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Original Article

FORMULATION DEVELOPMENT AND EVALUATION OF ELEMENTARY OSMOTIC TABLET OF LISINOPRIL DIHYDRATE

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ABSTRACT

Objective: Lisinopril Dihydrate is one of the antihypertensive drug used to control the high blood pressure. Osmotically Controlled release tablet of Lisinopril Dihydrate was performed for reducing dosing frequency and patient compliance.

Methods: Elementary osmotic tablets of Lisinopril Dihydrate were developed using Sodium chloride as a key ingredient which gives osmogent property which provides driving force inside the core tablet and which leads to release of the drug. Microcrystalline cellulose used as a release retardant material in the present work. Different formulations were prepared by varying the concentrations using 3^2 factorial designs. It was applied to see the effect of variables Sodium chloride (X1) and MCC (X2) on the response percentage drug release as a dependent variable. These formulations were evaluated for, Hardness, Flow property, Thickness, Friability, Drug content and *In vitro* drug release. Tablets were coated with a semipermeable membrane using 5% w/v cellulose acetate(CA) in acetone and PEG 400(1%) used as Plasticizer. Coated Elementary osmotic tablets were drilled for delivery orifice using a standard micro drill of diameter size 0.8 mm.

Results: Drug release rate was increased as the increase in the concentration of sodium chloride and release rate decreased on increasing the concentration of MCC. Drug release rate was directly proportional to delivery orifice size. SEM Study carried out for detection of diameter size of the delivery orifice. The FTIR studies demonstrate that there was no interaction between polymer and drug.

Conclusion: The optimized formulation was stable for 3 mo of accelerated stability study

Keywords: Lisinopril Dihydrate, Controlled Release, Elementary Osmotic Tablet, Semipermeable Membrane, Cellulose Acetate

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INTRODUCTION

The development of an improved method of drug delivery has received a lot of attention in the last two decades. The basic rational for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems and pharmacological parameters inherent in the selected route of administration [1]. Rate controlled dosage form and less or not at all, a property of the drug molecules inherent kinetic properties [2]. Thus the design of controlled release systems necessities a thorough understanding of the pharma-cokinetics and pharmacodynamics of the drug Lisinopril Dihydrate. It has been employed as a pharmaceutically active agent for the treatment of hypertension. It shows high solubility in gastric pH and falls rapidly in intestinal pH. The biological half life is 12 h. The dosing regimen is two or four times a day. Hypertension is an abnormal condition of the heart in which level of blood pressure is determined by the amount of blood heart pumps and the amount of resistance to blood flow in the arteries [3, 4]. Treatment of hypertension may require a continuous supply of the drug to the heart Single dose from that provides particular plasma profile of Lisinopril Dihydrate is desirable. Conventional formulations may require high dosing frequency to maintain the drug within the therapeutic concentration hence it is necessary to formulate Osmotically controlled release tablet of Lisinopril Dihydrate [5].

In elementary osmotic pump tablet (EOP) the delivery of a drug is in the form of a solution that releases the active material at controlled rates. These systems work with the principle of osmosis; osmotic pressure is produced by active material in itself and/or an accompanying osmotic agent. Preparation consists of the core that contains the active material and a semipermeable membrane that coats the core, having an orifice size 0.5 to 1.5 mm. Lisinopril Dihydrate is a gastric irritant in nature. To overcome this problem cellulose acetate coating is applied to the core tablet.

The aim of this study was to develop Osmotically controlled release tablet of Lisinopril Dihydrate by using 32 full factorial designs. Sodium chloride is a key ingredient which gives osmogent property which provides driving force inside the core tablet which leads to release of drug and microcrystalline cellulose used as a release retardant material. Core tablet was coated by cellulose acetate 5% and PEG 400 1% used as a plasticizer. Tablets were drilled 0.8 mm using mechanical driller [6].

MATERIALS AND METHODS

Lisinopril Dihydrate was obtained as a gift sample from Marksan Pharmaceutical Ltd., Verna, Goa. Cellulose acetate, Sodium chloride, Sodium Lauryl sulphate, Lactose, PVP–K30, PRG400, Acetone, Isopropyl alcohol, was procured from Research–Lab Fine Chem. industry, Mumbai. All other chemicals used in the study were of analytical grade.

Drug-excipients interactions

The physicochemical compatibilities of the drug and excipients were tested by FT-IR spectrometry. FT-IR spectra of the drug alone and drug-excipients physical mixtures (1:1 w/w) were derived from an IR Affinity-1, FT-IR, Bruker, Japan.

The FT-IR Spectra of pure Lisinopril Dihydrate showed the peaks at wave numbers (cm^{-1}) which correspond to the functional groups present in the structure of the drug.

