation is 99.02%. The optimized formulation was compared with a marketed product. Finally, short-term stability studies were conducted, which indicated that there was no significant change in disintegration time and drug content.

Keywords: Co-processed Excipients, Fast dissolving tablets, Central Composite Design, Losartan Potassium, In-vitro drug release.

1. INTRODUCTION

Oral drug administration is a widely accepted and preferred route for medication delivery, constituting a substantial portion of pharmaceutical dosage forms. Difficulties and resistance in taking tablets are widespread among various patient demographics, leading to compliance issues and compromising the effectiveness of treatments. Challenges such as swallowing difficulties (dysphagia) can affect individuals of all ages but are more prevalent among the elderly and those with dementia. Conversely, some patients, including geriatric, pediatric, and psychiatric populations, may refuse to swallow medication. Despite these hurdles, oral administration remains the preferred method for many medications due to its simplicity, adaptability, convenience, and patient preference. Recent advancements have introduced fast dissolving oral drug formulations to address swallowing difficulties. For treating hypertension, achieving a fast onset of action is crucial. The delay in drug action can be resolved by creating a suitable dosage form. Fast dissolving tablets that dissolve in the mouth have gained popularity in oral antihypertensive therapy. This newer formulation offers potential advantages over older ones in terms of convenience, side effects, efficacy, and quicker onset of action.

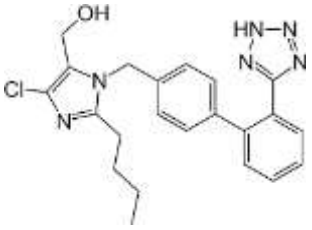


Fig.1 Chemical structure of Losartan potassium

Losartan Potassium, an antihypertensive medication categorized as an Angiotensin II receptor antagonist, has a molecular weight of 461.01g/mol, a half-life of 1.5 to 2 hours, and a bioavailability of 25 to 35%. It is primarily metabolized in the liver. Fast-dissolving tablets are soluble in saliva and are

absorbed through the mouth, pharynx, and esophagus as saliva travels to the stomach, thereby enhancing bioavailability by bypassing first-pass metabolism. These tablets also improve patient compliance and offer a faster onset of action. Considering these factors, developing fast-dissolving tablets of Losartan Potassium was deemed appropriate. Co-processed excipients and super disintergrants are used to develop fast dissolving tablets. Co-processed excipients refer to a combination of two or more excipients that have undergone physical changes without altering their chemical properties. Coprocessed excipients combine multiple functions, enhancing formulation efficiency, stability, and performance, cost effective.[8]

The selection and appropriate levels of commercially available excipients play a crucial role in optimizing formulations in terms of both cost and therapeutic effectiveness. For the development of pharmaceuticals, investigations have focused on useful statistical optimization designs. Central Composite Design (CCD) with Response Surface Methodology (RSM), involving factorial, axial, and center points, provides a comprehensive understanding of dependent variables while requiring fewer experiments. Response Surface Methodology (RSM), initially explored by Box & Hunter, employs statistical and mathematical models based on polynomial relationships to analyse the influence of formulation variables on response variables. In this study, Central Composite Design (CCD), introduced by Box & Wilson, is utilized for tablet optimization. CCD, a flexible response surface model, minimizes the number of experimental runs, offering a cost-effective and time-saving alternative to traditional trial-and-error approaches. CCD incorporates five different levels of variables coded as ±1, 0, and ± α for factorial, central, and axial points, respectively. It involves multiple regression analysis to determine coefficients (b1, b2,... bn), error (Y), and constant (b0) terms, incorporating linear (x1, x2,... xn) and squared values (x12, x22,... xn2) for each variable, along with first-order interaction values for paired combinations (x1x2, x1x3, xn–1, xn). The response model for three variables in this study is represented by Eq. [1].[1,3]

$$y = (b + x) + \sum_{i=1}^{3} b_i x_i + \sum_{i=1}^{3} b_{ii} x_i^2 + \sum_{i=1}^{3} \sum_{i=i+1}^{3} b_i |x|x| - (1) [1]$$

2. MATERIALS AND METHOD

Materials:

Chemicals: Losartan Potassium API, Disintequik MCC, Lubritose AN, Lubritose MCC, Disintequik ODT as co-processed excipients, Sodium Starch Glycolate (SSG)as Super Disintegrant, Mannitol was used as diluent, Aspartame , Magnesium stearate as lubricant, Talc as a glidant.[4,5,7,8,11,16]

Buffer: pH 6.8 Phosphate buffer.

Equipment: Shimadzu U.V -Visible Spectrophotometer, Bruker Alpha FTIR Spectrophotometer, Tablet Compression machine, Disintegration apparatus, USP type II Dissolution apparatus, Monsanto hardness tester, vernier callipers, Sonicator, Roche friabilator, Digital Weighing Balance, pH meter.

Preformulation Studies: During the assessment of a drug, its state, odour, colour, and taste are evaluated.

FTIR Studies: FT-IR spectrum of pure drug and drug-excipients were obtained by Bruker alpha FTIR spectrophotometer. The spectrum of drug-excipients and optimised formulation so obtained were compared with spectrum of pure drug for any interaction.[25]

Preparation of pH 6.8 phosphate buffer: Dissolve 28.80 g of disodium hydrogen phosphate and 11.45 g of potassium dihydrogen phosphate in sufficient water to produce 1000 ml.

Determination of λ max : Solution of Losartan potassium containing the concentration 10 µg/ ml was prepared using pH 6.8 phosphate buffer and UV spectrum was taken using Shimadzu UV-1800 double beam spectrophotometer. The solution was scanned in the range of 200 – 400 nm.