Infra-red spectra of drug and polymer mixture showed matching peaks with the drug spectra. The characteristics peak of the drug was also seen in the spectra of physical mixture.

DSC spectra of lisinopril dihydrate

Thermal analysis of drug was carried out using DSC and the sharp endothermic peak observed 148.28 °C corresponding to its melting, and indicating its crystalline nature and purity of the sample. The DSC thermogram is shown in (fig. 3).

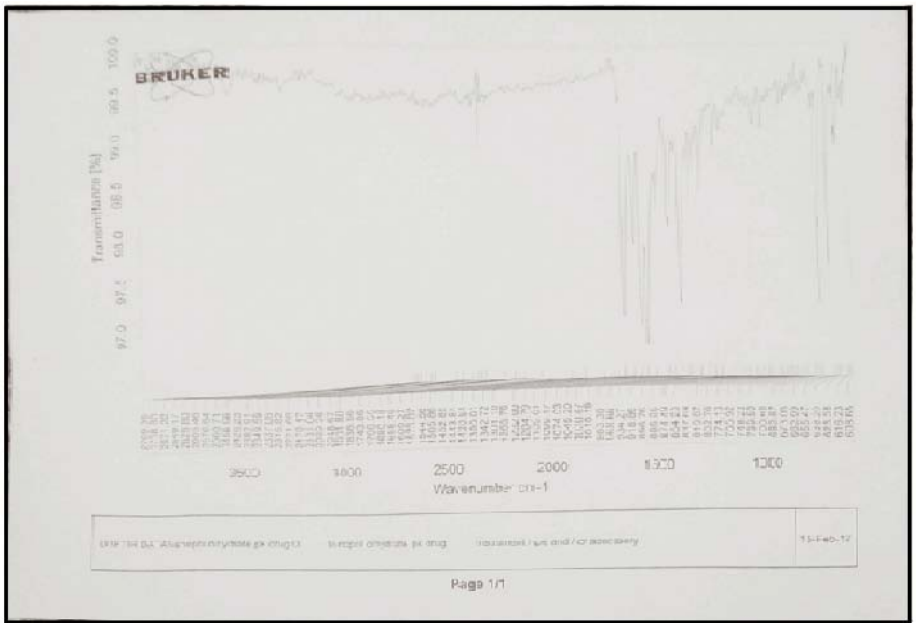


Fig. 1: FT-IR spectra of pure lisinopril dihydtrate

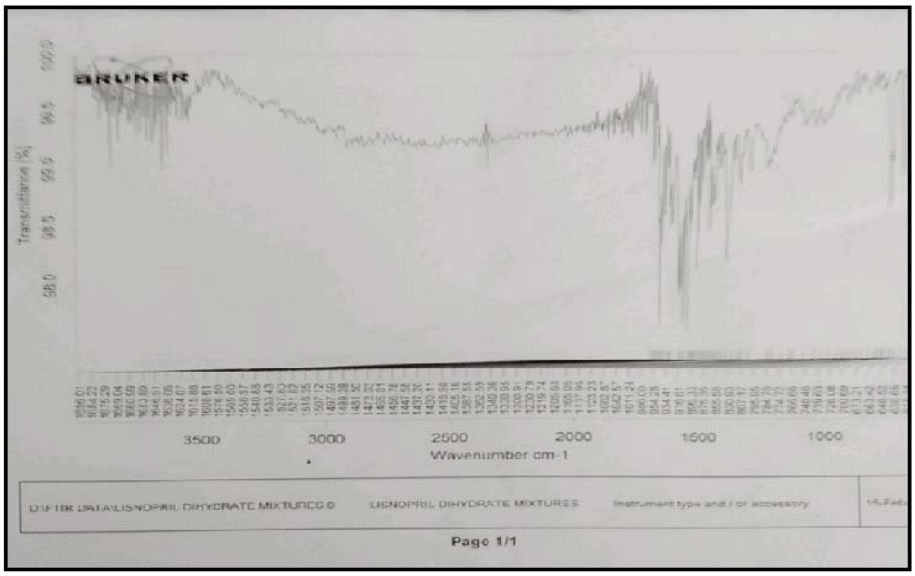


Fig. 2: FT-IR spectra of physical mixture

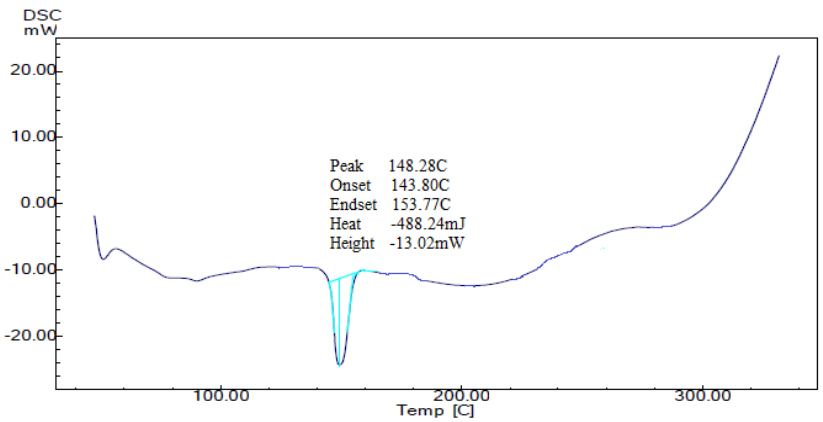


Fig. 3: DSC spectra of lisinopril dehydrate

Method of preparation of osmotic tablets

Wet granulation is the most famous, complex but reliable method of granulation most of the drugs can be granulated by this method. It includes the a wet mass of a solvent to form a wet mass of drug and excipients together followed by the drying and lubricating process. A core tablet of Lisinopril Dihydrate was prepared by wet granulation method. The composition of core tablets is given in (table 1). Lisinopril Dihydrate was mixed with Sodium chloride, Lactose, Sodium Lauryl Sulphate and Microcrystalline cellulose this powder blend was kneaded in the mortar and pestle for 15-20 min. The blend was granulated using PVP K30 as a binder in IPA. The wet mass was formed; resulting wet mass was passed through sieve # 22. Granules were dried in an oven at 50 °C for 2 h. Dried granules were lubricated with magnesium Stearate and talc. Lubricated blend was evaluated for powder characteristics and flow properties like bulk density, tapped density, Carr index, Angle of repose and Hausner's ratio. Then desired amount of blend was compressed into the tablet using Rimek tablet punch machine equipped with 8 mm punch, Weight of the tablet was kept to 280 mg.

Table 1: Composition of elementary osmotic pump tablet as per factorial design (All values are expressed in mg)

Ingredients	Formulation code								
Quantity(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Lisinopril Dihydrate	10	10	10	10	10	10	10	10	10
Sodium chloride	5	10	15	5	10	15	5	10	15
Microcrystalline cellulose	130	130	130	150	150	150	170	170	170
PVP K30	15	15	15	15	15	15	15	15	15
Lactose	100	95	90	80	75	70	60	55	50
Sodium Lauryl Sulphate	15	15	15	15	15	15	15	15	15
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Total	280	280	280	280	280	280	280	280	280

Coating of lisinopril dihydrate core tablets

The core tablets of Lisinopril Dihydrate were coated with 5% w/v solution of cellulose acetate in acetone. Cellulose acetate was used as a semipermeable membrane provider. PEG 400 was used 1% v/v as a plasticizer in the solution and solution was stirred for 20 min.

Coating method

The tablets were warmed to 40±2 °c before applying coating solution. Dip coating technique was used for the coating of osmotic tablet. Tablet was dip into a coating solution and dried for 40 °C.

Characterization

Evaluation of granules: [7, 8] flows properties of granules were evaluated by established methods. Angle of repose was determined using funnel method. Bulk Density, Tapped Density, Compressibility index and Hausner's ratio were calculated.

Evaluation of pre-coated tablets: [9, 10] The formulated core tablets were evaluated for different parameters like hardness, thickness, weight variation, Friability and drug content, uniformity of tablet.

Thickness: The uniformity of thickness was measured using digital vernier caliper. The average thickness of the tablet was calculated.

Weight Variation Tests: [11] 20 tablets were weighed individually average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the acceptable limits (±7.5%). The percent deviation was calculated.

Hardness: [12] the hardness of tablets was measured using Monsanto hardness tester. In this tablet was placed between the plungers, and was tightened from one end, and pressure required to break tablet diametrically was measured.

Friability: In this test 20 tablet was weighed and placed in a roche friability test apparatus. After 100 revolutions the tablets were removed, de-dusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

$$\% \text{ Friability} \frac{\text{Initial weight of tablet} - \text{Final weight of tablets}}{\text{Final weight of tablet}} \text{ x } 100$$

Uniformity of Content: [13, 14] twenty tablets weighed individually and powdered in a mortar, 10 mg of drug dissolved in the 100 ml of phosphate buffer 6.8. The solution was filtered and the content of Lisinopril Dihydrate in the solution was determined by measuring absorbance on double beam UV spectrophotometer (Shimadzu 1800) at 210 nm.

Evaluation of coated tablet: [11]

The thickness of tablet: All tablets were initially subjected for thickness measurement by using digital vernier caliper after coating to assess the thickness of coat.

Thickness of film: Thickness of film was calculated by considering the difference between a coated tablet and uncoated tablet.

$$\text{Thickness of coat} = \frac{\text{Thickness of coated tablet} - \text{Thickness of uncoated tablet}}{2}$$

Weight variation test: 20 tablets were weighed individually average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight.