Standard calibration curve of Losartan Potassium:

100mg of Losartan potassium was weighed accurately and dissolved in pH 6.8 phosphate buffer, which resulted in 1000 µg/ml. Then from the stock solution 100 µg/ml solution was prepared from this 2, 4, 6, 8, 10 µg/ml were prepared. The absorbance of the above dilutions were measured using UV-spectrophotometer at 205 nm using 6.8 pH phosphate buffer as blank. Graph is plotted by taking concentration on X-axis and absorbance on Y-axis. [22]

Preparation of Fast Dissolving Tablets of Losartan potassium Preliminary Batch: Losartan potassium fast dissolving tablets preliminary batch was prepared for CE1-CE4 batches using different co-processed excipients. Keeping total weight 100mg of tablet constant in formulations. To ensure better mixing, all elements are passed through sieve number 40. All ingredients were mixed in motor and pestle then magnesium stearate and talc were added. The resulting mixture is compressed into tablet using Direct Compression method and then tablets were evaluated.[13,27,34,38]

Table1: Formulation Table of Losartan Potassium Fast Dissolving Tablets Preliminary Batch

INGREDIENTS	CE 1 (mg)	CE 2 (mg)	CE 3 (mg)	CE 4 (mg)
Losartan potassium	25	25	25	25
Lubritose MCC	4	-	-	-
Disintequik MCC	-	4	-	-
Lubritose AN	-	-	4	-
Disintequik ODT	-	-	-	4
Mannitol	53	53	53	53
Aspartame	15	15	15	15
Magnesium stearate	0.5	0.5	0.5	0.5
Talc	0.5	0.5	0.5	0.5
Total	100	100	100	100

Experimental design: To enhance the production of high-quality tablets, a Central Composite Design CCD determine material characteristics and response variables impacting the hardness (Y1) and disintegration time (Y2) of the tablets. The attributes under scrutiny included the quantities of Disintequik ODT (X1) and SSG(X2). Through an analysis of the relationship between these attributes and the responses, the influence of each factor on the outcomes was determined using the statistical tool Design Expert (Statease 360) given in table 2 and 3. The responses were evaluated using a statistical model that encompassed polynomial and interactive terms, offering a comprehensive understanding of how these factors affect tablet quality. Tablets were prepared using 25mg Losartan potassium ,15mg Aspartame, 0.5mg Magnesium Stearate, 0.5 mg Talc constant and mannitol quantity sufficient along with quantities of Disintequik ODT (X1) and SSG(X2) by keeping tablet weight 100mg given in table 4.[2,39]

Table 2 Levels of Variables for Optimization

Code	Variable	Level of Variables				
		-α (%)	**-1 (%)**	**0 (%)**	**+1 (%)**	**+α (%)**
X1	Disintequik ODT	0.34	2	6	10	11.65
X2	SSG	1.58	2	3	4	4.41

Table 3 Central Composite Design for Two Factors by Design Expert

Runs	Batch Code	Disintequik ODT (X1)	SSG (X2)	Disintequik ODT (%)	SSG (%)
		Coded Levels of Variables		Actual Levels of Variables	
Factorial Points					
1	F1	-1	1	2	4
2	F2	1	-1	10	2
3	F3	-1	-1	2	2
4	F4	1	1	10	4
Axial Points					
5	F5	0	+α	6	4.41
6	F6	+α	0	11.65	3
7	F7	-α	0	0.34	3
8	F8	0	-α	6	1.58
Center Point					
9	F9	0	0	6	3

Table 4 Composition of Losartan Potassium tablets (100 mg) Experimental Design

S.No	Batch Code	Disintequik ODT (mg)	SSG (mg)	Mannitol (mg)	Aspartame (mg)	Losartan Potassium (mg)	Magnesium stearate (mg)	Talc (mg)
1	F1	2	4	53				
2	F2	10	2	47				
3	F3	2	2	55				
4	F4	10	4	45				
5	F5	6	4.41	48.59	15	25	0.5	0.5
6	F6	11.65	3	44.35				
7	F7	0.34	3	55.66				
8	F8	6	1.58	51.42				
9	F9	6	3	50				

Evaluation

Pre-compression Parameters:

Angle of repose:- Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation. [11]

Angle of repose (θ) = tan –1 H / R

Bulk density:- Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and cohesiveness of particles. [11]

Mathematically it is defined as:

Bulk Density (ρb) = w/Vb

Where, w = mass of powder; Vb= bulk volume

Tapped density:- Tapped density is defined as the mass of a powder divided by the tapped volume. It was determined by mechanically tapping the measuring cylinder and the volume was noted. [11]

Tapped density (ρt) = w / Vt Where, w = mass of powder; Vt = bulk volume

Carr's Compressibility Index It is also one of the simple methods to evaluate flow property of a powder by comparing the bulk density and tapped density. [11] It is calculated by

Carr's Index = Tapped Density-Bulk density/ Tapped density

Post-compression Parameters:

Thickness: The thickness of the tablets was determined using a Vernier callipers. Five tablets from each type of formulation were used and average values were calculated. It is expressed in mm.[6]

Friability: Five tablets of each formulation were tested. The friability of the tablets was measured in a Roche friabilator using the formula:[6]

$$\text{Friability (\%)} = \frac{\text{Initial weight - Final weight} \times 100}{\text{Initial weight}}$$

Hardness: The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. [6]

Weight variation test: 20 tablets of each type of formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight. [16]

Uniformity of drug content: Five tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 25 mg of Losartan potassium was weighed and dissolved in 100 ml of pH 6.8 phosphate buffer. This was the stock solution from which 0.2 ml sample was withdrawn and diluted to 10 ml with pH 6.8 phosphate buffer. The absorbance was measured at wavelength 205 nm using double beam UV-Visible spectrophotometer. [16]

Content uniformity was calculated using formula –

% Purity = 10 C (Au / As)

Where, C - Concentration, Au and As - Absorbance's obtained from unknown preparation and standard Preparation respectively.

Wetting time: The method was applied to measure tablet wetting time. A piece of tissue paper folded twice was placed in a small petri dish (i.d. = 6.5 cm) containing 10 ml of water, a tablet was placed on the paper, and the time for complete wetting was measured.[12]

Water Absorption Ratio: A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A tablet was put on the paper and was allowed for complete wetting. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation[7]

R = (WA-WB) /WB *100

Where, WA= Weight of tablet after water absorption

WB= Weight of tablet before water absorptio

In vitro disintegration Studies : The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using distilled water maintained at 37 ± 2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6.8 Phosphate buffer maintained at 37 ± 2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.[29]

In vitro dissolution studies: Dissolution rate was studied by using USP type-II apparatus (50 rpm) using 900 ml of pH 6.8 phosphate buffer as dissolution medium. Temperature of the dissolution medium was maintained at 37 ±0.5°C, aliquot of dissolution medium was withdrawn at every 3min interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 205 nm and concentration of the drug was determined from standard calibration curve.[11,15,30]

Analysis of Data: The Design-Expert programme was used to examine the hardness and disintegration time data (Stat-Ease 360). The essential interface and quadratic possessions of independent variables on dependent variables with CCD were the design's primary objectives.

Comparison of optimized formulation with a marketed tablet: Physio-chemical properties of optimized Losartan potassium formulation were then compared with marketed brand (Losar-25).

Stability studies: Stability testing is conducted by exposing the FDTs to temperatures and humidity conditions, such as 30°C ± 2°C.

RESULTS AND DISSCUSION

Preformulation studies: In this specific study, the organoleptic characteristics of Pure Drug were evaluated. As per the findings, Pure Drug is a white solid that has no odour and slightly bitter taste. The physical characteristics of the tablets, they have a round shape and are white in colour.

FTIR studies: There is no interaction between drug , drug-excipients and optimized formulation in table 5.

λ max of losartan potassium: UV spectrum analysis of Losartan Potassium revealed that the drug has a maximum absorbance at 205 nm shown in fig4.

Standard Calibration Curve of Losartan Potassium: Regression coefficient obtained is 0.991, indicating high level of accuracy and precision in the measurements and shows a linear relationship between concentration and absorbance obeys Beer- Lambert's law as shown in fig5.

Table 5 FTIR interpretation of Drug and optimised formulation

Functional group	**Reference peak Wavenumber Cm^{-1}**	**Losartan Potassium (pure drug) Cm^{-1}**	**Optimized formulation Cm^{-1}**
C-N stretch	1256-1392	1355	1351.4
C=C stretch	1340-1530	1499.3	1498.6
N-H stretch	3500-3100	3213.8	3201.9
C-O stretch	1300-1100	1258.3	1258.2
C-H stretch	2850-2975	2929.7	2955.3

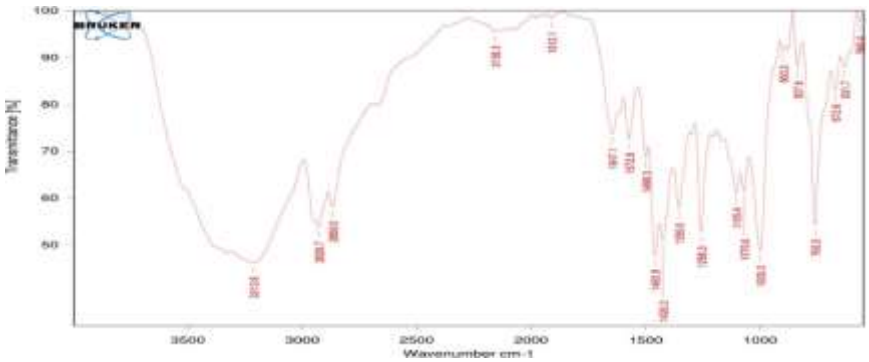


Fig 2 FTIR spectrum of pure drug

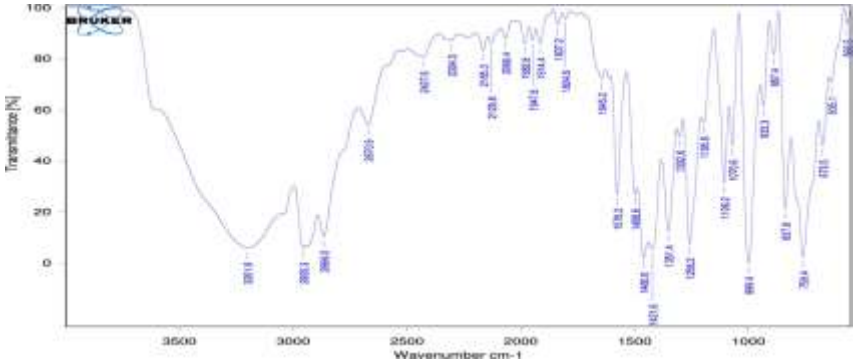


Fig 3 FTIR spectrum of optimised formulation

Table 6 Calibration curve of Losartan Potassium

Concentration(ug/ml)	**Absorbance(at 205nm) ***
2	**0.093±0.001**
4	**0.170±0.002**
6	**0.246±0.001**
8	**0.327±0.002**
10	**0.442±0.002**

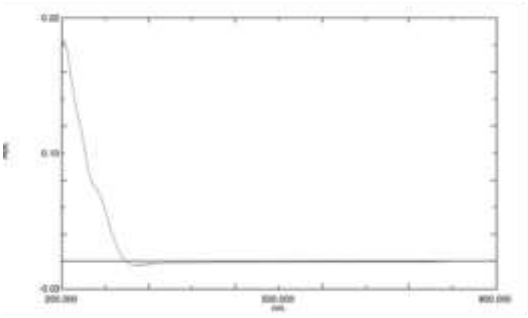


Fig 4 Absorption spectra of Losartan Potassium

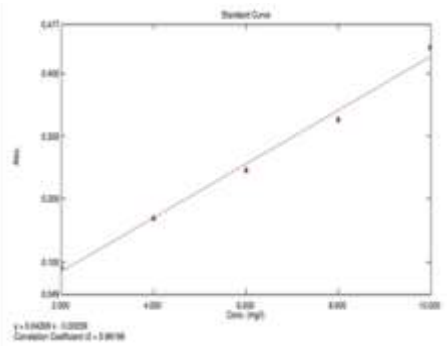


Fig 5 Calibration curve of Losartan Potassium

Initially coproceesed excipient is selected based on powder flow properties, disintegration studies , wetting time and water absorption ratio studies, tablets formulated CE4 Disintequik ODT (containing monohydrate lactose, mannitol, dextrose monohydrate, and crosspovidone) showed better flow properties and disintegration which is suitable for formulating fast dissolving tablets as shown in tables 7 and 8. Further studies are conducted to enhance fast disintegration using super disintegrant sodium starch glycolate along with co-processed excipient Disintequik ODT. Central composite design is used to design formulations using different concentrations. Combinations generated by software Design Expert (Statease 360); the levels of variables are shown

in Table 2. Precompression studies are performed where angle of repose (22.16-25.06), Hausner's ratio (1.12-1.385) and Carr's index (9.4-22.2) as shown in table 9. Majority of formulations exhibited smaller angle of repose, reflecting excellent and good flowabilities. Formulations exhibiting acceptable blend properties were subjected to compression and compressed tablets were then evaluated using different official and un-official tests including weight variation within acceptable limits, hardness (2.04-2.64 Kg/cm2),friability (0.14-0.18%), disintegration (25-46sec), wetting time (21-26sec), water absorption ratio (57-68), % In-vitro drug release (64.35-99.02 %CDR)and % drug content(96.24-98.90%) given in table 10 and table 11. Among various directly compressible formulations F9 were selected as optimized formulations in view of flow properties, better hardness (2.64 Kg/cm2) and faster disintegration (25 sec), % In-vitro drug release (99.02 %CDR).