Scanning electron microscopy: The surface morphology of the tablet coating layer before and after dissolution was examined by scanning electron microscope.

***In vitro* release studies: [14, 15]** *In vitro* drug release of the formulation was carried out in a USP dissolution apparatus (paddle type) set at a rotating speed of 50 rpm and temperature of 37±2 C. The dissolution medium (900 ml) was 0.1N HCL for the first 2 h and phosphate buffer (pH 6.8) thereafter up to 24 h sample (5 ml) were withdrawn at specific time intervals and the medium was replenished with fresh dissolution fluid.

Dissolution kinetics: [16] In order to investigate the mode of release from the tablets the release data were analyzed with the zero order, first order, higuchi square root, korsmeyer plot.

Stability study: [17, 18] Stability study of optimized formulation was carried out to point out any visual physical or chemical changes made in the formulation after storing it at elevated temperature and humidity conditions. Chemical and physical stability of optimized Lisinopril Dihydrate formulation was assessed at 40±2 0c/75±5% RH as per ICH Guidelines. Tablets were packed in aluminium foil and stored for 6 mo. The sample was analyzed after 6 mo for physical appearance, drug content and *in vitro* dissolution profile.

RESULTS AND DISCUSSION

Evaluation of granules

The angle of repose of all the formulations was within the range of 28°C-32°C, indicative of excellent and good flow ability. The bulk density of granules was found to between 0.31-0.33 gm/cm^3. The

value indicates good packing capacity of granules. The tapped density of granules of batches were found in the range of 0.36-0.38 gm/cm^3. The bulk density and tapped density was used to calculate the percent compressibility of the granules. The Carr's index of granules was observed in the range of 10% to 14%, indicating good compressibility of the granules. The values of Hausner's ratio were found to be in the range of 1.12 to 1.15, indicating good flow ability.

Table 2: Evaluation of powder bulk for tablets

Formulation code	Angle of repose(θ) (n=3)	Bulk density (gm/cm^3) (n = 3)	Tapped density (gm/cm^3) (n=3)	Compressibility index (%) (n=3)	Hausner's ratio (n=3)
F1	28.62±0.43	0.2869±0.006	0.3204±0.016	13.34±0.22	1.14±0.02
F2	28.88±0.75	0.2895±0.015	0.3212±0.003	15.07±0.95	1.15±0.01
F3	29.14±0.37	0.2718±0.004	0.3179±0.004	14.84±0.44	1.11±0.03
F4	28.75±0.05	0.2716±0.009	0.3312±0.016	14.63±0.60	1.18±0.02
F5	29.64±0.34	0.2822±0.006	0.3188±0.018	14.74±0.24	1.16±0.04
F6	29.73±0.07	0.2823±0.008	0.3726±0.005	14.51±0.15	1.15±0.03
F7	29.41±0.06	0.2893±0.007	0.3920±0.020	14.38±0.24	1.14±0.02
F8	27.21±0.28	0.2811±0.007	0.3461±0.030	13.97±0.21	1.13±0.02
F9	27.29±0.16	0.2809±0.015	0.3462±0.060	15.03±0.93	1.15±0.03

Pre-coating evaluation

All formulated coated osmotic tablet batches were evaluated for weight variation, hardness, thickness, friability and drug content. Weight variation, hardness, thickness, friability and drug content of uncoated tablets were found within the range.

Post coating evaluation

All formulated coated osmotic tablet batches were evaluated for Weight variation, thickness and Film thickness. Due to uniform coating weight variation and thickness of coated tablets were found within the rang. The thickness of the film was measured by calculating the difference between the thickness of coated and uncoated tablet.

Diameter of delivery orifice

Evaluation of diameter size of the delivery orifice was measured by Scanning Electron Microscope and was found to be 0.8 mm. SEM data give in (fig. 4).

Table 3: Pre-coating evaluation parameters of osmotic tablets

Formulation code	Average weight (mg) (n=20)	Hardness (kg/cm^3) (n=10)	Thickness (mm)	Friability (%) (n=20)	Drug content (%)
F1	278±0.3964	3.48±0.1725	3.19±0.1480	0.40±0.009	96.46±0.4164
F2	279.8±0.1844	2.78±0.1519	3.68±0.0901	0.24±0.005	98.01±0.2511
F3	275.4±0.3211	3.73±0.1421	3.81±0.0779	0.32±0.011	99.38±0.1655
F4	278.7±0.2515	4.08±0.0945	3.66±0.2252	0.38±0.017	98.55±0.1596
F5	279.6±0.2093	3.63±0.1975	3.62±0.1409	0.37±0.011	97.36±0.2022
F6	276±0.2630	3.53±0.1242	3.82±0.1129	0.41±0.011	98.86±0.1260
F7	280.5±0.2674	2.64±0.0801	3.79±0.1048	0.39±0.004	98.43±0.1366
F8	279.1±0.2514	2.78±0.1441	3.82±0.0933	0.40±0.008	97.86±0.2083
F9	277.3±0.2982	3.49±0.1313	3.85±0.1860	0.37±0.014	98.56±0.1894

From above data, it is confirmed that weight variation, hardness, thickness, friability and drug content of uncoated tablets was found within the range.