Table 7. Evaluation of precompression parameters of Preliminary batch

*mean ±standard deviation (SD), n=3

Formulation Trial code	**Bulk density (g/ml) ***	**Tapped density (g/ml) ***	**Compressibility index (%) ***	**Hausner's ratio***	**Angle of repose (°)***
CE1	0.52±0.081	0.60±0.02	13.33±0.009	1.11±0.008	29.24±0.084
CE2	0.54±0.041	0.63±0.01	14.28±0.009	1.18±0.009	31.36±0.092
CE3	0.50±0.014	0.60±0.01	16.7±0.008	1.20±0.008	34.85±0.082
CE4	0.52±0.047	0.58±0.02	11.9±0.008	1.10±0.008	26.6±0.094

Table 8. Evaluation of postcompression parameters of Preliminary batch

Formulation code	**Weight (mg) ***	**Hardness (Kg/cm^2) ***	**Thickness (mm)***	**Friability (%)***	**Disintegration time (sec)***	**Drug content uniformity (%)***	**Wetting time (sec)***	**Water absorption ratio***
CE1	100±0.47	3.25±0.081	4.2±0.047	0.12±0.04	64±1.24	95.24±0.36	52±0.47	36±1.81
CE2	100±0.81	3.44±0.016	4.1±0.047	0.15±0.004	48±1.24	96.04±0.56	385±0.47	44±1.64
CE3	100±0.96	3.21±0.016	4.1±0.047	0.14±0.004	68±0.81	97.24±0.94	56±0.52	38±2.05
CE4	100±0.94	3.52±0.024	4.2±0.047	0.15±0.001	42±0.81	98.54±0.56	30±0.64	50±1.64

*mean ±standard deviation (SD), n=3

Table 9 Evaluation of precompression parameters of experimental design

Formulation Trial code	**Bulk density (g/ml) ***	**Tapped density(g/ml) ***	**Compressibility index (%) ***	**Hausner's ratio***	**Angle of repose (°)***
F1	0.54±0.03	0.66±0.02	18.2± 0.20	1.222±0.008	24.31± 1.4
F2	0.58±0.04	0.65±0.04	10.8± 0.23	1.12± 0.006	22.16±1.2
F3	0.54±0.04	0.64±0.03	15.6± 0.37	1.143± 0.004	23.42±1.3
F4	0.56±0.02	0.70±0.01	20± 0.24	1.25±0.005	24.61±1.18
F5	0.52±0.03	0.64±0.01	18.8± 0.19	1.23±0.003	24.61±1.18
F6	0.58±0.02	0.64±0.02	9.4±0.33	1.19±0.006	23.29±0.89
F7	0.51±0.04	0.62±0.02	17.7± 0.26	1.215±0.003	23.44±1.45
F8	0.56±0.02	0.72±0.01	22.2± 0.33	1.385±0.007	23.06±0.64
F9	0.58±0.02	0.68±0.04	14.7± 0.24	1.21±0.004	25.06±0.90

*mean ±standard deviation (SD), n=3

Table 10 Evaluation of postcompression parameters of experimental design

Formulation code	**Weight (mg)***	**Hardness (Kg/cm^2)***	**Thickness (mm)***	**Friability (%)***	**Disintegration time (sec)***	**Drug content uniformity (%) ***	**Wetting time (sec)***	**Water absorption ratio***
F1	100±0.47	2.27±0.02	4.21±0.01	0.16± 0.01	36±1.24	97.25± 0.56	24±0.27	59± 1.33
F2	101±0.4	2.28±0.01	4.24±0.02	0.14± 0.02	32±1.69	97.84± 0.45	22±0.33	57 ± 1.10
F3	100±0.81	2.20±0.01	4.19±0.02	0.18± 0.02	46±1.24	96.24±0.70	25±0.24	58± 1.23
F4	99±0.75	2.47±0.04	4.22±0.01	0.15± 0.01	35±0.81	98.90±0.63	23±0.31	58± 1.07
F5	101±0.60	2.54±0.02	4.21±0.02	0.16± 0.01	35±1.24	95.12±0.69	26±0.52	57± 1.3
F6	102±0.81	2.23±0.04	4.18±0.02	0.16± 0.01	31±1.69	97.54±0.42	25±0.63	59± 1.12
F7	100±0.65	2.04±0.02	4.21±0.01	0.18± 0.02	42±0.81	98.24±0.37	23±0.81	61±1.03
F8	100±0.76	2.35±0.04	4.22±0.01	0.14± 0.03	40±0.47	98.51±0.64	21±0.64	65±1.5
F9	100±0.81	2.64±0.02	4.16±0.02	0.15± 0.04	25±0.81	98.94±0.40	21±0.43	68±1.64

*mean ±standard deviation (SD), n=3

Table 11 In-vivo Dissolution Studies of Experimental Batch

Time (min)	**%Cumulative Drug Release***								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
3	42.01± 0.39	49.10 ± 0.35	34.53 ± 0.25	58.54 ± 0.42	55.60± 0.35	49.52± 0.45	23.75± 0.65	53.75± 0.35	65.32 ± 0.43
6	51.05± 0.57	62.4 ± 0.33	40.65 ± 0.67	70.90 ± 0.37	67.75± 0.46	65.90± 0.33	35.65± 0.52	67.65± 0.76	74.80± 0.52
9	63.52± 0.43	77.41 ± 0.13	54.64 ± 0.44	82.54 ± 0.69	80.55± 0.54	77.85± 0. 52	44.35± 0.66	75.45± 0.66	85.92± 0.55
12	76.75± 0.45	86.34 ± 0.85	63.51 ± 0.37	89.45 ± 0.27	92.70± 0.44	89.75± 0.45	57.74± 0.75	88.75± 0.56	96.65± 0.33
15	82.15 ± 0.75	90.43 ± 0.65	74.02 ± 0.75	92.50 ± 0.54	95.82± 0.52	90.48± 0.37	64.35± 0.35	91.60± 0.45	99.02± 0.65