Table 4: Post coating evaluation parameters of osmotic tablets

Formulation Code	Average weight (mg) (n=20)	Thickness of coate tablet (mm) (n=10)	Thickness of film (mm)
F1	285±0.8767	4.55±0.0170	0.677±0.06
F2	287±0.9787	4.58±0.0227	0.447±0.04
F3	287±0.7251	4.59±0.0196	0.313±0.07
F4	289±0.7994	4.63±0.0131	0.484±0.11
F5	291±0.3590	4.66±0.0123	0.522±0.07
F6	280±0.3547	4.60±0.0394	0.390±0.05
F7	287±0.9907	4.61±0.0103	0.412±0.05
F8	291±0.6473	4.53±0.0105	0.427±0.19
F9	291±0.6549	4.56±0.0171	0.358±0.05

From above-evaluated data of coated osmotic tablets, it was confirmed that weight variation and thickness of the film was found within the range.

***In vitro* dissolution study of formulations (F1-F9)**

The result shows that with an increase in the concentration of Sodium chloride (NaCl) and decreasing the concentration of microcrystalline cellulose (MCC) the release rates gradually increases. The results showed that the osmotic tablet has the ability to extend the release of Lisinopril Dihydrate for the duration of about 24 h. On the basis of *in vitro* drug release profile, the optimum formulation F6 was selected as it release 98.88% drug within 24 h shown in (table 5).

Dissolution kinetics

In the present study, dissolution was analyzed by PCP Disso Version 3 software to study the dissolution kinetics is given in (table 6).

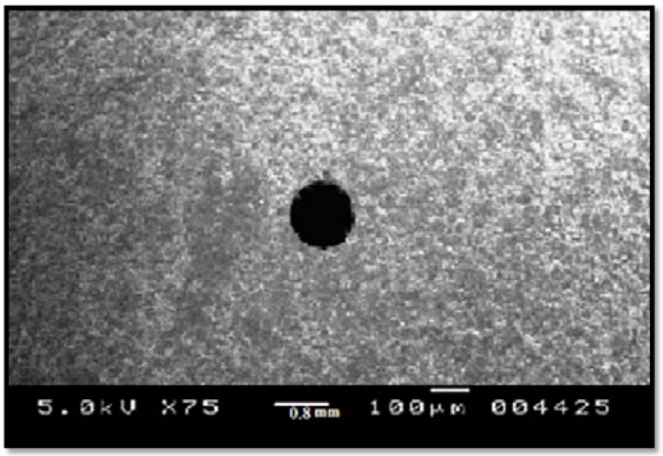


Fig. 4: Scanning electron microscopy (SEM) of delivery orifice

Table 5: Cumulative drug release of formulations (F1-F9)

Time (H)	Cumulative drug release (%)(mean±SD)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0.456± 0.21	0.875± 0.45	0.989± 0.32	0.880± 0.11	0.951± 0.34	0.608± 0.67	0.532± 0.55	0.852± 0.18	0.932± 0.03
2	0.845± 0.35	1.203± 0.98	1.375± 0.61	1.002± 0.15	1.261± 0.69	3.066± 0.25	1.201± 0.09	1.355± 0.08	2.440± 0.33
3	2.688± 0.66	3.225± 0.23	2.143± 0.67	1.736± 0.31	4.255± 0.52	4.244± 0.36	1.570± 0.08	1.738± 0.33	3.435± 0.74
4	5.256± 0.63	5.062± 0.72	4.616± 0.51	7.317± 0.38	5.270± 0.94	5.278± 0.44	2.204± 0.47	3.217± 0.79	5.235± 0.82
5	11.82± 0.74	11.42± 0.03	17.49± 0.19	9.236± 0.47	11.50± 0.78	15.85± 0.62	3.042± 0.56	4.264± 0.68	11.80± 0.88
6	21.53± 0.64	33.73± 0.11	20.71± 0.71	22.33± 0.28	16.25± 0.65	17.97± 0.88	3.518± 0.69	5.444± 0.56	17.98± 0.92
9	29.73± 0.52	54.93± 0.27	32.44± 0.28	28.97± 0.64	24.95± 0.37	32.05± 0.47	7.284± 0.26	17.92± 0.37	29.96± 0.73
12	45.84± 0.36	77.62± 0.52	53.02± 0.34	48.21± 0.53	40.65± 0.13	44.54± 0.33	19.19± 0.31	32.04± 0.24	42.51± 0.61
15	73.18± 0.71	85.87± 0.67	77.76± 0.17	62.03± 0.91	59.24± 0.09	52.80± 0.06	28.71± 0.19	47.05± 0.17	58.92± 0.07
18	94.03± 0.68	94.41± 0.81	94.02± 0.24	75.43± 0.82	73.05± 0.43	67.52± 0.72	40.31± 0.89	62.65± 0.63	75.61± 0.45
21	94.56± 0.41	94.96± 0.45	94.56± 0.18	86.70± 0.44	79.55± 0.37	88.23± 0.66	58.24± 0.72	76.55± 0.47	79.66± 0.38
24	94.99± 0.28	94.98± 0.28	94.91± 0.39	89.28± 0.67	83.30± 0.83	98.88± 0.85	79.34± 0.74	83.30± 0.22	86.67± 0.29