*mean ±standard deviation (SD), n=3

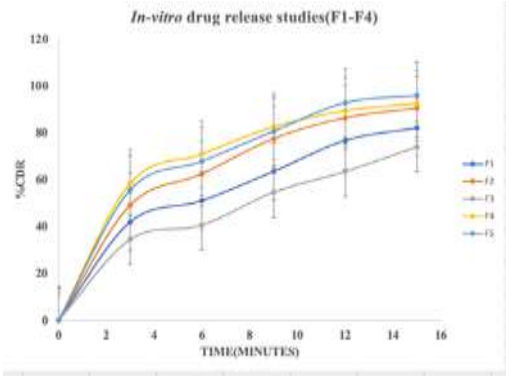


Fig 6 In-vitro drug release studies(F1-F4)

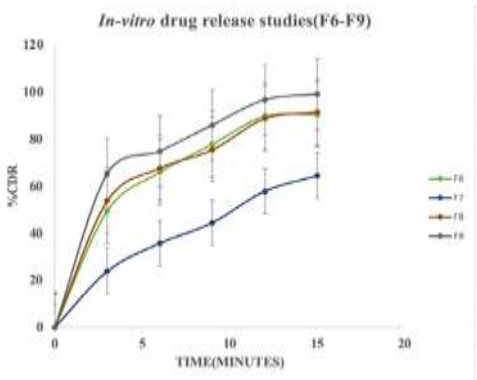


Fig 7 In-vitro drug release studies(F5-F9)

Response Surface Methodology:

This study is based on Response surface methodology to observe the influence of dependent variables (X1,X2) on different response variables (Y1,Y2). Quadratic models were applied to study the relationships of factors on Hardness and disintegration. The adjusted regression values (r2) of Hardness and disintegration were 0.9936, 0.9969 respectively reflecting the appropriateness of the model. [20,23]

Effect of excipients Disintequik ODT and SSG variables on Hardness:

The hardness of tablets refers to their ability to withstand mechanical stress or deformation, and it's a crucial parameter influencing tablet quality and performance. Disintequik ODT and SSG might lead to better tablet hardness due to its role in facilitating rapid disintegration. Response surface effects of excipients on Hardness shown in fig.8. The r2 value of hardness indicates excellent correlation between predicted (0.9777) and actual values (0.9930).

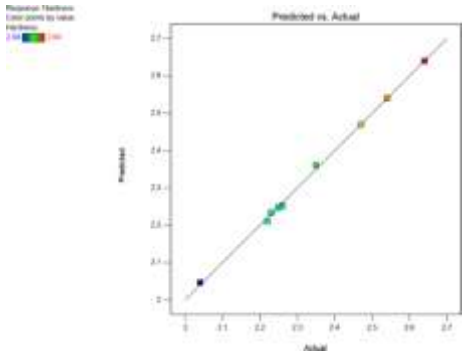
Effect of excipients Disintequik ODT and SSG on Disintegration Time:

All directly compressed formulations exhibited rapid disintegration due to the presence of Disintequik ODT and SSG (25-46 sec). Higher level of SSG accelerates the disintegration resulting in fine dispersion and rapid dissolution. Increase amount of SSG resulted in decrease of the disintegration time. a Response surface effects of excipients on Disintegration time shown in fig.9. The r2 value of DT indicates excellent correlation between predicted (0.9555) and actual values (0.9857).

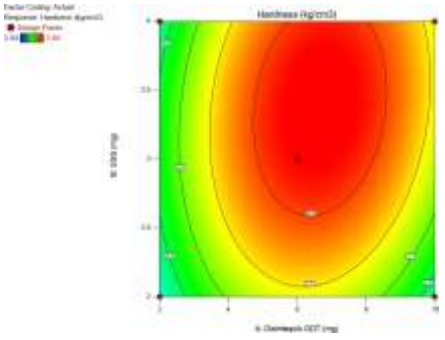
The F-value indicates significant importance of the model. It suggests that there's an extremely low probability (0.01%) that such a high F-value could happen by chance or random noise. When p-values are below 0.0500, it implies that model terms like A, B, AB, A^2, and B^2 hold significance.[1]

Table 12 Statistical model summary of response variables

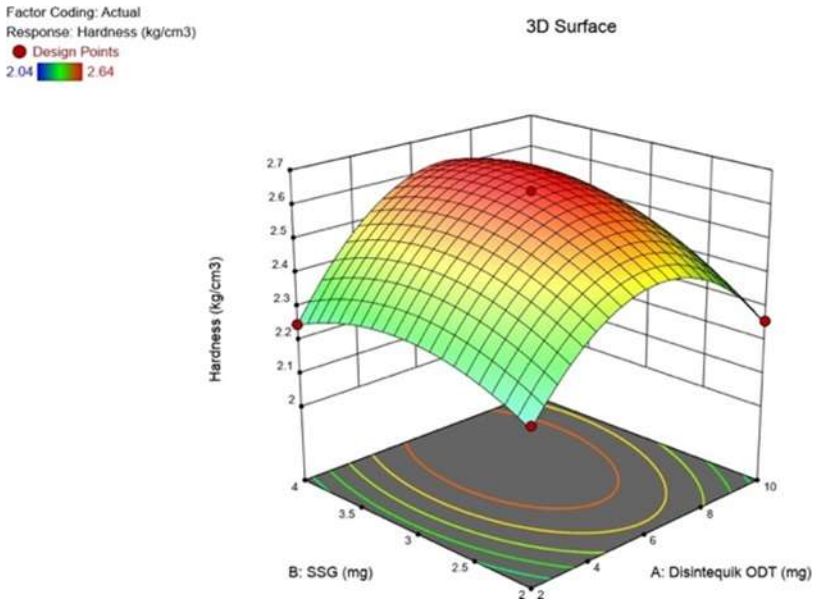
Factors	Sum of squares	Df	Mean Squares	F-value	P-value	Comment
Hardness Y1 (Quadratic Model)						
Model	0.2773	5	0.0555	532.52	0.0001	significant
A-Disintequik ODT	0.0349	1	0.0349	335.51	0.0004	
B-SSG	0.0323	1	0.0323	310.60	0.0004	
AB	0.0081	1	0.0081	77.78	0.0031	
A^2	0.1818	1	0.1818	1745.86	< 0.0001	
B^2	0.0263	1	0.0263	252.10	0.0005	
Residual	0.0003	3	0.0001	-	-	
Cor Total	0.2776	8	-	-	-	
Disintegration Y2 (Quadratic Model)						
Model	315.39	5	63.08	1151.61	< 0.0001	significant
A-Disintequik ODT	116.71	1	116.71	2130.78	< 0.0001	
B-SSG	24.75	1	24.75	451.85	0.0002	
AB	42.25	1	42.25	771.35	0.0001	
A^2	98.28	1	98.28	1794.36	< 0.0001	
B^2	115.92	1	115.92	2116.34	< 0.0001	
Residual	0.1643	3	0.0548	-	-	
Cor Total	315.56	8	-	-	-	



a)

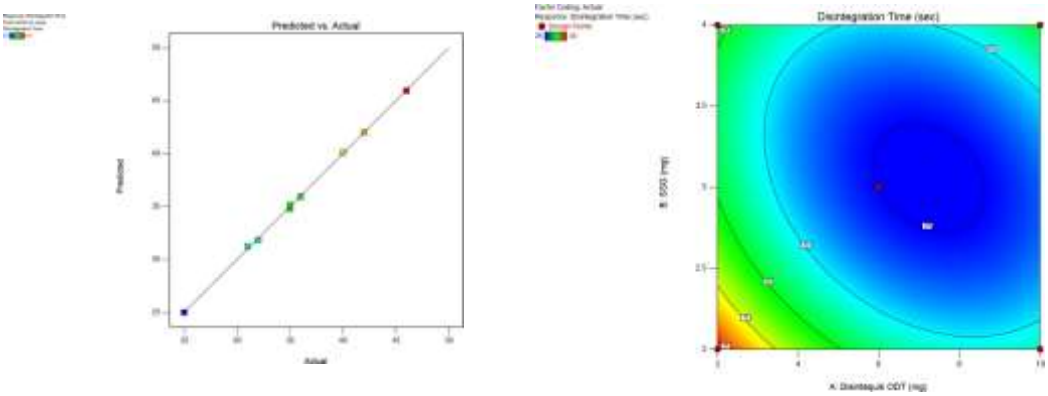


b)

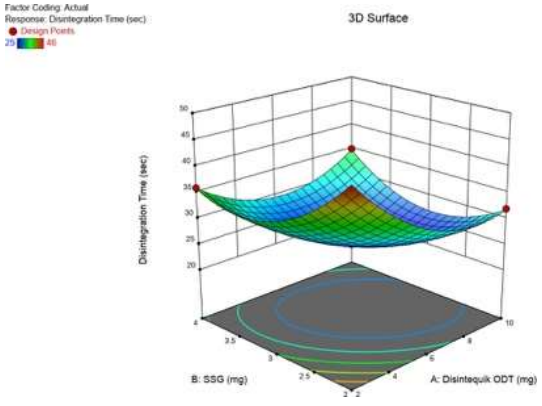


(c)

Fig 8. Effect of Disintequik ODT and SSG on Hardness (a) Predicted vs actual plot (b) contour plot (c) Response surface curve



a) b)



C)

Fig 9 Effect of Disintequik ODT and SSG on Disintegrtion time (a) Predicted vs actual plot (b) contour plot (c) Response surface curve

Table 13 Comparison of optimized formulation with a marketed tablet:

	Weight Variation	Hardness (kg/cm^2) *	Friability (%)*	Content Uniformity (%) *	Disintegration time(sec)*
Marketed Formulation (Losar-25)	**Passed**	**2.52±0.24**	**0.15±0.001**	**98.02±0.86**	**126±0.56**
Optimised formulation	**Passed**	**4.52±0.41**	**0.18±0.002**	**98.65±0.64**	**25±0.54**

*mean ±standard deviation (SD), n=3

Table 14 Invitro drug release of Marketed formulation and optimized formulation

Time (min)	%Cumulative Drug Release*	
	Marketed formulation	Optimized Formulation
0	**0**	**0**
3	**8.25±1.77**	**65.42±1.22**
6	**15.91±1.64**	**76.48±1.22**
9	**35.64±1.64**	**85.76±1.28**
12	**40.02±1.91**	**96.84±1.36**
15	**48.41±1.24**	**99.02±1.50**