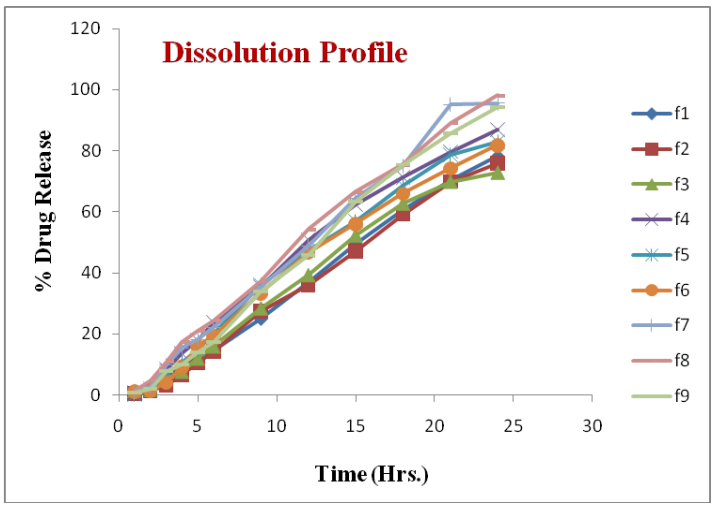


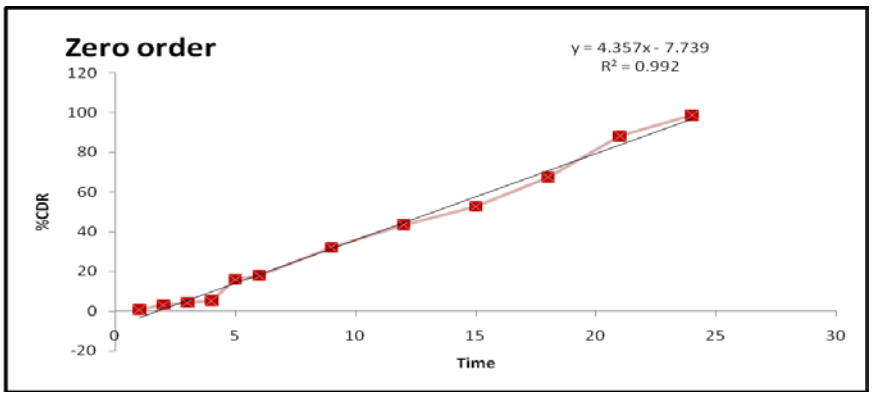
Fig. 5: Dissolution profile of formulation batches (F1-F9)

Table 6: Kinetic treatment of prepared Lisinopril Dihydrate osmotic tablet formulations

	Coefficient of determination (R^2)			
Formulation code	**Zero order**	**First order**	**Higuchi square root**	**Korsmeyer plot**
F1	0.9649	0.9066	0.9397	0.9686
F2	0.9047	0.9649	0.9387	0.9338
F3	0.9613	0.9251	0.9478	0.9472
F4	0.9847	0.9560	0.9603	0.9464
F5	0.9911	0.9069	0.9481	0.9784
F6	0.9921	0.7371	0.9465	0.9767
F7	0.9198	0.7993	0.8133	0.9598
F8	0.9773	0.9227	0.9075	0.9621
F9	0.9870	0.9625	0.9587	0.9831

Different kinetic treatments (zero order, first order, Higuchi's square root equation and Korsmeyer treatment) were applied to interpret the release of Lisinopril Dihydrate from different matrices. The best formulation i.e. optimized formulation F6 follow Zero order kinetics r^2=0.992. So the drug release is of Fickian release.