*mean ±standard deviation (SD), n=3

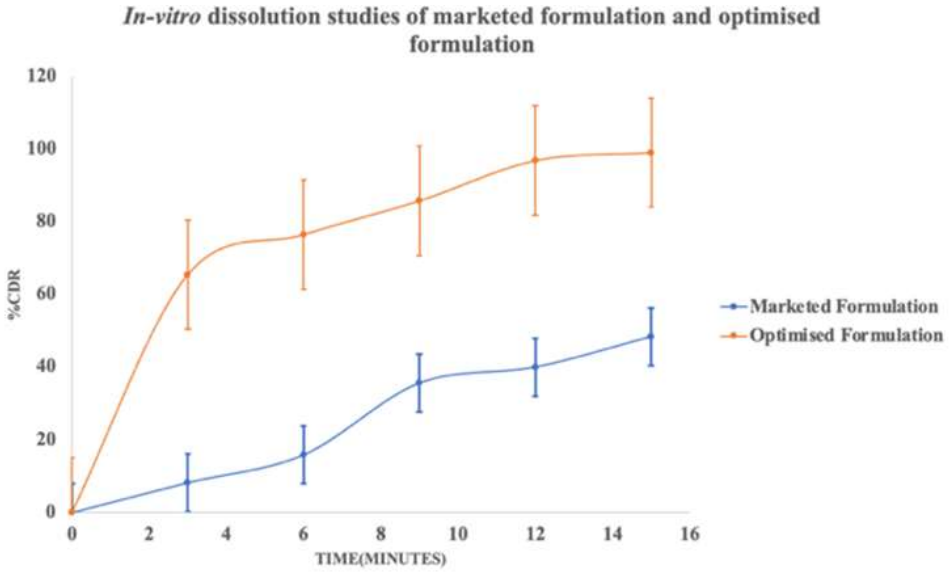


Fig 10 In-vitro drug release of Marketed formulation and optimized formulation

Table 15 Short-term Stability studies

Parameters	**Initial**	**1 month**	**2 months**	**3 months**
Appearance	**good**	**good**	**good**	**good**
Average Weight(mg) *	**100.1±0.001**	**100±0.001**	**99.99±0.001**	**99.99±0.001**
Thickness(mm) *	**4.16±0.02**	**4.16±0.01**	**4.15±0.02**	**4.15±0.02**
Hardness(kg/cm^2)	**2.64±0.04**	**2.63±0.06**	**2.63±0.04**	**2.63±0.04**
Friability (%) *	**0.15±0.03**	**0.15±0.04**	**0.14±0.06**	**0.14±0.06**
Disintegration(sec) *	**25±0.54**	**24±0.84**	**24±0.95**	**23±0.49**
***In-vitro* Dissolution studies(%CDR) ***	**99.02±1.26**	**98.92±1.48**	**98.88±2.05**	**97.82±1.65**

*mean ±standard deviation (SD), n=3

Comparison of optimized formulation with marketed tablet: Optimized formulation shows better disintegration and drug release as compared with conventional marketed tablets of losartan potassium given in table 13 and table 14.

Stability Studies: Short-term Stability studies were performed for optimized formulation showed satisfactory results given in table 15.

CONCLUSION

The study was to formulate and optimise fast dissolving tablets of Losartan potassium using co-processed excipients and statistical optimization with a central composite design approach. Four different co-processed excipients were assessed for their flow properties, and tablets were initially formulated using the excipient with the best flow properties, Disintequik ODT, resulting in improved disintegration time and adequate drug release. Subsequently, a more detailed statistical optimization was performed using Design Expert Stat-Ease software, with co-processed excipient (Disintequik ODT) and Super disintegrant (SSG) as independent variables. This optimization led to a formulation with faster disintegration and better tablet hardness, as demonstrated by contour plots and response surface curves. In-vitro dissolution studies confirmed the effectiveness of the optimized formulation. A comparison with the marketed formulation revealed the potential superiority of the optimized formulation. Furthermore, stability studies conducted showed satisfactory results, indicating the viability of the optimized formulation for further development and potential use.

Acknowledgments

Would like to thank Dr. M. Sunitha Reddy and K. A. Vijetha for proper Guidance and support and the Department of Pharmaceutics, Centre for Pharmaceutical Sciences, JNTUH UCEST, and JNTUH. For providing lab facilities for this research work. Disclosure of conflict of interest All the authors declare no conflict of interest.

REFERENCES

1. Patra RK, Sahu SK, Mahapatra AK, Das R. Enhancement of Solubility of Rivaroxaban and Formulation of its Fast-Disintegrating Tablets: Using Design of Experiments. Research Journal of Pharmacy and Life Sciences: Volume. 2023 May;4(2):40-55.

2. Ahad HA, Chinthaginjala H, Reddy G, Ganthala AK, Siddhartha TT. Optimized Rapid Disintegrating Tablets produced through Central Composite Design. Current Issues in Pharmacy and Medical Sciences. 2022;35(3):152-5.

3. Vlad RA, Antonoaea P, Todoran N, Rédai EM, Bîrsan M, Muntean DL, Imre S, Hancu G, Farczádi L, Ciurba A. Development, and evaluation of cannabidiol orodispersible tablets using a 23-factorial design. Pharmaceutics. 2022 Jul 14;14(7):1467.

4. Zade A, Wani M, Limaye D, Patil R, Patil P, Baheti A, Polshettiwar S, Tagalpallewar A. A systematic review on Co-processed formulation and development. Annals of the Romanian Society for Cell Biology. 2021 Apr 30:17140-7.

5. Salim I, Olowosulu AK, Abdulsamad A, Gwarzo MS, Khalid GM, Ahmad NT, Eichie FE, Kurfi FS. Application of SeDeM Expert System in the development of novel directly compressible co-processed excipients via co-processing. Future Journal of Pharmaceutical Sciences. 2021 Dec; 7:1-2.

6. Olayemi OJ, Nock-Anyebe S. Evaluation of Novel co-processed excipient for fast disintegration of aspirin tablet formulations. Journal of Pharmacy & Bioresources. 2021 May 28;18(1):1-11.

7. Rao SV, Sravya K, Padmalatha K. Formulation and Evaluation of Fast Dissolving Tablets of Atorvastatin Using Novel Co-Processed Excipients. Journal of Pharmaceutical Sciences and Research. 2021 Aug 1;13(8):474-80.

8. Syukri Y, Romdhonah AN, Sholehuddin RF, Perdana A. Formulation of Chlorpheniramine Maleate Tablets Using Co-Processed Excipient as A Filler and Binder. Jurnal Farmasi Sains dan Komunitas. 2019 May 31;16(1):29-35.

9. Aute S, Shirsand SB, Baig SA, Amrita S. Development of novel coprocessed excipients for the design of fast dissolving tablet. Indoamerican journal of pharmaceutical research. 2019.

10. Kumar RS, Suresh A. Design and Optimization of Mefenamic acid Fast Dissolving Tablets Employing Modified Starch by 23 Factorial Design. Journal of Drug Delivery and Therapeutics. 2019 Aug 25;9(4-s):933-44.

11. Raza SN, Kar AH, Wani TU, Khan NA. Formulation, and evaluation of mouth dissolving films of losartan potassium using 32 factorial designs. Int. J. Pharm. Sci. Res. 2019;10(3):1402-11.

12. Khan S, Shahi S, Borde S, Shaikh S. Formulation, and evaluation of methylphenidate hydrochloride fast dissolving tablet by QbD approach. Asian J. Pharm. Pharmacol. 2018; 5:33-42.

13. Bhatt P. Mouth Dissolving Tablets Challenges, Preparation Strategies with a Special Emphasis on Losartan Potassium–A Review. World J. Pharm. Pharm. Sci. 2018 Jun 22;7(9):271-87.