Zero order kinetic study



Batch	**F6**
R^2 value	0.9921

Fig. 6: Model graph for evaluation of zero order release kinetics

Optimization

Statistics are apply to the results obtained from General Factorial Design in which Two independent Variables varied namely Sodium chloride Nacl (X1) and Microcrystalline cellulose MCC (X2) and their effect is recorded on dependent Variable namely % drug release (Y1).

Evaluation and interpretation of research findings are almost important and the p-value serves a valuable purpose in these findings.

Shows ANOVA for the dependent variable % drug release. The values of X1 and X2 were found to be significant at $p<0.05$, hence confirmed the significant effect of both the variables on the selected responses. Decreasing the concentration of the Sodium chloride (Nacl) and microcrystalline cellulose (MCC) resulted in the decrease in the release of Lisinopril Dihydrate. Variable caused a significant change in the responses. From this data optimum concentration of Nacl 15 mg and MCC 150 mg was found. Design Summary for an osmotic tablet.

Drug release

Table 8: ANOVA for % drug release (Y1)

Source	**Sum of squares**	**Degree of freedom**	**Mean square**	**F value**	**P-value**	**Inference**
Model	258.19	2	129.10	11.36	0.0091	Significant
A-NaCl	47.32	1	47.32	4.16	0.0874	
B-MCC	210.87	1	210.87	18.55	0.0051	

Standard deviation = 3.37, R-Squared =0.7910

The Model F-value of 11.36 implies the model is significant. There is only a 0.91% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob>P" less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. The Variance Inflation Factor (VIF) measured how much the variance of that model coefficient was inflated by the lack of orthogonality in the design and was calculated for % drug release. It was found to be near one indicating a good estimation of the coefficient. Similarly, Ri-squared was near to zero which led to a good model. The values of Probability>F were less than 0.05, which indicated model terms were significant. The quadratic model obtained from the regression analysis used to build a 3-D graph's in which the responses were represented by curvature surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots.

The response surface plot was generated using Design Expert 7.1software presented in (fig. 7). To observe the effects of independent variables on the response studied % drug release. From response surface, 3 level factorial designs were chosen using

quadratic design mode. The range was set in percent from minimum 79.34 to maximum 98.88. The 9 run was performed for the response % drug release and model was found to be linear.

Contour plot

The contour plot showing the effect of Sodium chloride and Microcrystalline cellulose on release is shown in (fig. 8).

Design summary and response summary

Design summary and Response summary is shown in (table 9 and table 10)

Perturbation plot

The perturbation plot is shown in (fig. 9).

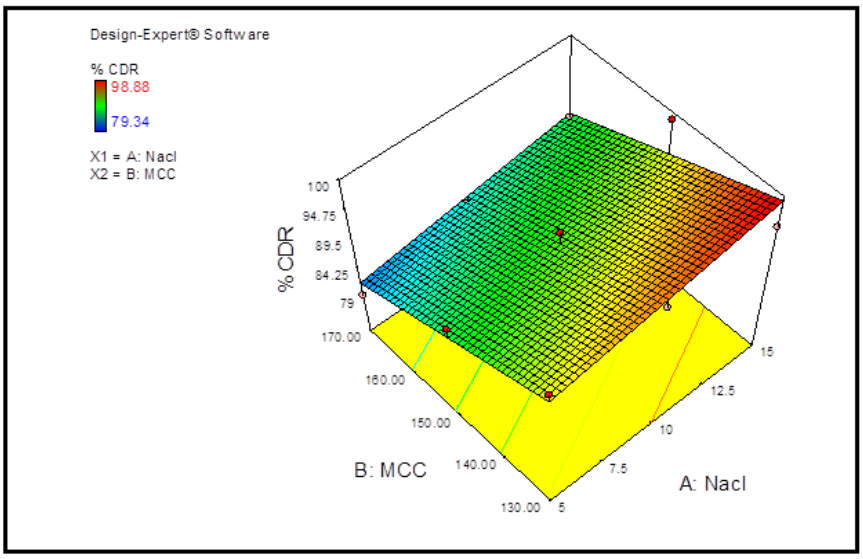


Fig. 7: Surface response plot showing effect of sodium chloride and microcrystalline cellulose on release