14. Soroush H, Ghorbani-Bidkorbeh F, Mortazavi SA, Mehramizi A. Formulation optimization and assessment of dexamethasone orally disintegrating tablets using box-behnken design. Iranian Journal of Pharmaceutical Research: IJPR. 2018;17(4):1150.

15. Amareshwar S, Swathi A, Prashanthi Y, Vishwanadham Y, Sreekanth D, Vivekananda B. Development and Invitro Characterization of Probencid Rapidly Disintegrating Tablets by Using Different Co-Processed Super Disintegrants. Novel Approaches in Drug Designing & Development. 2017 Oct 19;3(3):53-9.

16. Reddy MS, Kore N, Ul Haq S, Fazal M. Formulation, and evaluation of diltiazem HCl fast dissolving tablets using different co-processed excipients by direct compression method. International Journal of Pharmaceutical Sciences and Research. 2017 Jul 1;8(7):2853-61.

17. Kumari B, Soni A, Singla S, Goyal S, Thakur S, Mahant S. Formulation & Evaluation of Mouth Dissolving Tablets Containing Losartan Potassium Using Natural Superdisinigrants. International journal of Pharmaceutical Sciences and drug research. 2017;9(5):234-9.

18. Rao NR, Kistayya C, Kumar G. Design, and development of fast dissolving thin films of Losartan potassium. International Journal of Pharmaceutical Sciences and Drug Research. 2016;8(1):01-6.

19. Ankit A, Kiran Kumar GB, Madhu BK. Formulation, and evaluation of orodispersible tablets of dimenhydrinate by using co-processed superdisintegrants.2016.

20. Iancu V, Roncea F, Cazacincu RG, Lupu CE, Miresan H, Dănăilă CN, Rosca C, Lupuleasa D. Response surface methodology for optimization of diclofenac sodium orodispersible tablets (ODTs). Farmacia. 2016 Mar 1; 64:210-6.

21. Gandhi PP, Mundada AS. Formulation, and evaluation of coprocessed excipient for mouth dissolving formulation. Int J Drug Dev Res. 2016;8(1):30-5.

22. Reddy BV, Navaneetha K, Reddy KV, Reddy PP, Reddy PU, Lavanya T, Divya C. Formulation, and evaluation of fast dissolving tablets of losartan potassium. Indo American journal of pharmaceutical research. 2014;4(5):2573-84.

23. Bushra R, Shoaib MH, Ali H, Zafar F, Naeem MI, Aslam N, Yousuf RI. Formulation design and optimization of aceclofenac tablets (100 mg) using central composite design with response surface methodology. Lat. Am. J. Pharm. 2014 Jan 1;33(6):1009-18.

24. VinayakMundhe M, Burande S, Kondapure MA, Arsul MV, Zarekar S. Formulationand Evaluation of Mouth Dissolving Tablet of Olanzapine by Coprocessing Superdisintegrants. Asian Journal of Pharmaceutical Technology & Innovations. 2013;1(01):01-20.

25. Shailaja CJ, Karwa P, Nargund LV, Laxman SV. Development of fast dissolving tablets of losartan potassium using Kollidon CL-SF. Journal of Chemical and Pharmaceutical Research. 2013;5(5):119-27.

26. Darwish MK. Application of Quality by Design Principles to Study the Effect of Coprocessed Materials in the Preparation of Mirtazapine Orodispersible Tablets. International Journal of Drug Delivery. 2013 Jul 1;5(3):309.

27. Gattani MA, Singh VI, Shukla MA, Ahire KI, Singh ME. Development of directly compressible co-processed excipients for orally disintegrating tablets using rotary evaporation method. Int J Pharm Sci. 2013;5(3):390.

28. Bhanja S, Hardel DK, Sudhakar M. Mouth dissolving tablets of losartan potassium: formulation and evaluation. International Journal of Pharmaceutical Sciences and Research. 2012 Sep 1;3(9):3444.

29. Mangal M, Thakral S, Goswami M, Thakur N. Comparison study between various reported disintegration methods for fast dissolving tablets. African J Basic & Appl Sci. 2012;4(4):106-9.

30. Mohan V. Formulation and In Vitro Evaluation of Mouth Dissolving Tablets of Cinnarizine (Doctoral dissertation, JKK Nattraja College of Pharmacy, Komarapalayam, Tamil Nadu, India).2012.

31. Mourya AK, Prajapati SK, Jain SK, Kumar A, Thakran AK, Alok S. Formulation, and evaluation of fast dissolving tablets of acetaminophen. International Journal of Pharmaceutical Sciences and Research. 2012 Feb 1;3(2):610.

32. Pavani M. Formulation and Evaluation of Orodispersible Tablets of Taste Masked Nizatidine (Doctoral dissertation, Nandha College of Pharmacy, Erode).2012.

33. Swamy NG. Design and Characterization of Oral Dispersible Tablets of Enalapril Maleate Using a Co-Processed Excipient. Journal of Applied Pharmaceutical Science. 2012 Nov 30;2(11):040-9.

34. Chougule AS, Dikpati A, Trimbake T. Formulation development techniques of co-processed excipients. Journal of Advanced Pharmaceutical Sciences. 2012;2(2):231-49.

35. Bhosale Amol V. Development of Fast Dissolving Tablets of Bisoprolol Fumarate and Statistical Optimization by Using 32 Factorial Design (Doctoral dissertation, The Erode College of Pharmacy and Research Institute, Erode).2012.

36. Chandile GK, Kumar JA, Kakade SM, Rajasekar S, Jadhav RT. Development, and evaluation of haloperidol orally disintegrating tablets using novel co–processed superdisintegrants. Int J Res Pharm Sci. 2011;2(3):348-52.

37. Sharma S. Preparation and evaluation of coprocessed superdisintegrant in the design of prochlorperazine Maleate fast dissolving tablets. Journal of Drug Delivery and Therapeutics. 2011 Dec 9;1(2).

38. Sharma S, Bhardwaj P, Gupta GD. Formulation, evaluation, and optimization of mouth dissolving tablets of losartan potassium: effect of coprocessed superdisintegrants. International Journal of Pharma and Bio Sciences. 2010;1(1):76-83.

39. Raviteja R, Ramu B, Rajkamal B. Formulation of Losartan and Hydrochlorothiazide Orodispersible Tablets for Immediate onset of action by using Super Disintegrants.