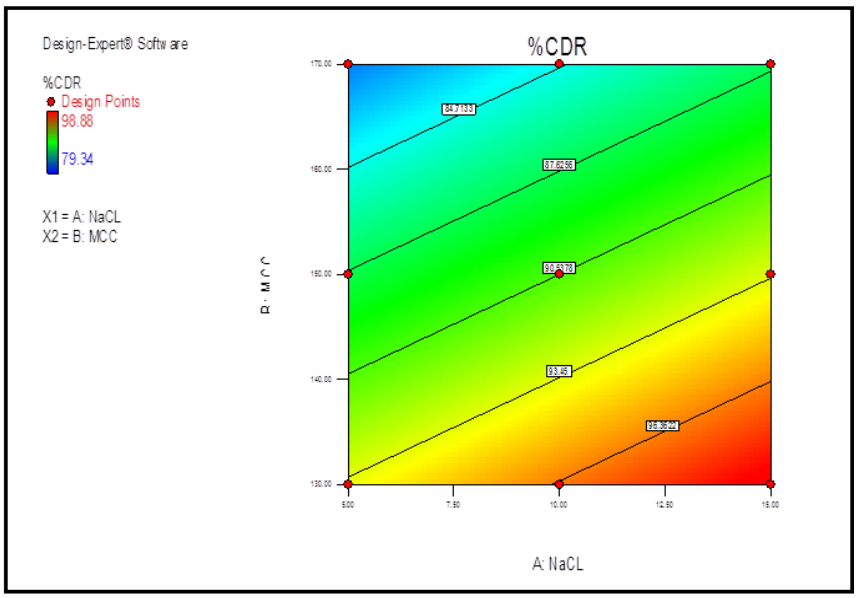


Fig. 8: Contour plot showing effect of sodium chloride and microcrystalline cellulose on drug release

Table 9: Design summary

Factor	Name	Units	Type	Minimum	Maximum	-1 Actual	+1 Actual	Mean	Std. Dev.
A	NaCl	Mg	Numeric	5	15	5	15	15	4.082
B	MCC	Mg	Numeric	130	170	130	170	150	16.33

Table 10: Response summary

Response	Name	Unit	ob	Analysis	Min.	Maxi	Mean	S. D	Ratio	Trans	Model
Y1	%CDR	%	9	Polynomial	79.34	98.88	90.53	6.38	1.24	None	Linear

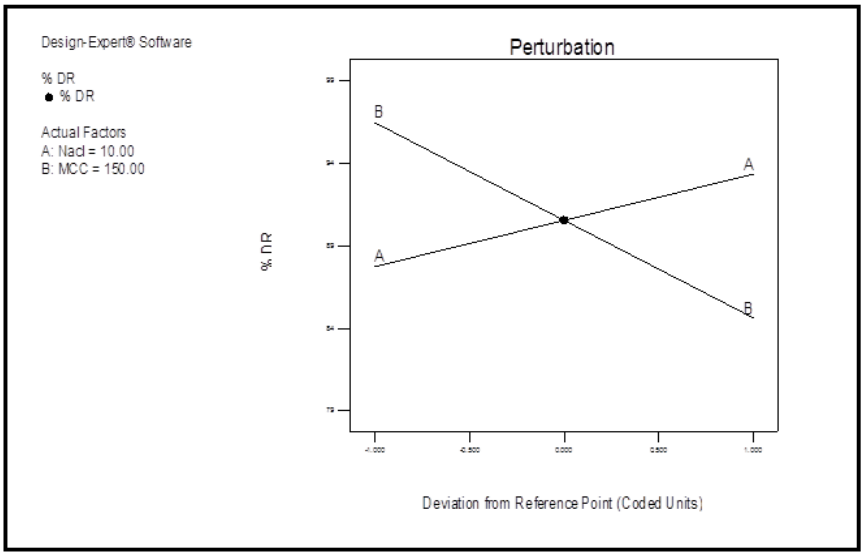


Fig. 9: Pertubation plot showing effect of NaCl and MCC on the drug release

Table 11: Characteristics of optimized formulation F6 after 3 mo storage

Parameter	Initial sample of optimized formulation	After storage at 40±2 °C/75±5% RH, for 3 mo
	F6	F6
Drug content	99.32%	99.31 %
% Drug Released	98.88%	98.45%

From design expert version 7.1. Solutions were found in which optimum batch

Sodium chloride (NaCl) 15 mg and microcrystalline cellulose (MCC) 150 mg with was found to be optimum. From this data F6 batch was selected as optimum formulation.

Accelerated stability study

CONCLUSION

The results of experimental studies of Lisinopril Dihydrate osmotic tablets proved that the granules of Lisinopril Dihydrate showed good flow properties, tablet evaluation tests are within the acceptable limits, IR spectral analysis proved that there was no drug-excipients interaction, the kinetic studies revealed that all the formulation followed zero order drug release kinetics and stability studies revealed that all formulations were found to be stable after storing at temperature of 40 °C±2 °C,75%±5% relative humidity for 3 mo. Thus the results of the above study clearly indicated that developed osmotically controlled release tablet of Lisinopril Dihydrate provide release of drug at a predetermined rate and for a predetermined time in a controlled manner.

CONFLICT OF INTERESTS

Declare none

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